HETEROCYCLES, Vol. 73, 2007, pp. 217 - 225. © The Japan Institute of Heterocyclic Chemistry
Received, 29th June, 2007, Accepted, 27th August, 2007, Published online, 28th August, 2007. COM-07-S(U)36

TOTAL SYNTHESIS OF (±)-KOMAROVIQUINONE[§]

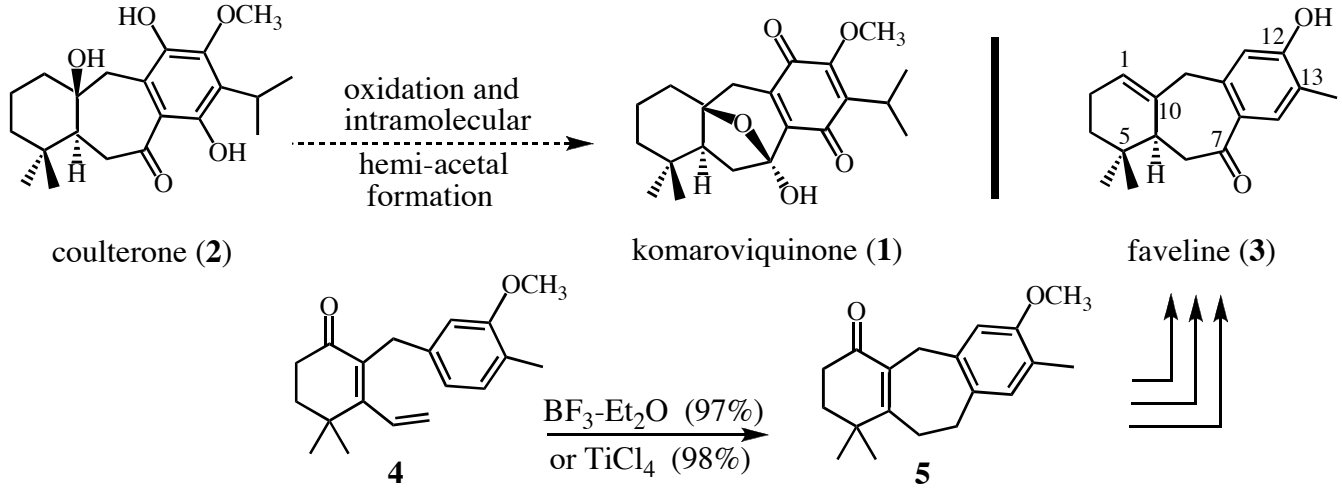
George Majetich,* Yang Li,† and Ge Zou

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

Abstract – (±)-Komaroviquinone (**1**) was synthesized from 3,4,5-trimethoxybenzoic acid in twenty-two steps. The key transformations in this synthesis are: (1) the construction of the cycloheptane ring via a Friedel–Crafts cyclialkylation; (2) a regiospecific benzylic oxidation; (3) a conformationally controlled introduction of the C(10) hydroxyl group and (4) intramolecular hemi-acetal formation.

The inhabitants of the mountains of Uzbekistan use the aerial parts of the perennial semishrub known as "buzbosh" to cure inflammatory diseases and hypertony.[1] In 2003, Honda and co-workers isolated komaroviquinone (**1**) and coulterone (**2**)[2] from buzbosh (Scheme 1).[3] Of these two diterpenoids, komaroviquinone has the more significant trypanocidal activity against epimastigotes of *T. cruzi*, the causative agent of Chagas' disease in Central and South America,[4] with a minimum lethal concentration (MLC) of 0.4 μM.[5] We recognized that komaroviquinone possesses many of the salient features of faveline (cf. **3**),[6] an anti-leukemic agent that we synthesized[7] by means of an intramolecular Friedel–

