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Total Synthesis of (−)-Salviasperanol§

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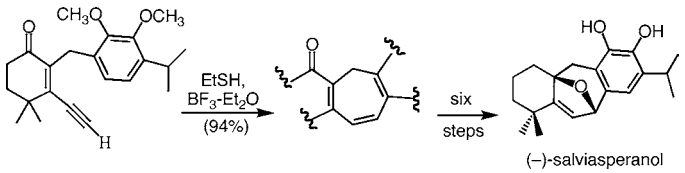
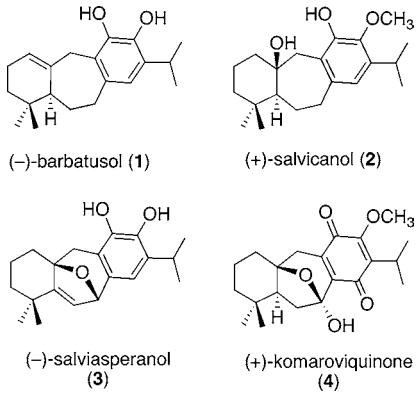
ABSTRACT



The achiral enynone shown cyclized to produce a tricyclic dienone that was converted in six steps to (−)-salviasperanol.

More than five hundred species of *Salvia* are found worldwide, and they have been widely used as folk medicines since ancient times.[1] The two subgenera of Salvia, *Salvia* and *Sclarea*, contain mostly rearranged abietane-type diterpenes, such as barbatusol (**1**),[2,3] salvicanol (**2**),[4] salviasperanol (**3**),[5,6] and komaroviquinone (**4**)[7,8] (Scheme 1). We have synthesized several icetexane diterpenoids by using an intramolecular Friedel−Crafts, or cyclialkylation strategy,[9] to efficiently assemble the carbocyclic skeleton.[10] Here we report a modification of our cyclialkylation strategy that facilitates the first total synthesis of (−)-salviasperanol (**3**).[11]

Scheme 1



In our synthesis of komaroviquinone we found that treatment of enone **5**[7,8] with Aren's reagent, the anion of ethoxyacetylene (cf. **6**),[12] produced enynone **7** (Scheme 2). While direct cyclization of enynone **7** to dienone **10** might be envisioned, analysis of Dreiding models of **7** indicated that the linear nature of the alkyne prevented the "6" carbon

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(1) (a) Fujita, E.; Node, M. *Prog. Chem. Org. Nat. Prod.* **1986**, *46*, 77−157. (b) Chopra, R. N.; Nayar, S. L.; Chopra, I. C. *Glossary of Indian Medicinal Plants*; CSIR: New Delhi, India, 1956; p 189. (c) Kirtikar, K. R.; Basu, B. D. *Indian Medicinal Plants*; Indian Press: Allahabad, India, 1918; p 1031.

(2) For a cyclialkylation-based synthesis of (±)-barbatusol, see: Majetich, G.; Zhang, Y.; Feltman, T. L.; Duncan, S., Jr. *Tetrahedron Lett.* **1993**, *34*, 445−448.

(3) For the synthesis of (+)-barbatusol, (+)-demethylsalvicanol, (+)-brussonol, and (+)-grandione, see: Majetich, G.; Zou, G. *Org. Lett.* **2008**, *10*, 81−84.

(4) For the isolation of salvicanol, see: Bruno, M.; Savona, G.; Piozzi, F.; De la Torre, M. C.; Rodriguez, B.; Marlier, M. *Phytochem.* **1991**, *30*, 2339−2343.

(5) For the isolation of salviasperanol, see: Esquivel, B.; Flores, M.; Hernandez-Ortega, S.; Toscano, R. A.; Ramamoorthy, T. P. *Phytochemistry* **1995**, *39*, 139−143.

(6) For the first synthesis of (±)-salviasperanol, see: Simmons, E. R.; Sarpong, R. *Org. Lett.* **2006**, *8*, 2883−2886.

(7) For our synthesis of (±)-komaroviquinone, see: Majetich, G.; Li, Y.; Zou, G. *Hetereocycles* **2007**, *73*, 217−225.

(8) For our synthesis of (+)-komaroviquinone, see: Majetich, G.; Yu, J.; Li, Y. *Hetereocycles* **2007**, *73*, 227−235.

(9) Brunson, H. A.; Kroeger, J. W. *J. Am. Chem. Soc.* **1940**, *62*, 36−44.

