Concise Synthesis of (±)-Perovskone†

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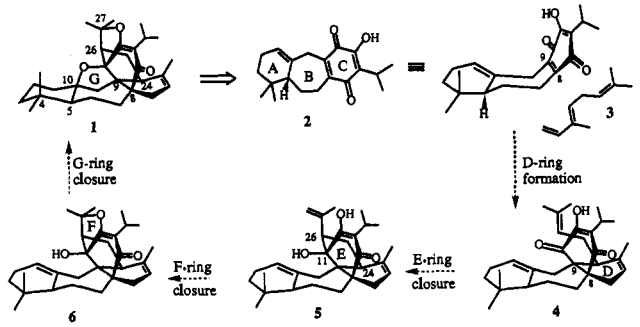
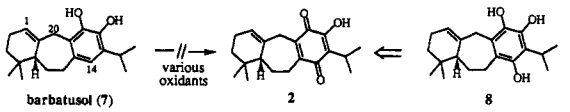
The structurally novel triterpene perovskone (**1**), isolated by Ahmad and co-workers from *Perovskia abrotanoides, Karel syn. P. artemisioides* Boiss (Labiatae) in 1992,[1] contains a complex array of seven fused and bridged rings as well as seven asymmetric centers, posing a formidable challenge to total synthesis. In this communication, we report an efficient total synthesis, in which three of the rings and five of the stereocenters are established in a single operation.

In a proposal for the biosynthesis of perovskone it has been suggested that the skeleton may be constructed by the addition of geranyl pyrophosphate to an icetexone precursor.[1,2] This suggestion prompted us to attempt to mimic Nature by using the Diels–Alder addition of *trans*-β-ocimene (**3**) to a related benzoquinone (**2**) to assemble the key D ring (Scheme 1). On the basis of NMR studies of St. Jacques and Vaziri, which showed that benzocycloheptenes favor a chair conformation,[3] the preferred conformation of quinone **2** should be cup-shaped with the α-face readily accessible, encouraging the diene to add from the α-face to create the correct relative configurations at C(8), C(9), and C(24). It was anticipated that the bulky isopropyl group would control the regiochemistry of this cycloaddition. Furthermore, the use of ocimene as the diene component would subsequently permit the formation of the key C(11)–C(26) bond of the final carbocyclic ring by an intramolecular ene reaction on adduct **4**, leaving only the acid-catalyzed formation of the two tetrahydrofuran rings to complete the synthesis.

Scheme 1



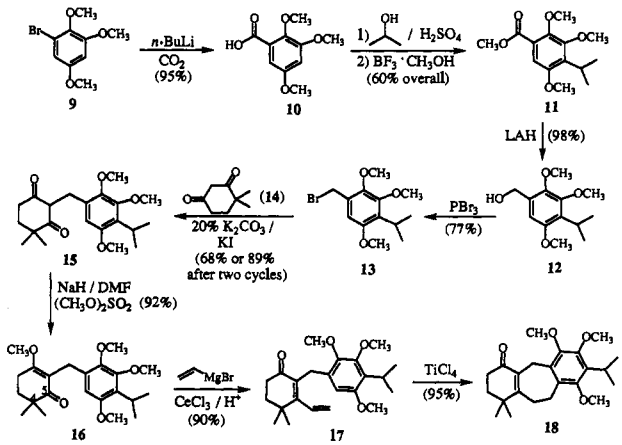
An attractive precursor for *p*-benzoquinone **2** was barbatusol (**7**), a known antihypertensive agent for which we had already devised an eight-step synthesis[4] featuring a new Friedel–Crafts-based strategy (eq 1).[5] Extensive work, however, showed that oxidation of barbatusol gave enones corresponding to oxidation of either the C(20) methylene or the C(1) position. These results led us to consider hydroquinone **8**, which should oxidize under mild conditions without affecting the C(10),C(1)-double bond.



(1)

Our synthesis[6] began with 1-bromo-2,3,5-trimethoxybenzene (**9**), available from vanillin in three steps.[7] Treatment of **9** with *n*-butyllithium, followed by quenching of the anion with gaseous carbon dioxide, gave acid **10** in 95% yield (Scheme 2). An acid-catalyzed Friedel–Crafts alkylation using 2-propanol introduced the required isopropyl unit at C(13). During this reaction, cleavage of one of the methoxy groups also occurred. Rather than isolate the unwanted phenolic byproducts, we treated the crude alkylation mixture with methanolic boron trifluoride etherate, which esterified the carboxylic acid group and remethylated any unmasked phenol. Reduction of **11** and conversion of alcohol **12** to bromide **13** was straightforward.