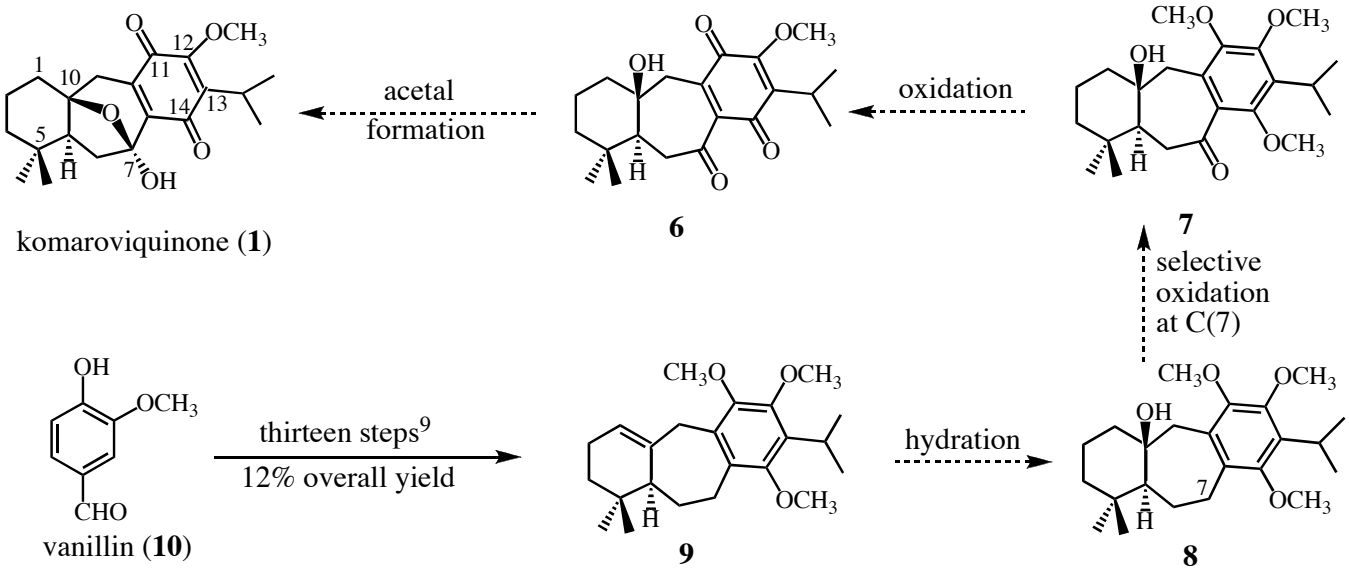
Scheme 1



Crafts process (cf. **4** → **5**),[8-10] also known as a cyclialkylation.[11] Both komaroviquinone and faveline have a carbonyl group at C(7) and alkyl substituents at C(13), whereas komaroviquinone has a β-oriented hydroxyl group at C(10) instead of a C(1),C(10)–double bond, and a more oxidized aromatic ring. Because of komaroviquinone's noteworthy trypanocidal activity and our ability to efficiently assemble the icetexane skeleton, we decided to attempt a synthesis of komaroviquinone[12] and thereby expand the utility of our methodology. The results of this study are described herein.[13]

Scheme 2 summarizes our retrosynthetic analysis of komaroviquinone. We were confident that a regio- and stereospecific hydration of alkene **9**, a key intermediate in our synthesis of perovskone,[9] would give alcohol **8**. Selective benzylic oxidation of alcohol **8** would produce key intermediate **7**. Deprotection of the C(11) and C(14) methyl ethers of **7**, followed by oxidation of the nascent hydroquinone, would furnish quinone **6**. The inspection of molecular models suggests that the planar nature of the aromatic ring in ketone **7** introduces sufficent ring strain within the central cycloheptane ring to favor a conformation which discourages hemi-acetal formation. In contrast, analysis of molecular models of quinone **6** reveals that *p*-quinone moiety (cf. **6**) is non-planar and rather flexible which favors intramolecular acetal formation, thereby producing komaroviquinone. Rather than repeat the thirteen-step sequence we developed to prepare alkene **9** from vanillin (**10**), we investigated a new route to prepare **9** in hope of improving the overall efficiency.

