# TOTAL SYNTHESIS OF (+)-KOMAROVIQUINONE[§]

George Majetich,* Jianhua Yu, and Yang Li[†]

Department of Chemistry, The University of Georgia, Athens, Georgia 30602, U.S.A. majetich@chem.uga.edu

Abstract – (+)-Komaroviquinone (**1**) was synthesized from enone **8** in twelve steps.   Three novel routes were developed to produce key intermediate dienone **11**.   Two additional noteworthy steps are a regiospecific bromohydrin formation to oxidize C(7) and a second regio- and stereospecific bromohydrin formation to introduce the β-C(10) alcohol.

During a systematic study of the organic extracts of the semishrub *Dracocephalum komarovi* Lipsky,[1] which grows between 2300-3600 meters above sea level in mountains of western Uzbekistan, Honda and co-workers isolated komaroviquinone (**1**)[2] and coulterone (**2**).[2,3]   These compounds exhibit trypanocidal activity against the causative agent of Chagas' disease in Central and South America.[4]   The preceding manuscript detailed our synthesis of (±)-**1**[5] (Scheme 1) featuring a cyclialkylation strategy[6] to construct
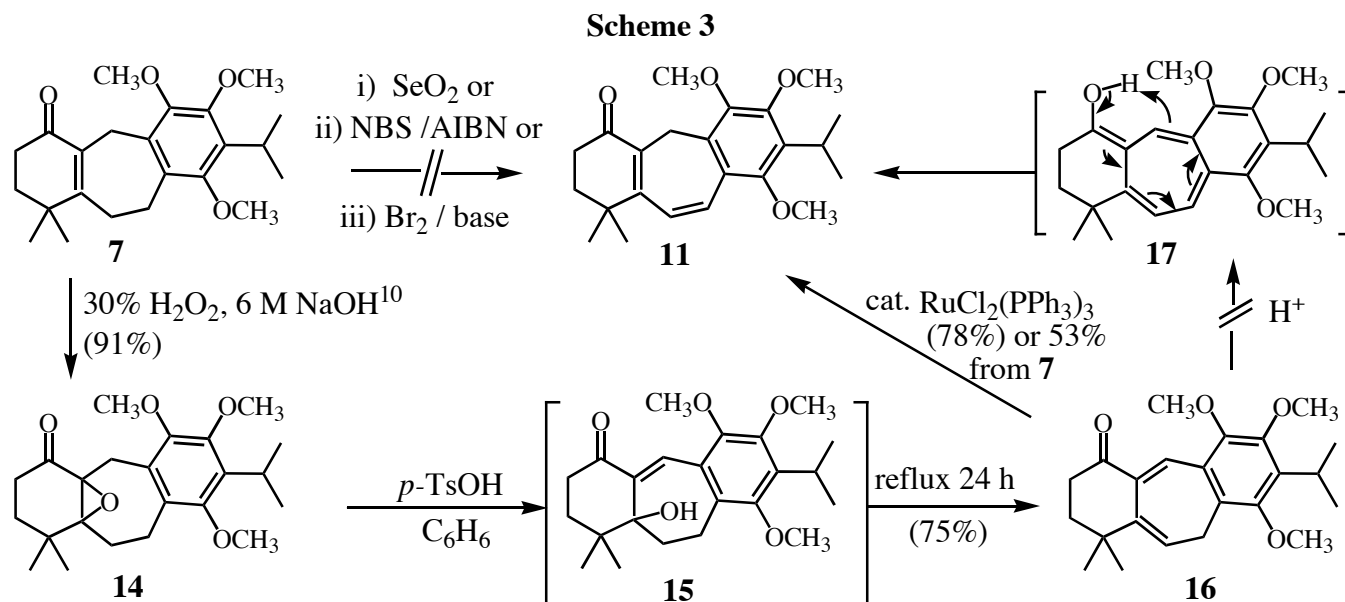
Scheme 1
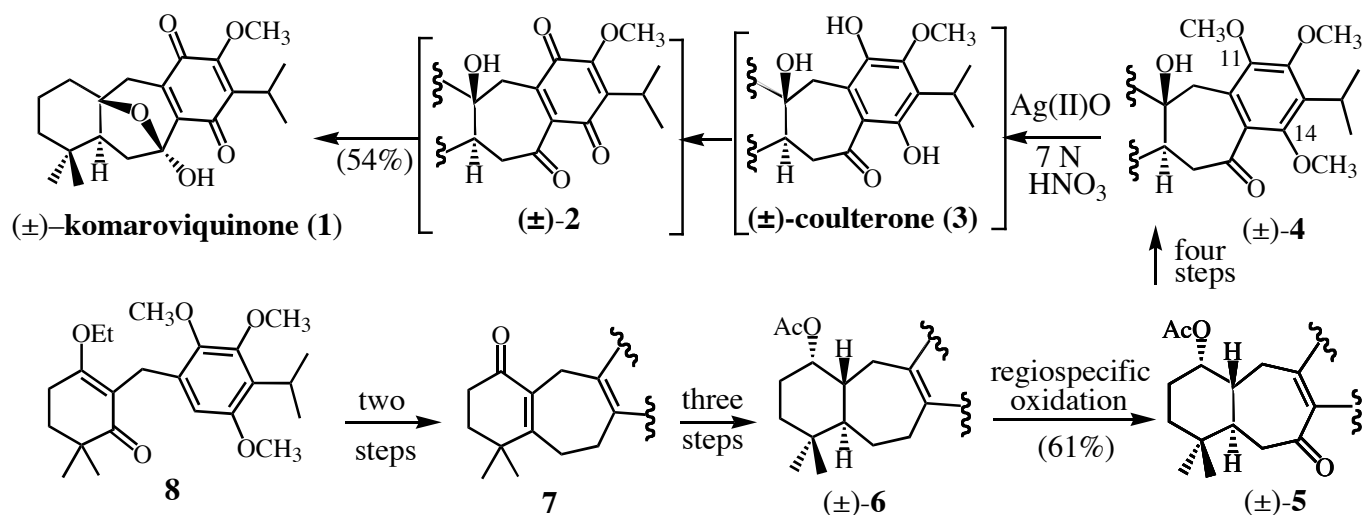
6,7,6-fused enone **7**, a selective benzylic oxidation of acetate **6** to provide ketone **5**, and the introduction of a β-oriented C(10) hydroxyl group (cf. **5 → 4**). The strongly acidic conditions used to deprotect the C(11) and C(14) methyl ethers of ketone **4** did not permit the isolation and characterization of coulterone (**3**) or *p*-benzoquinone **2**, both of which must be formed before intramolecular hemi-acetal formation produces komaroviquinone.

