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Ga(III)-Catalyzed Cycloisomerization Approach to (±)-Icetexone and (±)-*epi*-Icetexone

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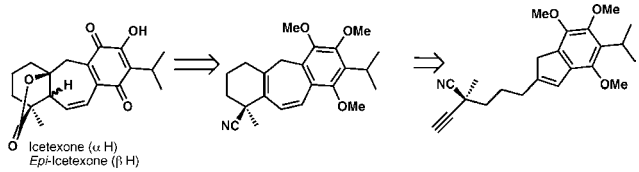
ABSTRACT



A Ga(III)-catalyzed cycloisomerization reaction provides expedient access to a benzannulated cycloheptadiene bearing a cyano group, which has been applied to the syntheses of several icetexane diterpenoids including icetexone and *epi*-icetexone. Key to the synthesis is a novel in situ generated diazene rearrangement.

The icetexane family of diterpenoids is a group of [6-7-6] tricyclic natural products, which are believed to arise in Nature from an oxidation-induced rearrangement of the structurally related abietane diterpenoids.[1] Biosynthetic modification of the abietane skeleton has led to a wide variety of icetexane natural products that possess unique structures as well as biological activity.[2] We became interested in the synthesis of members of the icetexane family as a prelude to a systematic investigation of their biological activity. Previously, we reported the syntheses of several members including salviasperanol (**1**, Figure 1), abrotanone (**2**), and 5,6-dihydro-6α-hydroxysalviasperanol (**3**).[3] In this paper, we report the extension of these studies to the formal syntheses of icetexone (**5**) and *epi*-icetexone (**6**).

Icetexone and *epi*-icetexone have been isolated from several Mexican *Salvia* plants including *Salvia ballotaeflora* and *Salvia gillessi*.[4] Of these two natural products, icetexone has been shown to possess trypanocidal activity against the trypomastigote form of *Trypanosoma cruzi*, the parasite that causes Chagas' disease.[5] In 2009, Majetich and Grove reported the first syntheses of **5** and **6**,[6] which exploited a cyclialkylation to forge the seven-membered ring,[7] as well as a late stage iodolactonization to construct the bridging lactone.

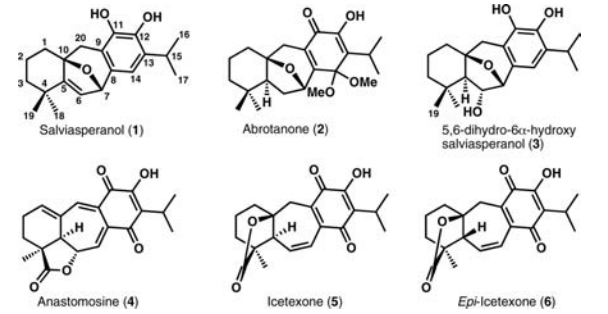


Figure 1. Selected icetexane natural products.

(1) Simmons, E. M.; Sarpong, R. *Nat. Prod. Rep.* **2009**, *26*, 1195–1217.

(2) For a review on abietane diterpenoids, see: (a) Uçar, G.; Fengel, D. *Phytochemistry* **1995**, *38*, 877–880. (b) Dev, S.; Misra, R. In *CRC Handbook of Terpenoids*; Dev, S., Ed.; CRC: Boca Raton, FL, 1986.

(3) (a) Simmons, E. M.; Sarpong, R. *Org. Lett.* **2006**, *8*, 2883–2886. (b) Simmons, E. M.; Yen, J. R.; Sarpong, R. *Org. Lett.* **2007**, *9*, 2705–2708.

(4) The structural assignments of icetexone and *epi*-icetexone were recently shown to be reversed (see ref 6). For isolation of icetexone and *epi*-icetexone, see: (a) Watson, W. H.; Taira, Z. *Tetrahedron Lett.* **1976**, *29*, 2501–2502. (b) Nieto, M.; Garcia, E. E.; Gordano, D. S.; Tonn, C. E. *Phytochemistry* **2000**, *53*, 911–915.

