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Total Synthesis of (−)-Barbatusol, (+)-Demethylsalvicanol, (−)-Brussonol, and (+)-Grandione§

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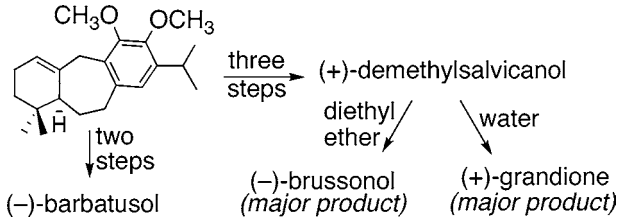
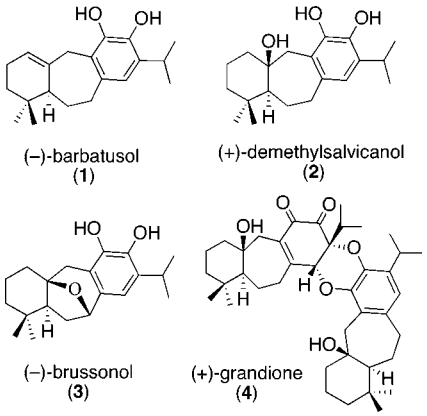
ABSTRACT



The icetexane-based diterpenes (−)-barbatusol, (+)-demethylsalvicanol, and (−)-brussonol were synthesized. Synthetic demethylsalvicanol was dimerized to produce (+)-grandione using aqueous Diels−Alder conditions.

In 1993, we reported two general strategies to synthesize the icetexane skeleton which is characteristic of the many rearranged abietane-type diterpenes[1] found throughout many species of Salvia.[2] We have since used this annulation strategy to synthesize several diterpenes,[3] such as the antihypertensive agent (±)-barbatusol (**1**),[4] as well as more complicated natural products (Scheme 1).[5,6] Recently, Takeya and co-workers oxidized natural demethylsalvicanol (**2**) and heated it in the solid state to produce grandione (**4**).[7] This observation has prompted us to report our syntheses of (+)-barbatusol (**1**), (+)-demethylsalvicanol (**2**),[8] as well as the identification of conditions to produce either (+)-brussonol (**3**)[9,10] or (+)-grandione (**4**).[11]

Scheme 1



In the course of our synthesis of (+)-perovskone,[12] we developed a two-step process to convert achiral enone **5** into alkene (*S*)-**7** (Scheme 2). The application of this strategy to

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(1) Majetich, G.; Zhang, Y.; Feltman, T. L.; Belfoure, V. *Tetrahedron Lett.* **1993**, *34*, 441−444.

(2) (a) Morton, J. F. In *Atlas of Medicinal Plants of Middle America*; Charles C. Thomas: Springfield, IL, 1981; pp 780−784. (b) Duke, J. A. In *Handbook of Medicinal Herbs*; CRC Press: Boca Raton, FL, 1985; pp 412−422. (c) Chang, H. M.; But, P. P. H. In *Pharmacology and Application of Chinese Materia Medica*; World Scientific: Singapore, 1986; Vol. 1, pp 255−268.

(3) (a) For our synthesis of (±)-komaroviquinone, see: Majetich, G.; Li, Y.; Zou, G. *Heterocycles* **2007**, *73*, 217−225. (b) For our synthesis of (+)-komaroviquinone, see: Majetich, G.; Yu, J.; Li, Y. *Heterocycles* **2007**, *73*, 227−235.

(4) (a) Majetich, G.; Zhang, Y.; Feltman, T. L.; Duncan, S. G., Jr. *Tetrahedron Lett.* **1993**, *34*, 445−448. (b) Majetich, G.; Hicks, R.; Zhang, Y.; Tian, X.; Feltman, T. L.; Fang, J.; Duncan, S. G., Jr. *J. Org. Chem.* **1996**, *61*, 8169−8174.

(5) (a) Majetich, G.; Zhang, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4979−4980. (b) Majetich, G.; Wang, Y.; Li, Y.; Vohs, J. K.; Robinson, G. H. *Org. Lett.* **2003**, *5*, 3847−3850.

