Total Synthesis of (–)-Salviasperanol§

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ABSTRACT



The achiral envnone 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

- (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 (\pm) -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,

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modification of our cyclialkylation strategy that facilitates the first total synthesis of (-)-salviasperanol (3).¹¹



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.

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.



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 hydrogenation¹³ of the triple bond in **7** cleanly gave cyclialkylation precursor **8**, which upon treatment with excess TiCl₄ first formed intermediate **9**, which subsequently lost ethanol to give dienone **10** in 66% isolated yield.



1,2-Addition of lithium acetylide to ketone **5**, followed by mild acid hydrolysis, produced enynone **11** in 92% yield. Stirring **11** with excess BF₃-etherate and a 10% stoichiometric quantity of ethanethiol in CH₂Cl₂ 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 observation⁶ 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 CH₂Cl₂ at 0 °C in the presence of NaHCO₃ for 1 h furnished only epoxy alcohol (1*R*)-**15** in good yield.



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.



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.

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 ¹H and ¹³C 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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⁽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.