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# Ga(III)-Catalyzed Cycloisomerization Strategy for the Synthesis of Icetexane Diterpenoids: Total Synthesis of (±)-Salviasperanol

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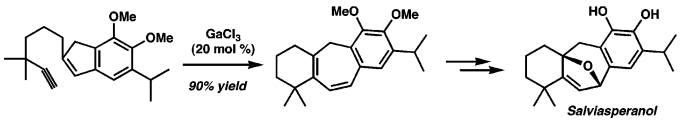
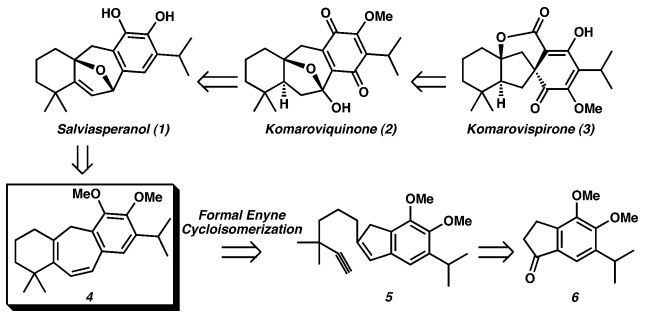
## ABSTRACT




**A general approach to the tricyclic core of the icetexane natural products via the cycloisomerization of alkynyl indenes using $GaCl_3$ is presented. This strategy provides an efficient synthesis of the natural product salviasperanol and sets the stage for access to other members of this family of diterpenoids.**

The icetexane diterpenoids encompass a variety of bioactive and structurally interesting compounds (Scheme 1). For example, komaroviquinone (**2**) and komarovispirone (**3**) were isolated from the Uzbekistani perennial semishrub *Dracocephalum komarovi*.[1] These compounds have shown in vitro trypanocidal activity against *Trypanosoma cruzi*, the parasite responsible for Chagas' disease, which is prevalent in Central and South America.[2] Although the biological activity of salviasperanol (**1**), isolated from the roots of *Salvia aspera*, has not been studied in detail, a number of related compounds derived from this genus show significant activity against *Mycobacterium tuberculosis*, the causative agent of tuberculosis.[3]

**Scheme 1.** Unified Approach to the Icetexanes




Because of their interesting bioactivity and structure, these compounds have begun to garner attention from the synthetic community, which has recently resulted in one total synthesis of komaroviquinone (**2**).[4]

As part of our ongoing interest in the synthesis of seven-membered ring-containing natural products, we envisioned a general and modular entry to this class of compounds via a common cycloheptadiene intermediate (**4**), which could

(1) (a) Uchiyama, N.; Kiuchi, F.; Ito, M.; Honda, G.; Takeda, Y.; Khodzhimatov, O. K.; Ashurmetov, O. A. *J. Nat. Prod.* **2003**, *66*, 128−131. (b) Uchiyama, N.; Ito, M.; Kiuchi, F.; Honda, G.; Takeda, Y.; Khodzhimatov, O. K.; Ashurmetov, O. A. *Tetrahedron Lett.* **2004**, *45*, 531−533.

(2) (a) Uchiyama, N.; Kabututu, Z.; Kubata, B. K.; Kiuchi, F.; Ito, M.; Nakajima-Shimada, J.; Aoki, T.; Ohkubo, K.; Fukuzumi, S.; Martin, S. K.; Honda, G.; Urade, Y. *Antimicrob. Agents Chemother.* **2005**, *49*, 5123−5126. (b) Bastien, J. W. *The Kiss of Death, Chagas' Disease in the Americas;* The University of Utah Press: Salt Lake City, 1998.

(3) Esquivel, B.; Flores, M.; Hernandez-Ortega, S.; Toscano, R. A.; Ramamoorthy, T. P. *Phytochemistry* **1995**, *39*, 139−143.