(6) Majetich, G.; Yu, J. *Org. Lett.* **2008**, *10*, 89−92.

(7) For the first synthesis of (+)-grandione, see: Aoyagi, Y.; Takahashi, Y.; Satake, Y.; Fukaya, H.; Takeya, K.; Aiyama, R.; Matsuzaki, T.; Hashimoto, S.; Shiina, T.; Kurihara, T. *Tetrahedron Lett.* **2005**, *46*, 7885−7887.

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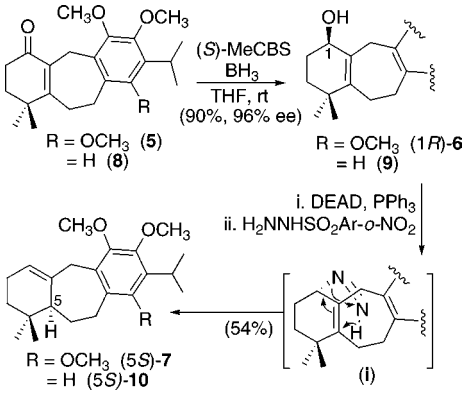
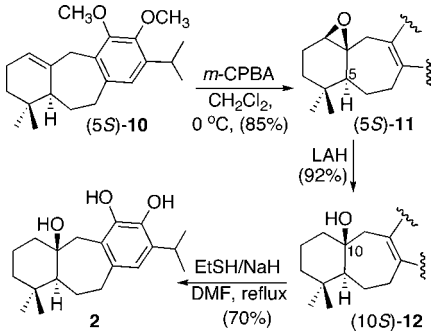
Scheme 2



Scheme 3



enone **8**, a key intermediate in our racemic barbatusol synthesis,[4] permitted its conversion to alkene **10**. In particular, the asymmetric 1,2-reduction of the C(1) carbonyl of **8** using Corey's CBS procedure[13] produced allylic alcohol **9** in high chemical yield and excellent enantiomeric excess. The use of Myers' Mitsunobu-based allylic transposition[14] to alcohol **9** generated diazene intermediate **i** in situ, which rearranged to give alkene (5*S*)-**10** in good overall yield. Deprotection of the methyl ethers of **10** using excess sodium ethanethiolate yielded (−)-barbatusol in 65% yield.

During the structure determination studies of demethylsalvicanol (**2**), Kelecom and Medeiros[8b,c] found that epoxidation of the C(1),C(10)-trisubstituted double bond occurs from the β-face of **2**, and that the opening of this epoxide with LAH introduces a β-oriented tertiary alcohol at C(10). This strategy was used to convert barbatusol dimethyl ether (**10**) into alcohol **12** (Scheme 3). Epoxidation of **10** with *m*-CPBA in methylene chloride gave epoxide **11** in 86% yield. Subsequent LAH opening of **11** afforded alcohol (10*S*)-**12** in 92% yield. The relative stereochemistry of **12** was confirmed by X-ray crystal analysis.[15] Treatment of **12** with excess sodium ethanethiolate in hot DMF cleaved the C(11) and C(12) methyl ethers to furnish (−)-demethylsalvicanol (**2**) in 65% yield. The spectral data for synthetic **2** (^{1}H and ^{13}C NMR) were identical to those reported for the natural material.[8]

With demethylsalvicanol in hand, we repeated Takeya and co-worker's unusual hetero-Diels−Alder dimerization of *o*-quinone **13** (Scheme 4). In our hands, heating neat *o*-quinone **13** at 50 °C for 60 h gave a 72% yield of (+)-grandione and a small amount of (−)-brussonol, which undoubtedly formed via an intramolecular Michael addition of the C(10) alcohol to quinone methide intermediate **ii**. We speculated that mild Lewis acid might promote the formation of intermediate **ii**. However, treatment of **13** with zinc chloride instead produced dihydrofuran **14**, which resulted from Michael addition of the C(10) hydroxyl group to C(8) of intermediate **iii**. The addition of bases, such as triethylamine, DBU, or sodium carbonate, to *o*-quinone **13** caused it to decompose. However, when a highly concentrated ethereal solution of **13** was heated at 60 °C in the dark for 40 h, brussonol was produced in 70% yield, along with about a 10% yield of grandione.