In this study an enantiospecific synthesis of (+)-komaroviquinone was achieved without having to oxidize the non-functionalized C(7) methylene unit.[7,8]   In related studies[9] we have converted achiral enone **7** into alkene (*S*)-**10** via a two-step process (Scheme 2), with the requisite C(5) chirality and a C(1),C(10)–double bond.   If achiral enone **7** can be converted into dienone **11**, then **11** should be converted into chiral diene **12** using the same reactions that transformed enone **7** into alkene (*S*)-**10**. Several well-known strategies can be envisioned to selectively oxidize the C(6),C(7)–double bond of diene (*S*)-**12**.   The conversion of the trisubstituted double bond of (*S*)-**13** to a β-oriented C(10) hydroxyl group (cf. **4**) utilizes the same route that we reported in our synthesis of racemic komaroviquinone. Thus, our initial goal was to develop an efficient synthesis of dienone **11**.
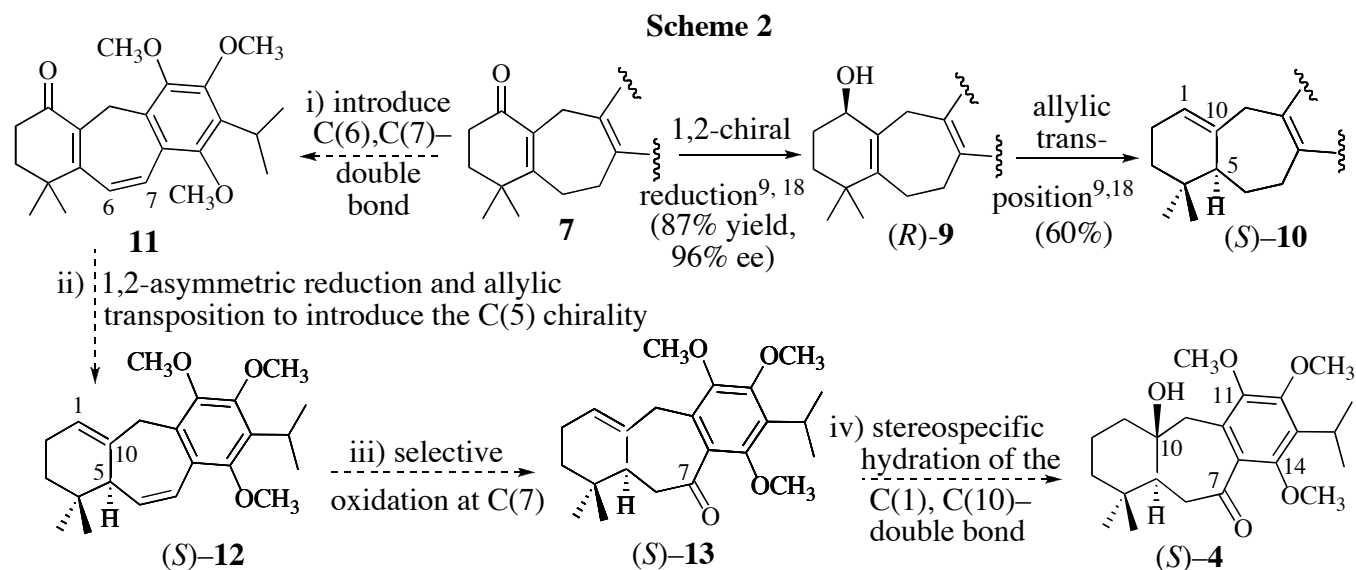
Scheme 2