(4) (a) Sengupta, S.; Drew, M. G. B.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. K. *J. Org. Chem.* **2005**, *70*, 7694−7700. For a synthetic approach, see: (b) Padwa, A.; Boonsombat, J.; Rashatasakhon, P.; Willis, J. *Org. Lett.* **2005**, *7*, 3725−3727.

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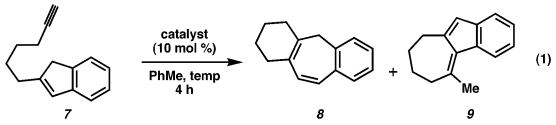
in turn arise from alkynyl indene **5**. Salviasperanol was chosen as an initial synthetic target with the expectation that it could serve as a precursor to komaroviquinone (**2**) via sequential diastereoselective hydrogenation and oxygenation. Komarovispirone (**3**) may in turn be synthetically or biogenetically derived from komaroviquinone via a formal ring contraction rearrangement as has been proposed by Uchiyama et al.[1b]

To the best of our knowledge, there are no reports of enyne cycloisomerizations involving indenes to produce cycloheptadienes. As a result, our initial investigations employed the simple model **7**,[5] with which we screened a variety of conditions known to catalyze enyne cycloisomerizations.

Several metal complex/additive combinations, including the Grubbs I and Grubbs II alkylidenes,[6] $Pt(PPh_3)_2Cl_2$/PhIO,[7] $[Rh(CO)_2Cl]_2$, $Rh(PPh_3)_3Cl$, $Rh(PPh_3)_3Cl/AgBF_4$, and $[Ru(CO)_3Cl_2]_2/AgBF_4$, gave either no reaction or only trace conversion. Other complexes (Table 1), including $PtCl_2$,[8]

**Table 1.** Screen of Cycloisomerization Complexes




| entry | catalyst | temp (°C) | concn (M)[a] | ratio (**8**/**9**)[b] |
|---|---|---|---|---|
| 1 | $PtCl_2$ | 50 | 0.05 | no reaction |
| 2 | $PtCl_2$ | 80 | 0.14 | 0.8:1 |
| 3 | $PtCl_2$ | 80 | 0.05 | 1.1:1 |
| 4 | $PtCl_2$ | 80 | 0.025 | 2:1[c] |
| 5 | $PtCl_4$ | 50 | 0.05 | 0.6:1 |
| 6 | $[Ru(CO)_2Cl_2]_2$ | 80 | 0.05 | 2.5:1 |
| 7 | $[Rh(CO)_2Cl]_2/AgBF_4$ | 23 | 0.05 | 3:1 |
| *8*[d] | *$GaCl_3$* | *23* | *0.05* | *1:0* |

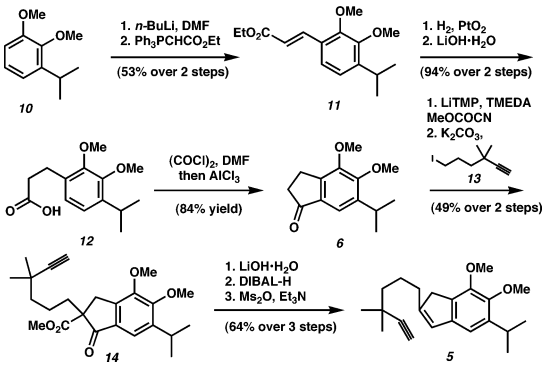
[a] Concentration of **7**. [b] Ratios based on integration of $^1H$ NMR signals. [c] Reaction was incomplete after 4 h; the ratio is based on converted material. [d] Reaction was judged complete (by TLC) after 1 h.

which has been extensively exploited by Fürstner for related purposes,[9] did promote the desired cycloisomerization (entries 2−7) but gave a mixture of the cycloheptadiene product **8**[10] along with the structural isomer **9** as an inseparable mixture.[11]

Following this screen of transition-metal complexes, we turned our attention to $GaCl_3$, which has been shown by Chatani and Murai to effect a skeletal reorganization of a variety of enynes under very mild conditions.[12] Gratifyingly, upon exposure of **7** to $GaCl_3$ (10 mol %) for 1 h at 23 °C (entry 8), cycloheptadiene **8** was obtained as the sole product, with no detectable formation of **9**.