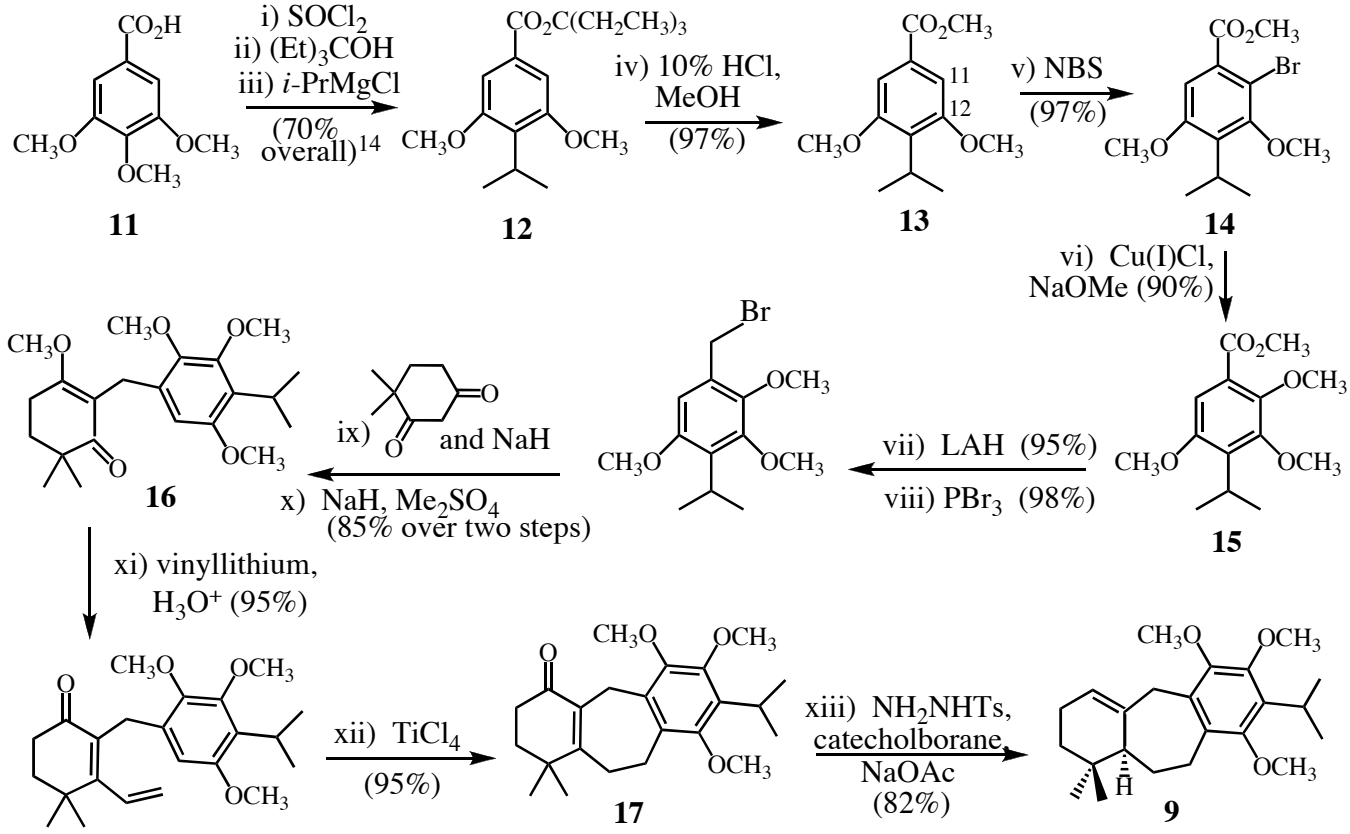
Scheme 2



Our synthesis of (±)-komaroviquinone began with 3,4,5-trimethoxybenzoic acid (**11**), which is converted to ester **12** using the three-step procedure reported by Kotsuki and co-workers (Scheme 3).[14] While the bulky triethylcarbinyl moiety precludes 1,2-addition to the ester carbonyl, it also hampered further

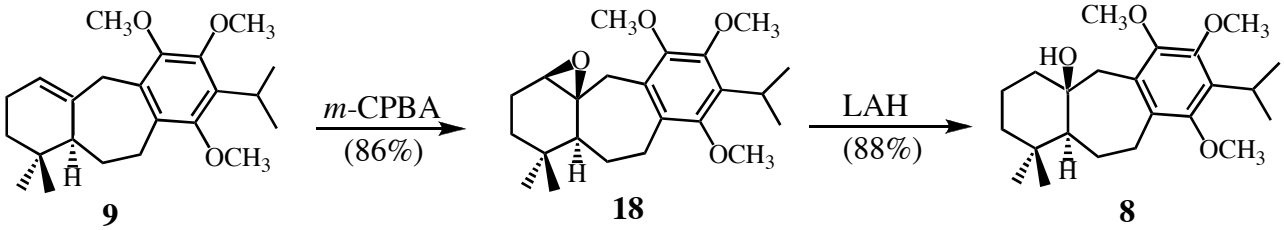
functionalization of the aromatic ring. It was only after triethylcarbinyl ester **12** was transesterified to methyl ester **13** that electrophilic bromination with NBS occurred. The presence of a bromine atom at C(11) permitted its conversion into an aryl methyl ether by treatment with sodium methoxide in the presence of copper(I) chloride (i.e., **14** → **15**).[15] The conversion of ester **15** to tricyclic alkene **9** used the same steps reported in our perovskone synthesis (cf., ester **15** → enone **16** → enone **17** → alkene **9**).[9] It is noteworthy that the preparation of alkene **9** from 3,4,5-trimethoxybenzoic acid also required thirteen steps but proceeded in 30% overall yield.

Scheme 3



Epoxidation of alkene **9** with *m*-CPBA in methylene chloride gave epoxide **18** in 86% yield (Scheme 4). The facial selectivity of this epoxidation was confirmed by means of an X-ray crystal structure of epoxide **18**.[16] Subsequent opening of this epoxide with LAH produced tertiary alcohol **8** in 88% yield.