One of the goals of this study was to synthesize grandione without relying on Takeya's solid-state Diels−Alder reaction. Toward this end, two alternative strategies were investigated. The first strategy was based on the observation by Horner and Merz that styrene and tetrachloro-*o*-benzoquinone (**15**) undergo a Diels−Alder reaction in the dark at room temperature to give adduct **16**,[16] whereas in sunlight 1,4-dioxane **17** is formed (Scheme 5).[17] Presumably, dioxane formation involves a triplet excited state of the quinone, such as **iv**, which adds either in a concerted or in a stepwise

(8) For the isolation of demethylsalvicanol, see: (a) Gonzalez, A. G.; Andres, L. S.; Luis, J. G.; Brito, I.; Rodgriquez, M. L. *Phytochemistry* **1991**, *30*, 4067−4070. (b) Kelecom, A.; Medeiros, W. L. B. *Bull. Soc. Chem. Belg.* **1989**, *98*, 413−414. (c) Kelecom, A. *Tetrahedron* **1983**, *39*, 3603−3608. For a synthesis of (±)-demethylsalvicanol, see: (d) Wang, X.; Pan, X.; Cui, Y.; Chen, Y. *Tetrahedron* **1996**, *52*, 10659−10666.

(9) For the isolation of brussonol, see: Fraga, B. M.; Diaz, C. E.; Guadano, A.; Gonzalez-Coloma, A. *J. Agric. Food Chem.* **2005**, *53*, 5200−5206.

(10) Simmons, E. M.; Yen, J. R.; Sarpong, R. *Org. Lett.* **2007**, *9*, 2883−2886.

(11) 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.

(12) Majetich, G.; Zhang, Y.; Tian, X.; Britton, J. F.; Wang, Y.; Li, Y., manuscript in preparation.

(13) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012.

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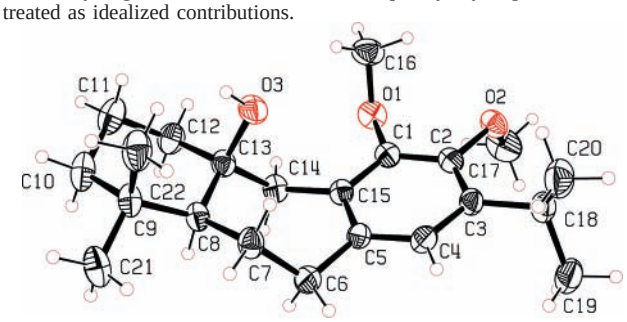
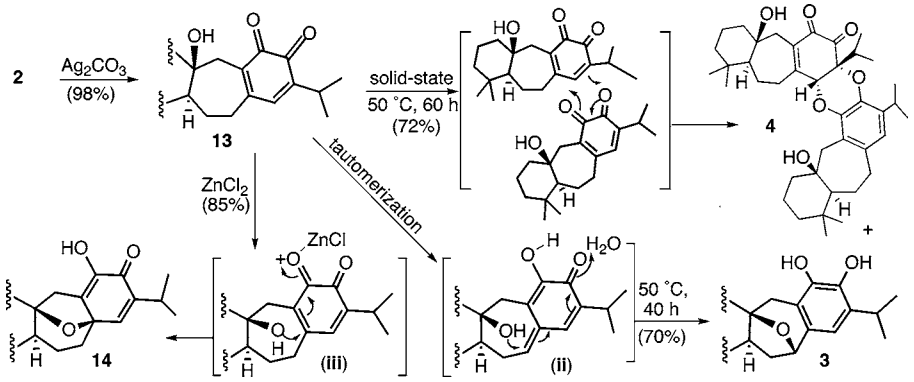
(15) Crystal data for $C_{20}H_{30}O_3$ (**12**); MW = 318, orthorhombic, *Pbca*, *a* = 8.070(6) Å, *b* = 10.105(7) Å, *c* = 24.258(18) Å, α = 90°, *β* = 97.035(11)°, *γ* = 90°, *V* = 1963(2) Å^3, *Z* = 4, *T* = 273(2) K, *μ* = 0.076 mm^{-1}, *d* = 1.172 g/cm^3, *R*(1) = 0.076 for 2313 observed reflections ($I > 2\sigma(I)$). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were treated as idealized contributions.