Scheme 2



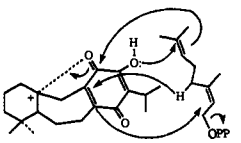
The next step required the alkylation of the enolate of 4,4-dimethyl-1,3-cyclohexanedione (**14**) with bromide **13**. The use of a concentrated solution of compounds **13** and **14** in 20% aqueous potassium carbonate furnished the monoalkylated dione **15** in 68% yield, or 98% yield based on recovered **13**.[8] Repeating this alkylation with recovered bromide provided **13** in 89% yield. Treatment of dione **15** with sodium hydride in DMF and dimethyl sulfate provided enol ether **16** in 92% yield. 1,2-Addition of vinylmagnesium bromide to **16**, followed by mild acid hydrolysis, completed the preparation of cyclization precursor **17**. This Grignard reaction required activation of the C(5) carbonyl by cerium chloride[9] presumably due to steric hindrance imparted by the C(4) *gem*-dimethyl substituents. Cyclialkylation of **17** was accomplished in 95% yield using $TiCl_4$ as catalyst.

The route used to convert enone **18** into quinone **2** is shown in Scheme 3. A Wolff–Kishner reduction of **18** reduced the C(11)

† The authors dedicate this work to Professor Hiroshi Irie of Nagasaki University, Japan, out of respect and appreciation.

(1) 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.

(2) Ahmad and co-workers have postulated the following biogenesis for perovskone.



See also: Watson, W. H.; Taira, Z. *Tetrahedron Lett.* **1976**, 2501.

(3) St. Jacques, M.; Vaziri, C. *Org. Magn. Reson.* **1972**, *4*, 77.

(4) Majetich, G.; Zhang, Y.; Feltman, T. L.; Duncan, S. G., Jr. *Tetrahedron Lett.* **1993**, *34*, 445.

(5) Majetich, G.; Zhang, Y.; Feltman, T. L.; Belfoure, V. *Tetrahedron Lett.* **1993**, *34*, 441.

(6) (a) All structures drawn here represent racemates, with only one enantiomer shown. (b) Reaction conditions have not been optimized. (c) All yields are isolated yields. (d) The spectroscopic and elemental data (±0.3% for C, H) obtained for all new compounds were consistent with the assigned structures.

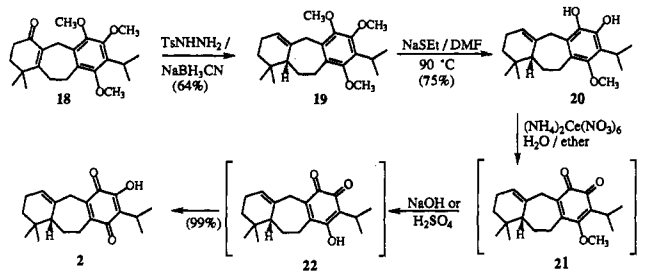
(7) Dorn, H. W.; Warren, W. H.; Bullock, J. C. *J. Am. Chem. Soc.* **1939**, *61*, 145.

(8) Stetter, H.; Dierichs, W. *Chem. Ber.* **1952**, *85*, 1061.

(9) Imamoto, T.; Kusumoto, T.; Yokoyama, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1042.

0002-7863/94/1516-4979$04.50/0

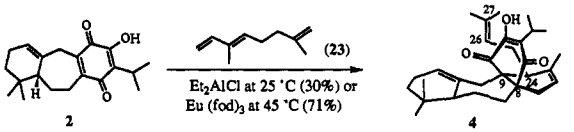
Scheme 3



carbonyl and effected the isomerization of the C(5),C(10)-double bond to the C(1),C(10)-position (cf. **7**).[10] Demethylation of two of the methyl ether moieties was achieved in 75% yield without isomerization of the trisubstituted double bond either into conjugation or into the A/B ring fusion using the nucleophilic conditions developed by Feutrill and Mirrington.[11] Catechol **20** resisted all attempts at further deprotection. *p*-Benzoquinone **2** was nevertheless furnished in nearly quantitative yield by treating **20** with ammonium cerium(IV) nitrate, followed by the addition of either sodium hydroxide or sulfuric acid. In this reaction three transformations occur: (a) generation of *o*-benzoquinone **21**; (b) hydrolysis of the vinylogous ester moiety; and (c) isomerization of *o*-benzoquinone **22** to *p*-benzoquinone **2**.

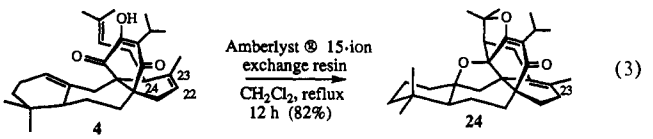
Although quinone **2** gave a single Diels–Alder adduct in 94% yield with 2,3-dimethyl-1,3-butadiene, *trans*-β-ocimene failed to produce an adduct under a variety of thermal conditions.[12] The use of Lewis acids to promote cycloaddition resulted in the rapid isomerization of the *trans*-β-ocimene to alloocimene and subsequently the formation of other products.