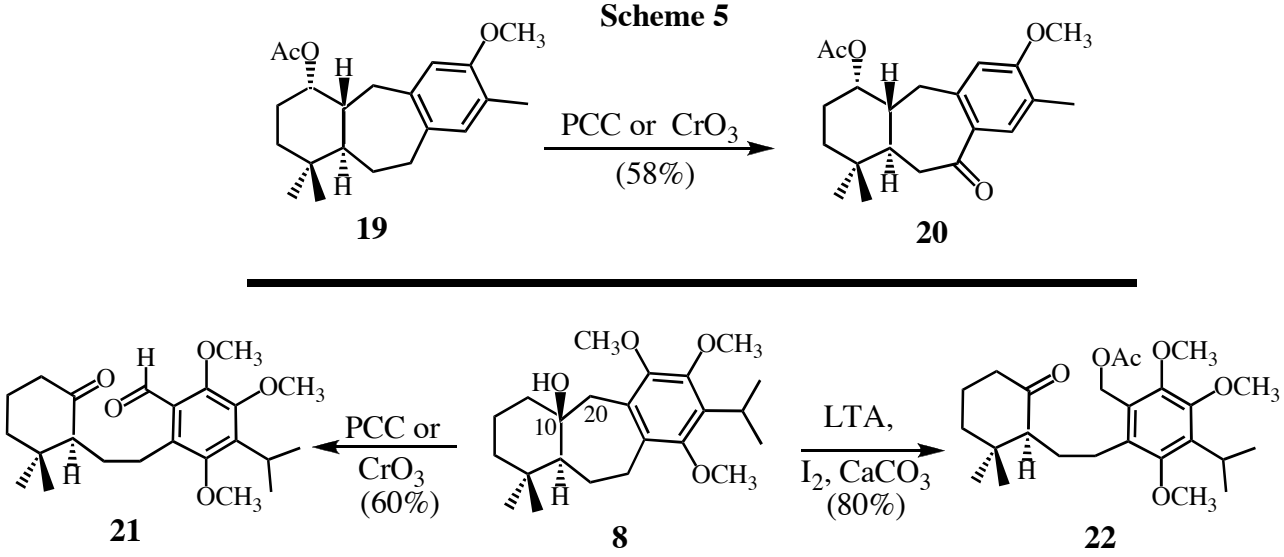
Scheme 4



In contrast to the oxidation of acetate **19** which produced ketone **20** in 58% yield, the treatment of

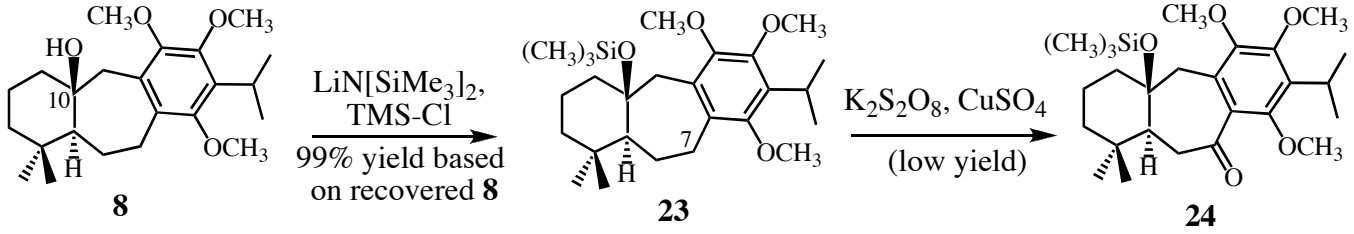
alcohol **8** with PCC or CrO_3 instead gave only keto-aldehyde **21** via cleavage of the C(10),C(20)–bond (Scheme 5). The free radical nature of this fragmentation was confirmed when alcohol **8** was treated with lead tetraacetate and iodine[17] and the only product formed was acetate **22**.

Scheme 5



After learning that tertiary alcohol **8** would not tolerate oxidative conditions, we decided to protect the C(10) hydroxyl group in order to preclude this fragmentation (Scheme 6). As one would expect, the hindered nature of alcohol **8** resisted all efforts to convert it into an acetate, a methyl ether, or a MOM ether. Surprisingly, treatment of **8** with an excess of both lithium hexamethyldisilazide and trimethylsilyl chloride produced silyl ether **23** in 68% isolated yield along with a 31% yield of unreacted alcohol **8**. The oxidation of **23** with PCC or CrO_3/CH_3COOH gave only unreacted starting material. Less common reagents known to oxidize a benzylic methylene were then studied. For example, copper(II) sulfate pentahydrate and potassium peroxydisulfate (oxone)[18] produced ketone **24** but in low yield.

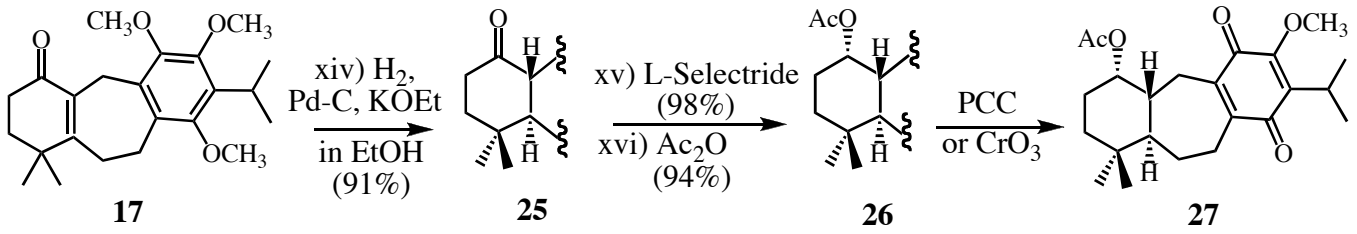
Scheme 6



Since having an alcohol or ether at C(10) did not permit oxidation at C(7), this led us to prepare acetate **26**, a more functionalized analogue of acetate **19**, in hope that it would oxidize at the C(7) position (Scheme 5). The preparation of acetate **26** is shown in Scheme 7. Hydrogenation of enone **17** initially produces a *cis*-fused ketone, but because of the potassium ethoxide present in the reaction medium,