With conditions for the key conversion of indenyl alkynes to cycloheptadienes defined using **7** as a model, we embarked on a synthesis of the more complex substrate **5**. Our synthetic efforts commenced with the preparation of indanone **6** as outlined in Scheme 2. Formylation of isopropyl veratrole

**Scheme 2.** Synthesis of the Indene Precursor **5**




(**10**)[13] followed by Wittig reaction of the resulting aldehyde with the stabilized carbethoxymethylidene triphenylphosphorane ylide provided enoate **11**. Hydrogenation with Adam's catalyst followed by saponification of the ethyl ester then afforded acid **12** in excellent yield over the two steps. At this stage, Friedel−Crafts acylation of the corresponding acid chloride gave indanone **6** in good yield.

Direct alkylation of indanone **6** was pursued using iodide **13**, which is readily available from the corresponding alcohol.[14] However, this was complicated by competitive overalkylation, which was obviated by an initial Claisen reaction with Mander's reagent to install a carbomethoxy group followed by alkylation to afford $\beta$-ketoester **14**. Saponification of the methyl ester proceeded with subsequent decarboxylation upon workup. Reduction of the resulting carbonyl followed by a net dehydration ($Ms_2O$, $Et_3N$) yielded alkynyl indene **5** as a single alkene regioisomer in good yield. With the fully functionalized indene **5** in hand, our attention turned to the viability of the formal enyne metathesis reaction on this more elaborate substrate.

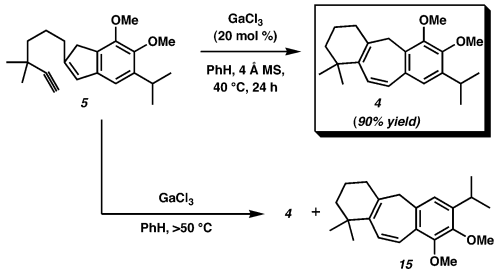
Indene **5** was found to react slowly under the initially established cycloisomerization conditions. Our studies have revealed that the sluggish rate of reactivity of **5** is attributable to the steric congestion of the *gem*-dimethyl substitution adjacent to the alkyne.[15] Substrates devoid of an adjacent

(5) For full synthesis details of **7**, see the Supporting Information.
(6) For a review on enyne metathesis using the Grubbs ruthenium alkylidene complexes, see: Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317−1382.
(7) Bhanu Prasad, B. A.; Yoshimoto, F. K.; Sarpong, R. *J. Am. Chem. Soc.* **2005**, *127*, 12468−12469.
(8) Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901−903.
(9) For applications in natural product synthesis, see: (a) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305−8314. (b) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785−6786. (c) For a seminal report, see: Chatani, N.; Kataoka, K.; Murai, S.; Furukawa, N.; Seki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9104−9105.
(10) Tricycle **8** has been reported previously; see: Paquette, L. A.; Chamot, E.; Browne, A. R. *J. Am. Chem. Soc.* **1980**, *102*, 637−643.
(11) The reason for the observed dependency of product ratios on concentration (entries 2−4) is under active investigation.
(12) Chatani, N.; Inoue, H.; Kotsuma, T.; Murai, S. *J. Am. Chem. Soc.* **2002**, *124*, 10294−10295.
(13) Majetich, G. A.; Liu, S. *Synth. Commun.* **1993**, *23*, 2331−2335.
(14) Malezcka, R. E.; Gallagher, W. P. *Org. Lett.* **2001**, *3*, 4173−4176. For preparation of **13**, see the Supporting Information.
(15) For related prior observations, see: Trost, B. M.; Chang, V. K. *Synthesis* **1993**, 824−832.

quaternary carbon center (e.g., **7**) readily isomerized in high yield to the corresponding cycloheptadienes. However, increasing the reaction temperature beyond 50 °C in an attempt to accelerate the rate of reaction of **5** led to significant formation of **15**, which presumably arises from isomerization of the indene double bond prior to cycloisomerization.