Substituting *trans*-α-ocimene (**23**) as the diene slowed the rate of diene decomposition and led to a 30% yield of adduct **4** at room temperature when diethylaluminum chloride was used as catalyst (eq 2). Under these conditions the disubstituted double bond of the Diels–Alder adduct isomerized to the more stable trisubstituted position after the cycloaddition had taken place. Further work showed that the reaction of **2** with *trans*-α-ocimene in the presence of the mild Lewis acid tris-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium [Eu(fod)$_3$][13] in a sealed tube at 45 °C for 24 h gave a 71% yield of tetracycle **4**. A 17% yield of an isomeric C(8),C(9)-Diels–Alder adduct was also isolated.



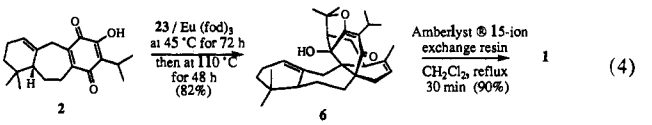
(2)

Although various acids catalyze intramolecular ene reactions, the convenience of using Amberlyst resins to catalyze this process was especially appealing to us. We were delighted to find that heating adduct **4** with this acidic resin achieved not only the desired ene reaction but also bis-tetrahydrofuran formation (eq 3). This sequence of steps proceeded in 82% yield. While these three ring closures were quite welcome, the migration of the C(22),C(23)-trisubstituted double bond to the C(23),C(24)-position was not.[14]



(3)

It is conceivable that under acid catalysis the tandem Diels–Alder reaction/double-bond isomerization/intramolecular ene reaction/F-ring closure/G-ring formation cascade might occur in a single operation. While this optimistic goal has not yet been totally achieved, we have synthesized (±)-perovskone using a two-step sequence (eq 4). After the Eu(fod)$_3$-catalyzed Diels–Alder reaction mixture was heated at 45 °C for 24 h, the mixture was then heated at 110 °C for an additional 48 h. These conditions resulted in the isolation of alcohol **6** in 82% yield.[15,16] Reaction of alcohol **6** with Amberlyst resins in CH_2Cl_2 under reflux for 30 min promoted the final ring closure in 90% yield without migration of the C(22),C(23)-trisubstituted double bond. Our synthetic pervoskone displays ^1H and ^{13}C NMR, IR, and mass spectra that are indistinguishable from those reported for the natural material.



(4)

In summary, we have achieved the first synthesis of (±)-perovskone. This novel triterpene was prepared in only 13 steps in greater than a 5% overall yield starting from 1-bromo-2,3,5-trimethoxybenzene (**9**). Other interesting aspects of this work include the use of a single chiral center to establish all of the stereocenters present and a remarkable cascade of transformations in which four bonds, three rings, and five stereocenters are created in a single step.

Acknowledgment. The authors thank Rodgers Hicks for his assistance in the early stages of this work. Funds provided by a PRF-AC grant for other chemistry were used to support this investigation. Special appreciation is extended to Dr. A. P. S. Narula of International Flavors and Fragrances for a generous sample of *trans*-α-ocimene and to Dr. M. Gary Newton (UGA) for carrying out a single-crystal X-ray diffraction analysis on **24**. Portions of this work were presented at the 10th Marvel Symposium held on March 12, 1993, at The University of Arizona and at the 206th National Meeting of the American Chemical Society held in Chicago on August 26, 1993; ORGN Abstract 425.

(10) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662.

(11) Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* **1970**, 1327.

(12) *trans*-β-Ocimene is thermally stable and does not isomerize to its various allocimene isomers. See: Wolinsky, J.; Chollar, B.; Baird, M. D. *J. Am. Chem. Soc.* **1962**, *84*, 2775.

(13) Gandhi, R. P.; Ishar, M.; P. S.; Wali, A. *J. Chem. Soc., Chem. Comm.* **1988**, 1074.

(14) The structure assigned to compound **24** was verified by means of a single-crystal X-ray diffraction study.

(15) In our hands the reaction of geranyl pyrophosphate with quinone **2** fails, undoubtedly because this ester decomposes to form a complex mixture of acyclic and cyclic terpenes. See: Haley, R. C.; Miller, J. A.; Wood, H. C. S. *J. Chem. Soc. (C)* **1969**, 264.

(16) Under these reaction conditions, the Diels–Alder adduct produced by the addition of *trans*-α-ocimene to the β-face of quinone **2** underwent the same cascade of reactions to give a 9% yield of alcohol **25**.