(16) (a) Schönberg, A.; Latif, N. *J. Am. Chem. Soc.* **1950**, *72*, 4828−4829. (b) See also: Schönberg, A.; Mustafa, A. *Chem. Rev.* **1947**, *47*, 181−200.

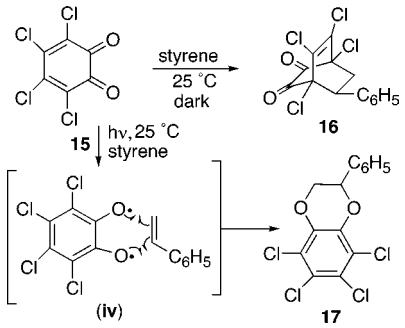
(17) (a) Horner, L.; Merz, H. *Ann.* **1950**, *570*, 89−120. (b) Schönberg, A.; Latif, N.; Moubasher, R.; Sina, A. *J. Chem. Soc.* **1951**, 1364−1368. (c) Schönberg, A; Mustafa, A. *J. Chem. Soc.* **1944**, 387. (d) Schönberg, A; Mustafa, A. *J. Chem. Soc.* **1945**, 551−553.

Scheme 4



fashion to the double bond of the alkene present. We were curious to see whether *o*-quinone **13**, which is sterically hindered and electron-rich, would undergo cyclodimerization to form (+)-grandione upon photochemical excitation. Unfortunately, exposing **13** to sunlight in either THF or cyclohexane at room temperature gave no reaction.

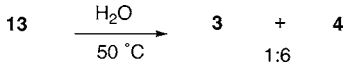
Scheme 5



A common way to overcome the large negative activation entropy associated with the bimolecular Diels−Alder reaction is to use water as the solvent.[18,19] When nonpolar substrates are suspended in water, their relative insolubility causes them to associate together, which often results in an increase in the reaction rate. We hoped that water's ability to bring the cycloaddition components together would facilitate the dimerization of *o*-quinone **13**. Adding a small amount of water to crude **13** and allowing the resulting mixture to stir at room temperature gave no reaction; however, warming the reaction medium to 50 °C overnight gave a 61% yield of (−)-brussonol (**3**) and (+)-grandione (**4**) and in a 1:6 ratio (Scheme 6). Further work established that the ratio of **3**:**4** varied as a function of concentration.

The above results suggest that π-stacking interactions in the crystalline state[20] cause the *o*-quinone molecules to assume a fixed spatial orientation that controls the regiospecificity of the Diels−Alder reaction. Although a preorganization of the Diels−Alder components does not exist in solution, the cycloaddition in water must benefit from the *o*-quinone molecules being forced closely together so as to mimic the situation in the solid state.

Scheme 6



Brussonol can only be formed if **13** tautomerizes. Since intermolecular proton-transfer reactions are precluded in the solid state, the dimerization to form grandione is favored. Conducting the cycloaddition reaction as a solution facilitates proton transfer and hence tautomerization. In enol−keto tautomerizations, keto formation usual benefits from solvents having high dielectric constants (water = 78.39 at 25 °C), whereas the enol form is favored by solvents with low dielectric constants of diethyl ether (4.335 at 20 °C). Diethyl ether was the solvent used to prepare brussonol in good yield. In this case, the formation of quinone methide **ii** may benefit from an internal hydrogen bond.

In summary, (−)-barbatusol was converted into (+)-demethylsalvicanol, which enabled us to duplicate its novel dimerization to produce (+)-grandione using thermal conditions. Although we were disappointed that we were not able to produce grandione photochemically, carrying out the cycloaddition in water gave grandione as the major product in good yield. In contrast, heating an ethereal solution of *o*-quinone **13** favored the production of (−)-brussonol. Further work in the area of icetexane-based diterpenes is forthcoming.[3,6]

Acknowledgment. We thank the National Science Foundation for support of this research (CHE-0506486).

Supporting Information Available: Detailed experimental procedures for the transformations described here and the spectroscopic data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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