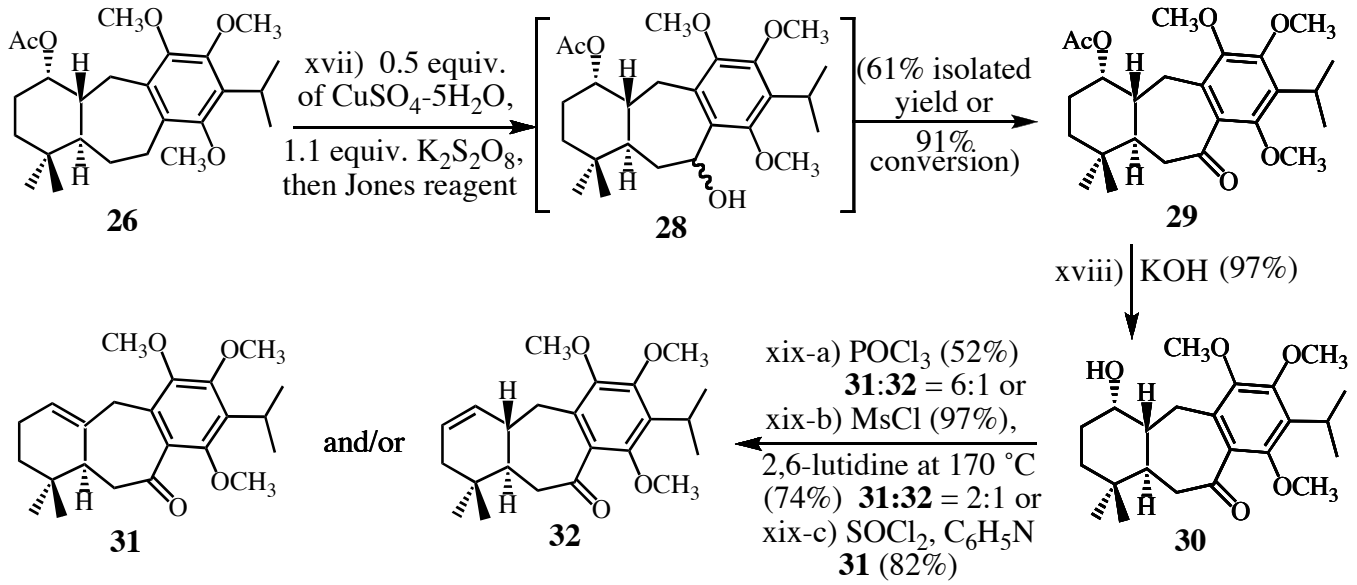
epimerization of the C(10) methine leads to the formation of the thermodynamically favored ketone **25**, having a *trans* A/B-ring fusion. 1,2-Reduction of ketone **25** with L-Selectride at –78 ˚C gave excellent facial selectivity (>99:1); this alcohol was directly acetylated. Once again, we fully expected the oxidation of **26** to mimic our faveline success; however, instead of oxidizing either of the benzylic sites, PCC, CrO_3, or PDC only oxidized the electron-rich arene moiety to produce *p*-benzoquinone **27**.

Scheme 7



Other conditions known to oxidize a benzylic methylene unit were studied, including IBX/DMSO,[19] CAN/HOAc,[20] PFC,[21] *m*-CPBA/air/$NaHCO_3$,[22] and *t*-BuOOH/CuI,[23] but all gave either no reaction or decomposition. Fortunately, heating acetate **26** with oxone ($K_2S_2O_8$) and wet copper sulfate gave a 43% yield of ketone **29** (Scheme 8). The first mechanistic step of this oxidation[18] is the formation of a benzylic free-radical which is further reduced by the Cu^{3+} species present to generate a benzylic carbocation; since water is present in the reaction medium, two diastereomeric benzylic alcohols are produced (cf. **28**) prior to their subsequent oxidation to ketone **29** due to excess oxidant. We noted that the benzylic alcohols were formed rapidly, whereas ketone formation was slow, and that the excess oxidant also promoted eliminations. These observations caused us to use 1.1 equivalents of oxone but only 0.5 equivalents of copper sulfate to produce alcohols **28**, followed by the addition of Jones reagent,