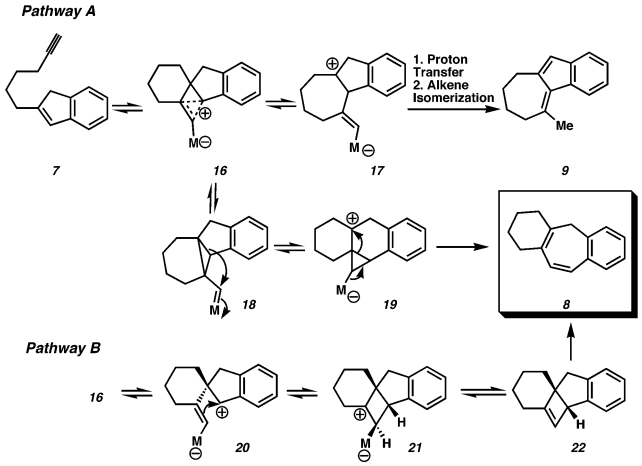
After a screen of various additives,[16] an optimal set of conditions was identified (20 mol % of $GaCl_3$, 4 Å MS, 0.04 M in PhH, 40 °C, 24 h) that converted **5** to cycloheptadiene **4** in excellent yield (Scheme 3).[17]

**Scheme 3.** Cycloisomerization of **5**




Mechanistically, the cycloisomerization of alkynyl indene substrates such as **7** (eq 1) may proceed via two alternate pathways (Scheme 4).[18] These pathways are distinguished

**Scheme 4.** Potential Cycloisomerization Mechanisms




by the intermediate zwitterions (**17** and **18** or **20**) that may arise from an initially formed nonclassical zwitterion intermediate, **16**.[19] In pathway A, conversion of **16** to **17** followed by proton transfer and isomerization yields tricycle **9**.

Alternatively, reversible isomerization of **16** via cyclopropanes **18** and **19** may culminate in the formation of cycloheptadiene **8**.[20] Pathway B also begins with the common nonclassical zwitterion **16**, which may interconvert with **20**, which contains a spiro quaternary carbon center and a benzylic carbocation. Attack of the alkene onto the benzylic carbocation would lead to zwitterion **21**, which may be in equilibrium with cyclobutene **22**.[21] At this stage, formal retro $4\pi$ electrocyclization of **22** should yield cycloheptadiene **8**.[22] Although pathway A clearly accounts for the formation of products such as **9**, the genesis of the cycloheptadiene products (i.e., **8**) is less obvious. The isolation of cyclobutene intermediates in the $GaCl_3$-catalyzed enyne cycloisomerizations reported by Murai and Chatani gives strong support to pathway B for the formation of cycloheptadienes such as **8**.[23,24] Furthermore, our preliminary studies have shown an increase in the rate of formation of cycloheptadiene products (e.g., **8**) with increasing electron density on the aromatic core (by substitution of electron-donating alkoxy groups for the phenyl hydrogens).[25] This observation is most readily explained by increased stabilization of the benzylic carbocation intermediate **20** (pathway B) relative to **17** (pathway A), lending further support to pathway B for the formation of the cycloheptadiene products. Additionally, a related precedent by Trost[26] and Fürstner[9b] suggests pathway B may be the primary reaction path and a conversion of **20** to **18** may provide the pathway to the observed byproduct **9**. This interconversion may result because canonical nonclassical resonance structures such as **16** and intermediates such as **18** may experience added stabilization from transition metals.[27] This characteristic most likely dictates the superior selectivity in the gallium-catalyzed cycloisomerization reactions (where intermediates such as **18** are less stabilized) as compared to the transition-metal-mediated processes.