Several reactions were tried to extend the conjugation of enone **7**, however, these attempts either failed to effect reaction or gave unwanted products (Scheme 3).   Stirring **7** with 30% aqueous hydrogen peroxide and 6 M aqueous NaOH[10] produced epoxide **14** in 91% yield.   When **14** was treated with *p*-toluenesulfonic acid in refluxing dichloromethane, allylic alcohol **15** was generated, which rapidly dehydrated to give diene **16**.   We hoped that diene **16** would rearrange to dienone **11** under acidic conditions via intermediate **17**, but prolonged reaction times and/or harsher reaction conditions failed to achieve this isomerization.   Knowing that transition metals can rearrange isolated double bonds to a

styrenyl position,[11] we heated diene **16** in the presence of a catalytic amount of $Ru(PPh_3)_3Cl_2$. These conditions produced dienone **11** in 78% yield.

Scheme 3

Concurrent with our efforts to prepare dienone **11** from enone **7** were efforts to synthesize additional cyclialkylation precursors having an ether substituent either at C(6) or at C(7), i.e., dienones **19** and **23**, respectively (Scheme 4). We believed that treatment of either dienone with a Lewis acid would form the central seven-membered ring (cf. **20** and **24**), followed by the *in situ* loss of ethanol, to give dienone **11**.
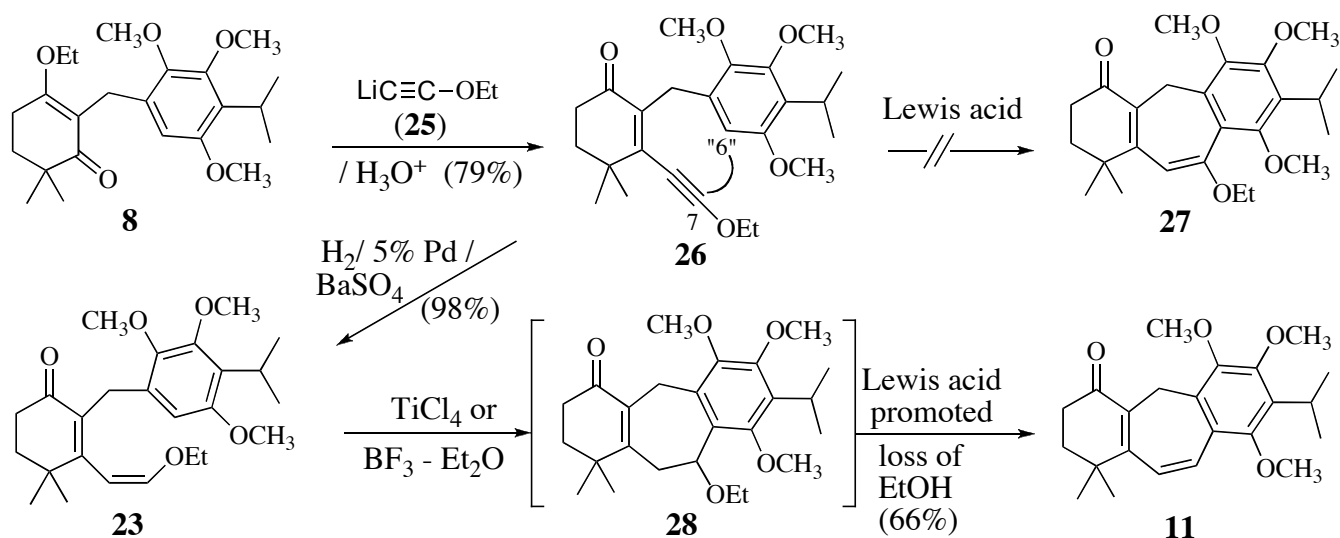
Scheme 4
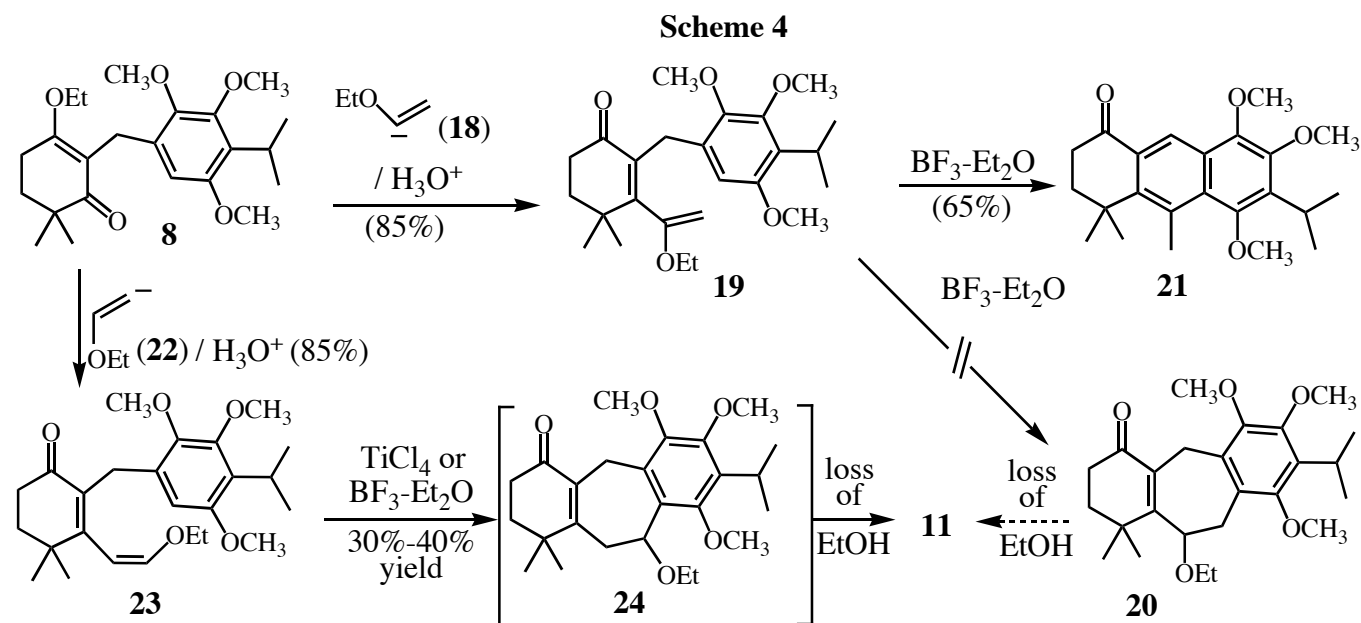
Addition of 1-lithio-1-ethoxyethylene (**18**)[12] to ketone **8**,[13] followed by careful hydrolysis, gave an 85% yield of cyclialkylation precursor **19**. To our disappointment, treatment of **19** with a Lewis acid did not

produce tricycle **20** but instead gave compound **21**[14] in 65% yield.   Similarly, cyclialkylation precursor **23** was obtained in 85% yield by adding the anion derived from Z-2-ethoxyvinyl bromide (**22**)[15] to **8**, followed by mild acid hydrolysis.   In contrast to dienone **19**, exposure of cyclialkylation precursor **23** to excess BF_3-Et_2O provided dienone **11** in 30% yield along with several unknowns; $TiCl_4$ gave a 40% yield of **11** and similar byproducts.