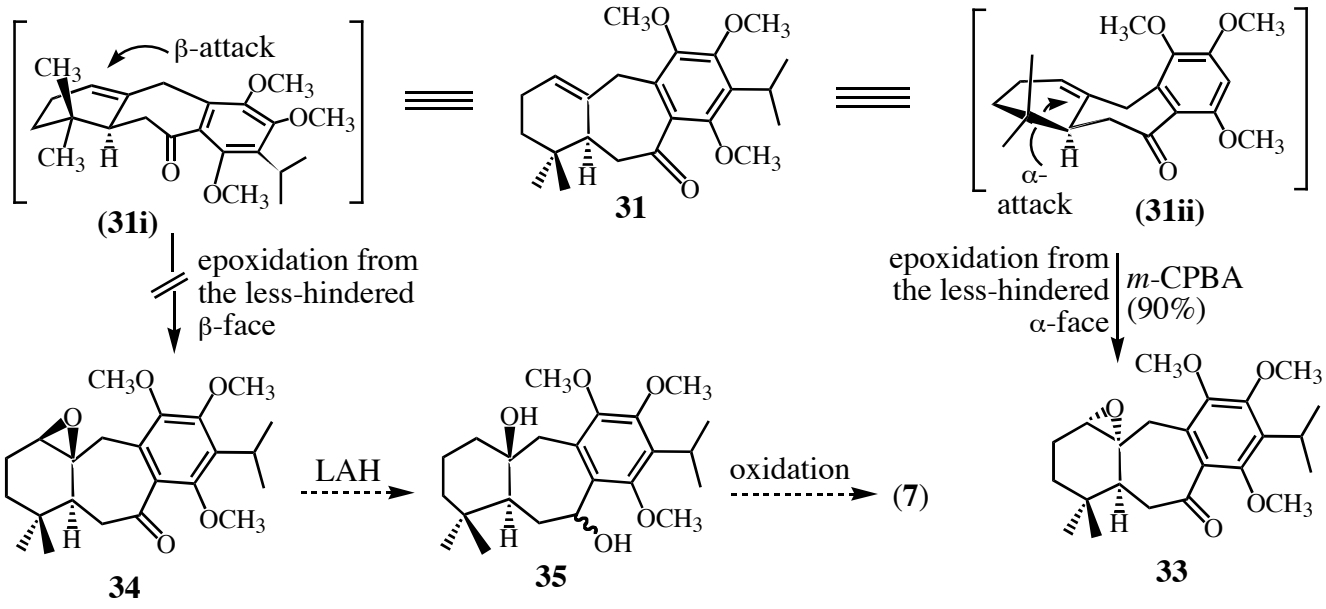
Scheme 8



which is a more powerful oxidant and less prone to cause eliminations. Using these conditions ketone **29** was isolated in 61% yield, along with 33% of unreacted acetate **26** for a 91% conversion.[24] Scheme 8 also depicts how we converted key intermediate **29** into trisubstituted alkene **31**. Acetate **29** was saponified with KOH in hot ethanol in 97% yield. Dehydration of secondary alcohol **30** using $POCl_3$ gave a 6:1 ratio of alkenes **31**:**32**, whereas generation of the corresponding mesylate, followed by treatment with refluxing 2,6-lutidine, gave a 2:1 mixture of these alkenes. Treatment of alcohol **30** with excess thionyl chloride[25] in pyridine at 0 ˚C produced only alkene **31** in 82% yield.

Extensive work established that the C(1),C(10)–double bond must be hydrated before the aromatic ring is oxidized, which then allows hemi-acetal formation (Scheme 9). Since acid-catalyzed hydration of the trisubstituted double bond produced complex mixtures, we considered turning to an epoxidation / epoxide opening strategy (cf. Scheme 3) to introduce the β-oriented C(10) hydroxyl group. In the case of alkene **31**, however, MM3 calculations indicated that the C(7) carbonyl causes preference for the chair-like conformer, i.e., **31ii**, which leads to epoxidation from the α-face (cf. **33**). Even if the epoxidation of alkene **31** occurred from the β-face via the less favorable boat-like conformer (cf. **31i)**, the opening of epoxide **34** using hydride reagents would produce diol **35**, which requires another oxidation in order to produce ketone **7**. Indeed, treatment of alkene **31** with *m*-CPBA produced only epoxide **33**, thus verifying that the α-face of alkene **31** is less hindered.