(16) Additives were explored to curtail catalyst decomposition due to adventitious water and resulting acid-catalyzed product decomposition.

(17) Interestingly, $GaI_3$, $GaBr_3$, and $InCl_3$ are also effective albeit at higher temperatures (60−80 °C) and provide **4** along with **15**. On the other hand, $Ga(OTf)_3$ is completely ineffective. For recent examples of In(III)-catalyzed enyne cycloisomerizations, see: Miyanohana, Y.; Chatani, N. *Org. Lett.* **2006**, *8*, 2155−2158.

(18) For a recent discussion of possible enyne cycloisomerization pathways of transition and main group metal complexes, see: Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328−2334.

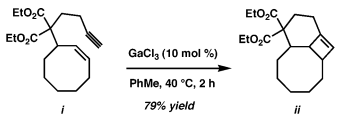
(19) Nonclassical intermediates such as **16** have been previously proposed; see: refs 9b and 12.

(20) For an initial proposal of cyclopropylmetallocarbenoid intermediates, see ref 9c.

(21) Zwitterion intermediate **21** may also lead to product; see: Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244−8245.

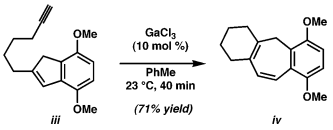
(22) A direct thermal $4\pi$ electrocyclic ring opening of **22**, which should proceed via conrotation, is unlikely as a concerted process because of the constraints of the *trans*-alkene geometry that would result in the formation of the cycloheptadiene product. See: Baldwin, J. E.; Gallagher, S. S.; Leber, P. A.; Raghavan, A. *Org. Lett.* **2004**, *6*, 1457−1460.

(23) For example, cycloisomerization of **i** yielded cyclobutene **ii**. See ref 12.




(24) Cyclobutenes have also been observed as intermediates in other enyne cycloisomerization reactions. See, for example, ref 15.

(25) Example substrates such as **iii** displayed an accelerated rate of reaction (i.e., shorter times to reach completion) compared to **7**.

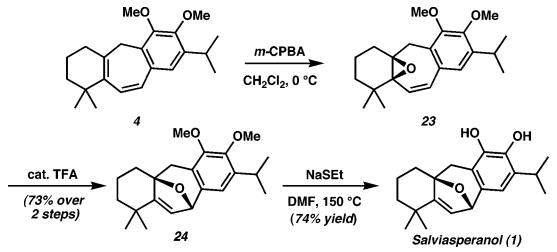



(26) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636−1638.

(27) We would like to thank a referee for this suggestion.

With tricycle **4** in hand, several methods were then investigated for the oxygenation of the cycloheptadiene moiety. In the end, the most efficient strategy entailed selective epoxidation to obtain **23** (Scheme 5), which, upon

**Scheme 5.** Completion of Salviasperanol




treatment with catalytic trifluoroacetic acid, isomerized to dihydrofuran **24** in high yield. Conversion of dimethylsalviasperanol (**24**) to salviasperanol (**1**) was achieved by bismethyl ether cleavage using sodium ethanethiolate. Spectral data for synthetic salviasperanol ($^{1}$H, $^{13}$C NMR, IR, and MS) were identical to those reported for the natural sample.

In summary, we report the first total synthesis of the icetexane diterpenoid salviasperanol via a unique synthetic strategy, which employs a cycloisomerization of alkynyl indenes to access a key cycloheptadiene intermediate. The modular and efficient synthesis of the icetexane core reported herein provides a platform for the syntheses of the related natural products komaroviquinone and komarovispirone. Furthermore, a late-stage epoxidation to access salviasperanol presents the possibility of an enantioselective synthesis of this class of natural products, which is currently under investigation in our laboratory.

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**Supporting Information Available:** Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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