(10) (a) For our synthesis of (±)-perovskone, see: Majetich, G.; Zhang, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4979−4980. (b) For the synthesis of (+)-salvadione-A, see: Majetich, G.; Wang, Y.; Li, Y.; Vohs, J. K.; Robinson, G. H. *Org. Lett.* **2003**, *5*, 3847−3850.

(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) (a) Jacobs, T. L.; Cramer, R.; Hanson, J. E. *J. Am. Chem. Soc.* **1942**, *64*, 233−235. (b) Raucher, S.; Bray, B. L. *J. Org. Chem.* **1987**, *52*, 2332−2333.

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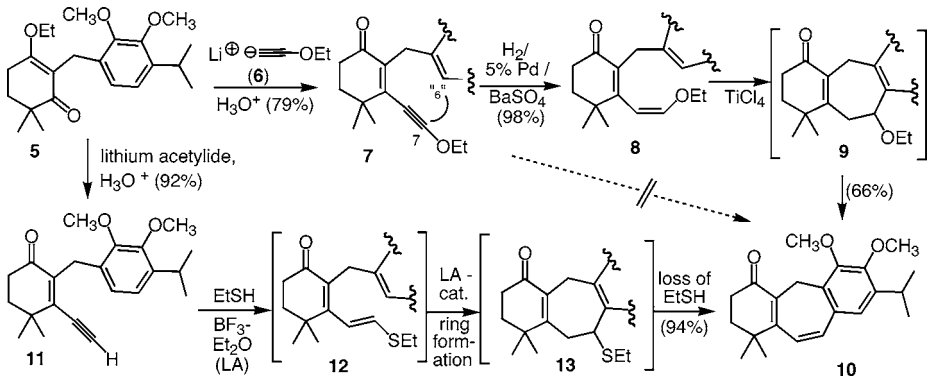
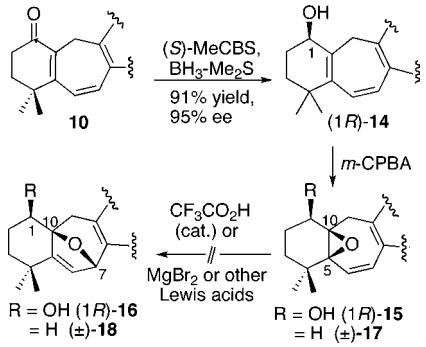
Scheme 2



of the aryl ring and C(7) of the alkyne from ever becoming spatially close enough to react. Not surprisingly, the cyclialkylation of **7** was unsuccessful. In contrast, Lindlar hydrogenation[13] of the triple bond in **7** cleanly gave cyclialkylation precursor **8**, which upon treatment with excess $TiCl_4$ first formed intermediate **9**, which subsequently lost ethanol to give dienone **10** in 66% isolated yield.

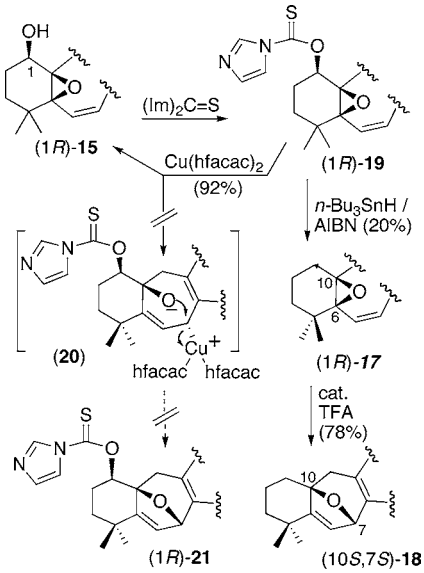
Scheme 3



1,2-Addition of lithium acetylide to ketone **5**, followed by mild acid hydrolysis, produced enynone **11** in 92% yield. Stirring **11** with excess BF_3-etherate and a 10% stoichiometric quantity of ethanethiol in CH_2Cl_2 at room temperature for 12 h gave dienone **10** in 94% yield. Under these conditions, vinyl sulfide **12** was formed rapidly (<1 h). If an aliquot of the reaction mixture was worked up intermediate **12** could be isolated and characterized; however, longer reaction times permitted the cyclialklyation of **12** to give the seven-membered ring, and subsequent elimination of ethanethiol from intermediate **13**. This two-step sequence represents a more efficient way to functionalize the central carbocyclic ring in comparison with the Aren's reagent/reduction/and cyclialkylation route.