Besides vinyl anions **18** and **22**, we found that the anion of ethoxyacetylene, or Aren's reagent (**25**),[16,17] also reacts in 1,2-fashion with sterically hindered enone **8** (Scheme 5).   In theory, enynone **26** could cyclize to produce dienone **27**, having a latent C(7) carbonyl moiety.   However, analysis of Drieding models of enynone **26** indicated that the distance between the terminal C(7) alkyne carbon and the "6" carbon of the aryl ring is much greater than that of a carbon–carbon single bond;   not surprisingly, enynone **26** does not undergo cyclialkylation.   Lindlar reduction of the triple bond of **26** cleanly gave dienone **23**, which formed dienone **11** in 66% yield upon treatment with excess Lewis acid.   In retrospect, our initial synthesis of dienone **11** began with enone **7** and required only three steps to give a 53% overall yield of **11** (Scheme 3).   The most direct sequence (i.e., Scheme 4) converted enone **8** to cyclization precursor **23**, but formed tricyclic dienone **11** in <34% overall yield.   However, reacting Aren's reagent with enone **8**, followed by Lindlar hydrogenation and cyclialkylation, gave a 51% yield of dienone **11** and avoided the conversion of enone **8** into enone **7**.   Thus, the Aren's reagent/Lindlar reduction/cyclialkylation sequence represents our best route to prepare key intermediate **11**.

Scheme 5

As outlined in Scheme 2, the asymmetric 1,2-reduction of the C(1) carbonyl of **7** using Corey's CBS procedure[18] produced allylic alcohol **9** in excellent chemical yield and high ee, while the use of Meyer's

Mitsunobu-based allylic transposition[19] to alcohol **9** furnished alkene (*S*)-**10** in good yield.   The application of these procedures to dienone **11** gave (*S*)-diene **12** (Scheme 6).   Diene (*S*)-**12** was treated with Jones reagent in hopes of first hydrating the styrenyl double bond, followed by the *in situ* oxidation of the intermediate benzylic alcohol.   However, dienone **11** was obtained in quantitative yield.[20] Conformational analysis indicated that diene (*S*)-**12** favors a conformation (cf. **12i**) in which the C(6),C(7)-π system is not coplanar with, and hence <u>not</u> conjugated with, the aromatic ring;   therefore, it reacts as a simple alkene.   Treating (*S*)-diene **12** with *m*-CPBA gave epoxide **30** through addition to the more accessible α-face of the molecule.   Exposure of **30** to LAH produced tertiary alcohol **31** in high yield.[21]

Scheme 6
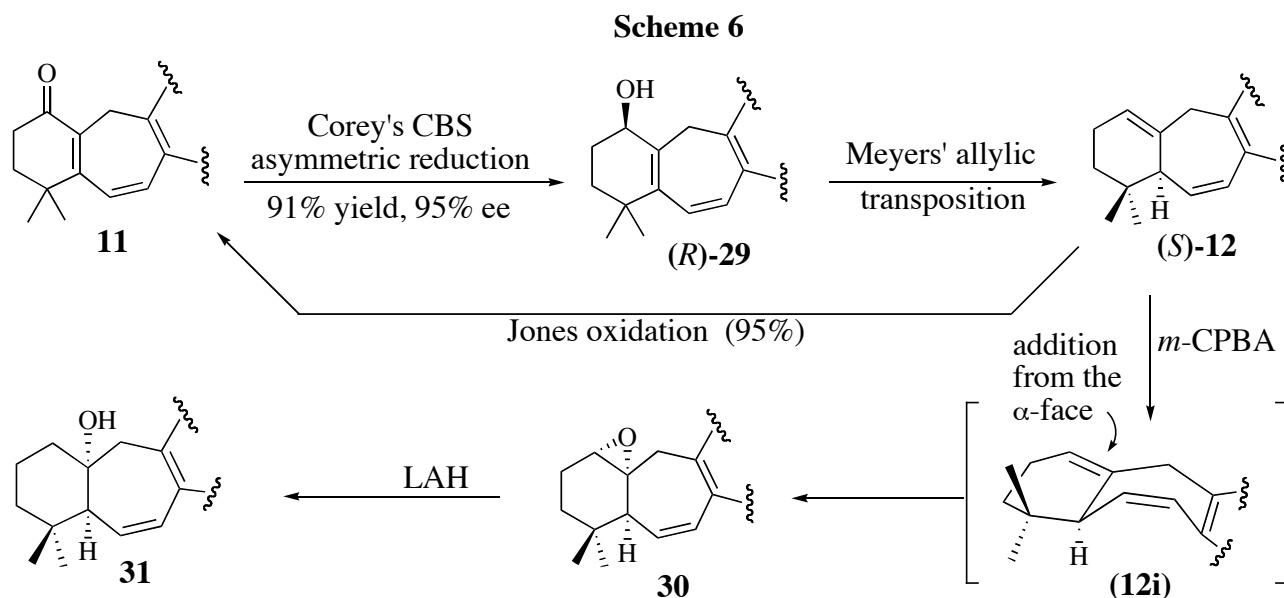
Examination of a Drieding molecular model of dienone **11** suggested that, while the C(5), C(10)–double bond was coplanar with the C(1) carbonyl, the C(6),C(7)–double bond was not conjugated with either the aryl ring or the A-ring enone.   This suggested that bromohydrin formation would involve only the electron–rich C(6),C(7)–double bond to give bromonium ion **32** and that the steric influence of the C(4) gem-dimethyl group would cause the nucleophile present to add in a *trans* fashion to the C(7) benzylic position (Scheme 7).   When dienone **11** was treated with NBS in glacial acetic acid as the solvent, *trans* bromo acetate **33** was produced as a racemic mixture.   Removal of the C(6) bromine atom from **33** was accomplished using free radical conditions to provide racemic **34**.   Asymmetric reduction of the C(1) carbonyl of **34** using Corey's CBS procedure afforded diastereomeric allylic alcohols **35** and **36**, which were then converted into isomeric alkenes **37** and **38** in 88% combined yield using Meyer's allylic transposition protocol.   Removal of the acetate moiety by means of LAH reduction, followed by oxidation of the resulting benzylic alcohols with Jones reagent, gave ketone (*S*)-**39** in excellent overall yield.