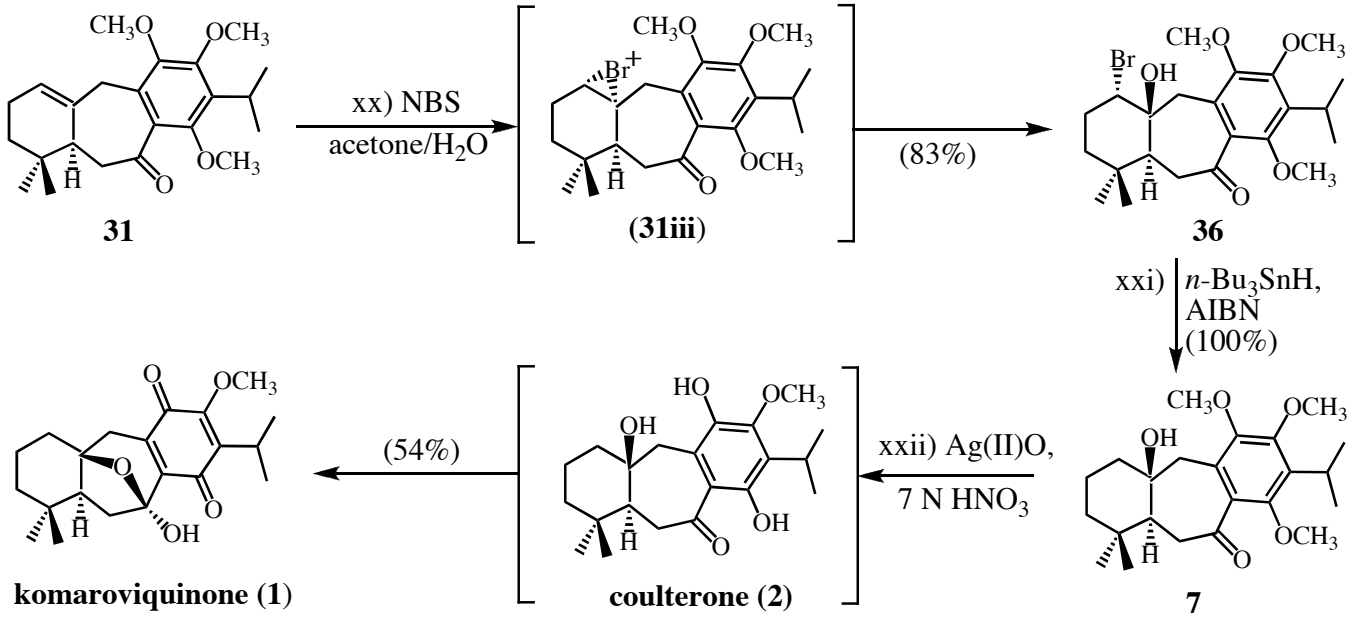
Scheme 9



Knowing that electrophilic reagents add to the α-face of alkene **31** led us to treat it with NBS in aqueous acetone (Scheme 10).[26] Bromohydrin **36** results from opening of bromonium ion **31iii** by water which

introduces a β-oriented hydroxy group at C(10). Treatment of bromohydrin **36** with tri-*n*-butyltin hydride and AIBN reduces the bromide substituent without affecting the C(7) carbonyl. While keto alcohol **7** was inert to mild oxidants such as CAN, PCC, Fremey's salt, or HgO, harsher oxidizing conditions, such as Ag(II)O in acetone with 7 *N* nitric acid,[27] gave (±)-komaroviquinone in 54% yield. In this transformation demethylation of the C(11) and C(14) methyl ethers occurs first, followed by the rapid oxidation of the resulting hydroquinone intermediate **2**, which is itself the natural product coulterone, with subsequent intramolecular transannular acetal formation. Our synthetic (±)-komaroviquinone displays ^{1}H and ^{13}C NMR, IR, and MS spectra that are indistinguishable from those reported for the natural material.[3]

Scheme 10



In the course of this synthesis, invaluable insight was gained into the oxidation of the benzylic position of electron-rich arenes. In addition, two seemingly straightforward transformations, the elimination of a secondary alcohol to produce a trisubstituted double bond, followed by its subsequent hydration, were governed by conformational biasing. Finally, the knowledge we gained in the course of this study has enabled us to achieve a chiral synthesis of komaroviquinone.[28]

ACKNOWLEDGMENTS

We thank the National Science Foundation (CHE-0506486) for support of this research. Appreciation is extended to Dr. Zhongfang Chen (UGA) for the MM3 calculations of compound **31**.

REFERENCES AND NOTES

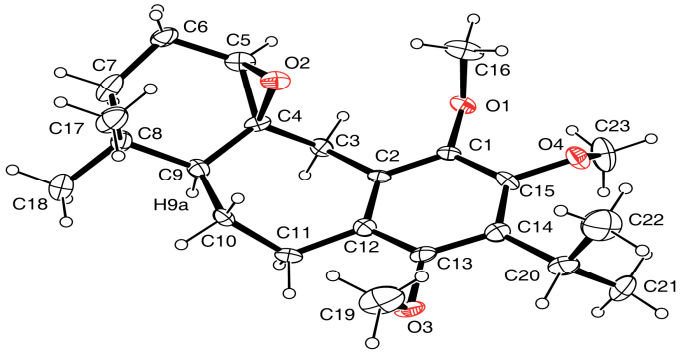
§ In memory of Professor Ivar Ugi who died on September 27, 2005.