Asymmetric reduction of the C(1) carbonyl would create enantiomerically enriched allylic alcohol **14**, which would faciliate the introduction of the C(10) and C(7) asymmetric centers (Scheme 3). 1,2-Reduction of **10** using Corey's CBS protocol gave alcohol (1*R*)-**14** in 91% yield and excellent enantioselectivity.[14] The final steps of our (−)-salviasperanol synthesis benefitted from Simmons and Sarpong's observation[6] that epoxide **17** isomerizes to dihydrofuran **18** under acidic conditions. We expected that the C(1) hydroxyl group would direct the epoxidation to only the C(5), C(10)−double bond,[15] and that the subsequent rearrangement of epoxide **15** would produce dihydrofuran **16** with the desired configuration at C(7) and C(10). Indeed, treatment of dienol **14** with *m*-CPBA in CH_2Cl_2 at 0 °C in the presence of $NaHCO_3$ for 1 h furnished only epoxy alcohol (1*R*)-**15** in good yield.

Scheme 4



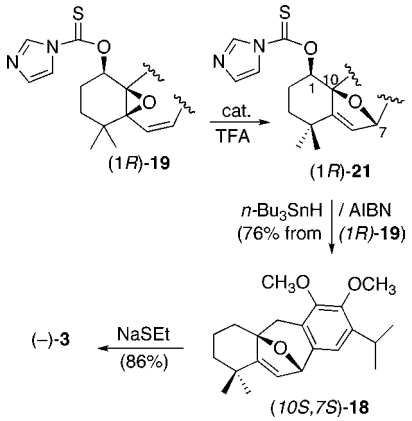
Epoxy alcohol (1*R*)-**15**, however, was acid sensitive precluding its acid-promoted isomerization. This dictated that the C(1) hydroxyl group must either be protected or removed before attempting to rearrange the C(5), C(10) epoxide.

(13) (a) For experimental conditions, see: Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248−2256. (b) Lipshutz, B. H.; Tirado, R. *J. Org. Chem.* **1994**, *59*, 8307−8311.

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

(15) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958−1965.

Scheme 5



Instead of using a common protecting group for the C(1) hydroxyl group, crude **15** was treated with 1,1-thiocarbonyldiimidazole to give *O*-thiocarbamate **19** which could be chromatographed and characterized (Scheme 4).[16] Free radical deoxygenation of **19**, followed by isomerization of vinyl epoxide **17** using catalytic trifluoroacetic acid (TFA), produced salviasperanol dimethyl ether **18**, but in low overall yield. The isomerization of vinyl epoxides to dihydrofurans, via a π-allyl copper intermediate, such as **20**, is known even in the presence of ethers and esters.[17] However, treatment of vinyl epoxide **19** with copper *bis*-hexafluoroacetylacetonate [Cu(hfacac)$_2$] only cleaved the *O*-thiocarbamate.

(16) RajanBabu, T. V.; Fukunaga, T.; Reddy, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 1759−1769.

In contrast, *O*-thiocarbamate **19** could be rearranged to **21** using trifluoroacetic acid (Scheme 5).[6] The removal of the thiocarbamate moiety was achieved by heating a toluene solution of (1*R*)-**21**, with a catalytic amount of AIBN and excess tri-*n*-butyltin hydride at 110 °C for a 30-min period. These conditions provided salviasperanol dimethyl ether **18** in 76% yield from epoxide **19**. Treatment of **18** with excess sodium ethanethiolate in hot DMF cleaved the C(11) and C(12) methyl ethers to furnish (−)-salviasperanol (**3**) in 86% yield. Our synthetic **3** displays ^{1}H and ^{13}C NMR, IR, and MS spectra identical to those reported for the natural sample.[5] The application of this modified cyclialkylation strategy to synthesize other icetexane natural products is underway.[18,19]

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

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(17) Batory, L. A.; McInnis, C. E.; Njardarso, J. T. *J. Am. Chem. Soc.* **2006**, *128*, 16054−16055.

(18) Grove, J. L.; Majetich, G. Presented at the 233rd National Meeting of the American Chemical Society, Chicago, IL, March 2007; Paper ORGN No. 375.

(19) For the synthesis of (+)-komarovispirone, see: Majetich, G.; Yu, J. *Org. Lett.* **2008**, *10*, 89−92.