Scheme 7 also depicts the final steps needed to convert alkene **39** into the dimethyl ether of coulterone (**4**). Treatment of alkene **39** with NBS in the presence of water introduces a C(10) β-oriented hydroxyl group, as well as an α-oriented bromine atom at C(1). The stereochemistry shown ensues because

Scheme 7
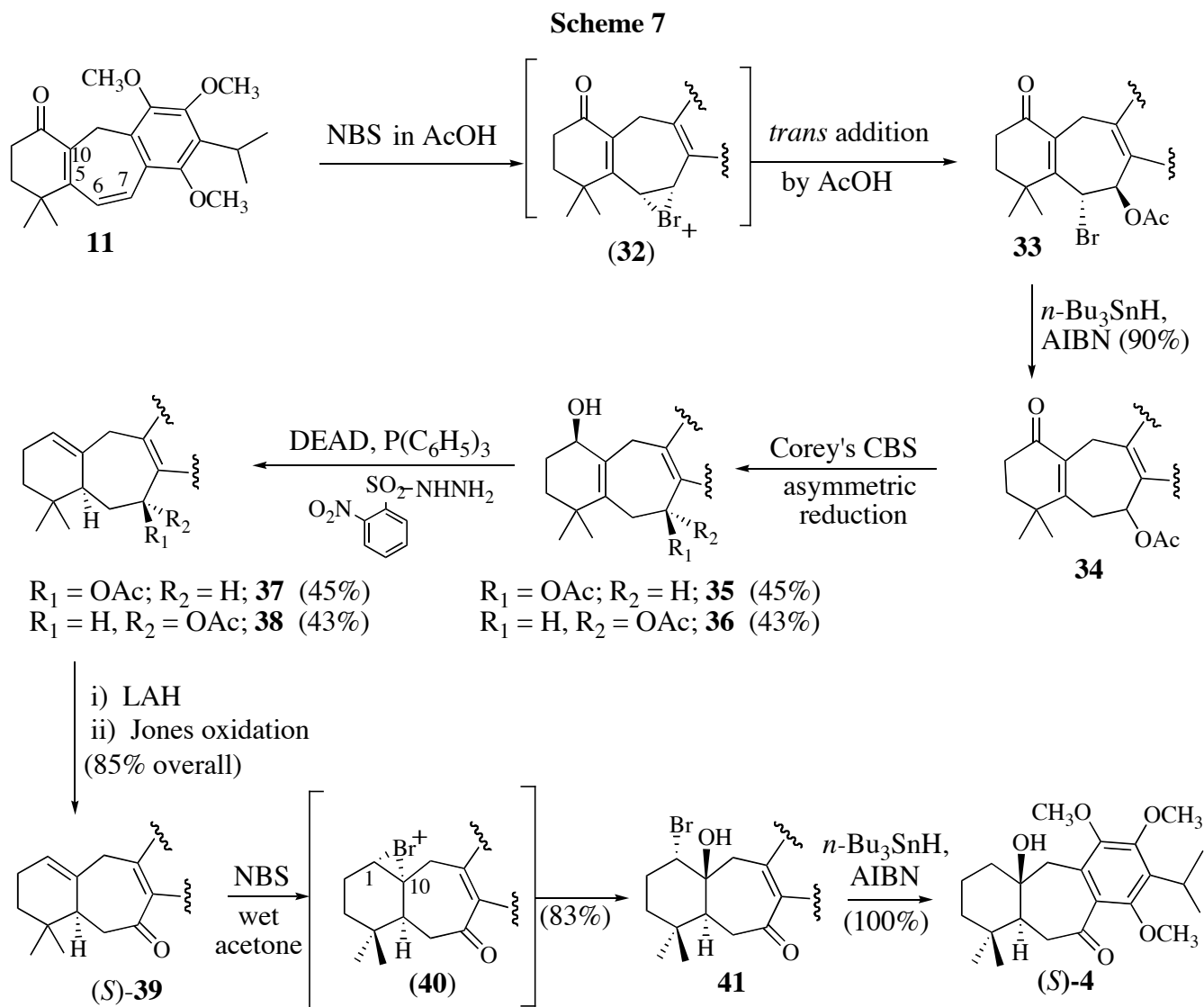
bromonium ion formation (cf. **40**) occurs from the α-face of the trisubstituted double bond which introduces the C(10) hydroxyl group from the β-face of the molecule. Removal of the C(6) bromine atom from ketone **41** using *n*-Bu₃SnH and AIBN produced hydroxy ketone (*S*)-**4** as a single product in 83% overall yield from ketone (*S*)-**40**. Treatment with Ag(II)O / 7 *N* HNO₃ deprotected the methyl aryl ethers and oxidized coulterone to *p*-benzoquinone **2** which underwent rapid intramolecular hemi-acetal formation to give komaroviquinone in good yield. Our synthetic (+)-komaroviquinone displays ¹H and ¹³C NMR, IR, and MS spectra which are indistinguishable from those reported for the natural material and the optical rotation matches that of the natural material within experimental error.[2]