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

1. Buzbosh, i.e., *Dracocephalum komarovi* Lipsky, grows in the west Tian Shan Mountain system at around 2300-3600 meters above sea level, see: A. I. Vvednski, *Flora Uzbekistana;* Editio Academiae Scientiarum USSR: Tashkent, 1961; Vol. 5, p. 313.
2. For the isolation of coulterone from other plants see: B. Frontana, J. Cardenas, and L. Rodriguez-Hahn, *Phytochem.,* 1994, **36**, 739.
3. N. Uchiyama, F. Kiuchi, M. Ito, G. Honda, Y. Takeda, O. K. Khodzhimatov, and O. A. Ashurmetov, *J. Nat. Prod.,* 2003, **66**, 128.
4. J. W. Bastien, "The Kiss of Death, Chagas' Disease in the Americas," University of Utah Press, 1998.
5. For the determination of trypanocidal activity of komaroviquinone against epimastigotes of *Trypanosoma cruzi* (Tulahuen strain) see: F. Kiuchi, Y. Itano, N. Uchiyama, G. Honda, A. Tsubouchi, J. Nakajima-Shimada, and T. Aoki, *J. Nat. Prod.,* 2002, **64**, 509.
6. Y. Endo, T. Ohta, and S. Nozoe, *Tetrahedron Lett.,* 1991, **32**, 3083.
7. For a synthesis of (±)-faveline see: G. Majetich, R. Hicks, Y. Zhang, X. Tian, T. L. Feltman, J. Fang, and S. Duncan, Jr., *J. Org. Chem.,* 1996, **61**, 8169.
8. For a synthesis of (±)-barbatusol, a icetexane-based natural product, see: G. Majetich, Y. Zhang, T. L. Feltman, and S. Duncan, Jr., *Tetrahedron Lett.,* 1993, **34**, 445.
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].
10. For a synthesis of (+)-salvadione-A, an icetexane-based natural product, see: G. Majetich, Y. Wang, Y. Li, J. K. Vohs, and G. H. Robinson, *Org. Lett.,* 2003, **5**, 3847.
11. H. A. Brunson and J. W. Kroeger, *J. Am. Chem. Soc.,* 1940, **62**, 36.
12. For the first synthesis of (±)-komaroviquinone (**1**) see: S. Sengupta, M. G. B. Drew, R. Mukhopadhyay, B. Achari, and A. K. Banerjee, *J. Org. Chem.,* 2005, **70**, 7694. For a novel cycloaddition-based construction of the icetexane skeleton of **1** see: A. Padwa, J. Boonsombat, P. Rashatasakhon, and J. Willis, *Org. Lett.,* 2005, **7**, 3725.
13. 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.
14. T. Kojima, T. Ohishi, I. Yamamoto, T. Matsuoka, and H. Kotsuki, *Tetrahedron Lett.,* 2001, **42**, 1709.

15. P. C. Manchand, J. M. Townsend, P. S. Belica, and H. S. Wong, *Synthesis*, 1980, 409; H. L. Aalten, G. V. Koten, D. M. Grove, T. Kuilman, O. G. Piekstra, L. A. Hulshof, and R. A. Sheldon, *Tetrahedron*, 1989, **45**, 5565.

16. Crystal data for $C_{23}H_{34}O_4$ (**18**); 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.



17. J. F. Bagli, P. F. Morand, and R. Gaudry, *J. Org. Chem.,* 1963, **28**, 1207.

18. M. V. Bhatt and P. T. Perumal, *Tetrahedron Lett.,* 1981, **22**, 2605; C. Arnoldi, A. Citterio, and F. Minisci, *J. Chem. Soc., Perkin Trans. 2,* 1983, 531; F. M. Hauser and S. R. Ellenberger, *Synthesis*, 1987, 723.

19. K. C. Nicolaou, P. S. Baran, and Y. Zhang, *J. Am. Chem. Soc.,* 2001, **123**, 3183.

20. W. Y. Lee, C. H. Park, and H. Kim, *J. Org. Chem.,* 1994, **59**, 878.

21. E. J. Parish, H. Sun, and S. A. Kizito, *J. Chem. Res., Synopses*, 1996, **12**, 544.

22. D. Ma, C. Xia, and H. Tian, *Tetrahedron Lett.,* 1999, **40**, 8915.

23. G. Rothenberg, L. Feldberg, H Wiener, and Y. Sasson, *J. Chem. Soc., Perkin Trans. 2: Phys. Org. Chem.*, 1998, **11**, 2429.

24. In our hands, this oxidation is limited to batches of < 500 mg.

25. V. Boekelheide and W. M. Schilling, *J. Am. Chem. Soc.,* 1950, **72**, 712; W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.,* 1955, **77**, 1028.

26. N. L. Wendler, D. Taub, S. Dobriner, and D. K. Fukushima, *J. Am. Chem. Soc.,* 1956, **78**, 5027.

27. C. D. Snyder and H. Rapoport, *J. Am. Soc. Chem.,* 1972, **94**, 227.

28. G. Majetich, J. Yu, and Y. Li, "Total Synthesis of (+)-Komaroviquinone." This issue of this journal.