ACKNOWLEDGMENTS

REFERENCES AND NOTES

§   In memory of Professor Ivar Ugi who died on September 27, 2005.

†   Taken in part from the Ph.D. dissertation of Yang Li, *University of Georgia* (2006).

1.   A. I. Vvednski, *Flora Uzbekistana;* Editio Academiae Scientiarum USSR: Tashkent, 1961; Vol. 5, p. 313.

2.   N. Uchiyama, F. Kiuchi, M. Ito, G. Honda, Y. Takeda, O. K. Khodzhimatov, and O. A. Ashurmetov, *J. Nat. Prod.,* 2003, **66**, 128.

3.   For the isolation of coulterone from other plants, see: B. Frontana, J. Cardenas, and L. Rodriguez-Hahn, *Phytochem.,* 1994, **36**, 739.

4.   J. W. Bastien, "The Kiss of Death, Chagas' Disease in the Americas," University of Utah Press, 1998.

5.   For the first synthesis of (±)-komaroviquinone, see: S. Sengupta, M. G. B. Drew, R. Mukhopadhyay, B. Achari, and A. K. Banerjee, *J. Org. Chem.,* 2005, **70**, 7694.

6.   H. A. Brunson and J. W. Kroeger, *J. Am. Chem. Soc.,* 1940, **62**, 36.

7.   For our synthesis of (±)-komaroviquinone, see the preceding manuscript.

8.   The spectroscopic data obtained for all new compounds were fully consistent with the assigned structures.   Reaction conditions have not been optimized. All yields are isolated yields.

9.   For a synthesis of (±)-perovskone, see: G. Majetich and Y. Zhang, *J. Am. Chem. Soc.,* 1994, **116**, 4979.   A manuscript describing a synthesis of (+)-perovskone is under review [G. Majetich, Y. Zhang, X. Tian, J. F. Britton, Y. Wang, and Yang Li].   For our synthesis of (+)-salvadione-A, see: G. Majetich, Y. Wang, Y. Li, J. K. Vohs, and G. H. Robinson, *Org. Lett.,* 2003, **5**, 3847.

10.   G. B. Payne and P. H. Williams, *J. Org. Chem.,* 1961, **26**, 651; B. Zwanenburg and J. Ter Wiel, *Tetrahedron Lett.,* 1970, **11**, 935.

11.   S. K. Sharma, V. K. Srivastava, P. H. Pandya, and R. V. Jasra, *Cat. Commun.,* 2005, **6**, 205; T. A. Stephenson and G. J. Wilkinson, *J. Inorg. Nucl. Chem.,* 1966, **28**, 945;   A. Zoran, Y. Sasson, and J. Blum, *J. Org. Chem.,* 1981, **46**, 255.

12.   J. E. Baldwin, G. A. Höfle, and O. W. Lever, Jr., *J. Am. Chem. Soc.,* 1974, **96**, 7126; U. Schöllkopf and P. Hanssle, *Liebigs. Ann. Chem.,* 1972, **763**, 20; J. S. Brimacombe and A. M.

Mather, *J. Chem. Soc., Perkin Trans. 1*, 1980, 269.

13.   The preparation of enone **8** is detailed in the preceding manuscript of this journal.

14.   We believe that capricious water causes the Lewis acid to hydrolyze the enol ether to form enedione **19a**.   Intramolecular addition of the arene to ketone **19a**, followed by rearomatization of the C ring, produces **19b**.   Dehydration of the tertiary alcohol results in the aromatization of the B-ring.
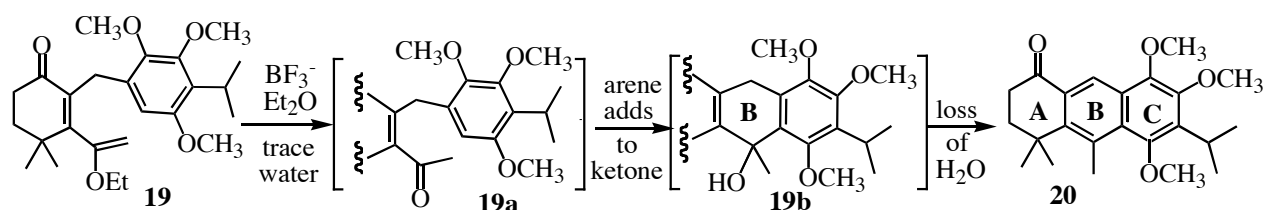
15.   M. A. Pericas, F. Serratosa, and E. Valenti, *Tetrahedron,* 1987, **43**, 2311; R. H. Wollenberg, K. F. Albizati, and R. Peries, *J. Am. Chem. Soc.,* 1977, **99**, 7365.

16.   T. L. Jacobs, R. Cramer, and J. E. Hanson, *J. Am. Chem. Soc.,* 1942, **64**, 233; S. Raucher and B. L. Bray, *J. Org. Chem.,* 1987, **52**, 2332; D. L. J. Clive, T. L. B. Boivin, and A. G. Angoh, *J. Org. Chem.,* 1987, **52**, 4943; L. Duhamel, F. Tombret, and Y. Miller, *J. Organomet. Chem.,* 1995, **280**, 1; D. A. Engel and G. B. Dudley, *Org. Lett.,* 2006, **8**, 4027.

17.   For experimental conditions, see: L. E. Overman and A. S. Thompson, *J. Am. Chem. Soc.,* 1988, **110**, 2248; B. H. Lipshutz and R. Tirado, *J. Org. Chem.,* 1994, **59**, 8307.

18.   E. J. Corey and C. J. Helal, *Angew. Chem. Int. Ed.,* 1998, **37**, 1986.

19.   A. G. Meyers and B. Zheng, *Tetrahedron Lett.*, 1996, **37**, 4841; A. G. Meyers, B. Zheng, and M. Movassaghi, *J. Org. Chem.,* 1997, **62**, 7507.

20.   In related work, we have found that the C(1),C(10)-double bond of diene **12** readily isomerizes into conjugation with the C(6),C (7)-double bond upon exposure to either protic or Lewis acids. Thus in the first step, the oxidant adds to the C(1) carbon with migration of the double bond into the ring fusion (cf. **12ii**).   This intermediate is then further oxidized to generate conjugated dienone **11**.
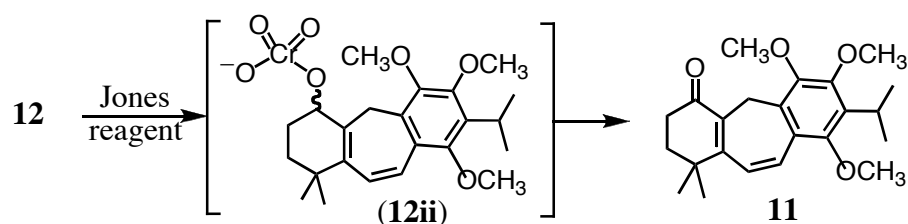
21. Crystal data for $C_{23}H_{34}O_4$ (**31**); MW = 374.50, orthorhombic, Pbca, a = 20.550(5)Å, b = 8.198(2) Å, c = 25.071(7) Å , α = 90 º, β = 90 º , γ = 90 º, V = 4223.7(19) Å^3, Z = 8, T = 273(2) K, μ = 0.079 mm-1, d = 1.178 g/cm^3, R(1) = 0.0842 for 1721 observed reflections ($I > 2$ $\sigma(I)$). All non-hydrogen atoms were refined anisotropically.   Hydrogen atoms were treated as idealized contributions.