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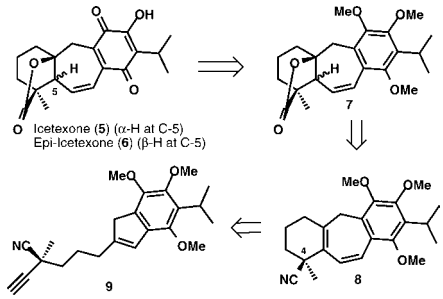
In principle, the related natural products anastomosine (**4**), icetexone (**5**), and *epi*-icetexone (**6**) could arise from hydroxyl-directed oxygenation of the β-methyl group at C-19 (see **3**) followed by a series of oxidations and dehydrations. However, the anticipated instability of potential alkoxy radical intermediates,[8] as well as uncertainties regarding the stereoselectivity of the C−H functionalization process, dissuaded us from this line of inquiry.

Encouraged by our previous synthetic studies on the icetexane diterpenoids, we were drawn to the use of benzannulated cycloheptadienes (e.g., **8**) as key precursors to **5** and **6** (see Scheme 1). Importantly, a cyano group at

Scheme 1. Retrosynthetic Analysis of **5** and **6**



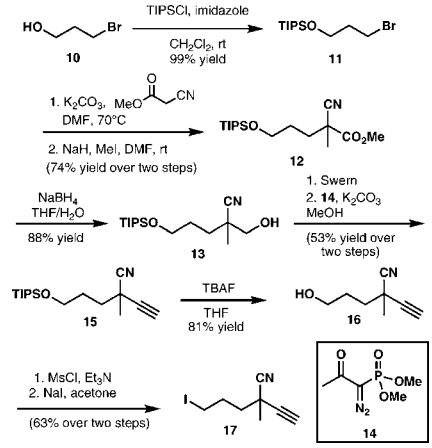
C-4 could serve as a masked carboxylic acid group that would be unveiled at a late stage. Benzannulated cycloheptadiene **8** could in turn be prepared from alkynyl indene **9** via a Ga(III)-catalyzed cycloisomerization.

The incorporation of a cyano group as a part of the alkynyl indene substrate for the cycloisomerization reaction has not been previously demonstrated. Thus, the present plan would seek to advance the substrate scope of this seven-membered ring forming cycloisomerization reaction.

In this paper, we present the realization of this synthetic strategy, which has led to the formal syntheses of (±)-icetexone (**5**) and (±)-*epi*-icetexone (**6**).

Our efforts commenced with the preparation of iodide **17** as outlined in Scheme 2. The sequence started with 3-bromo-1-propanol (**10**), which was converted to TIPS ether **11** under standard conditions. Bromide **11** served as an electrophile for the alkylation of methyl cyanoacetate, the product of which yielded **12** upon subsequent methylation. The ester group of **12** was then selectively reduced to provide the corresponding alcohol (**13**). Swern oxidation of **13** followed

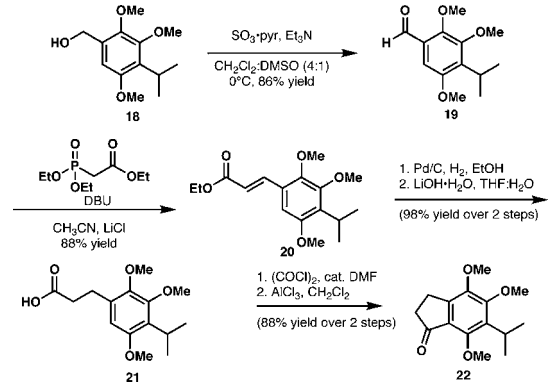
Scheme 2. Synthesis of Alkyl Iodide **17**



by homologation of the resulting aldehyde with the Ohira−Bestmann reagent (**14**) gave alkyne **15**. Subsequent transformation of **15** to iodide **17** proceeded via a sequence involving silyl ether cleavage to yield **16**, followed by conversion of the hydroxy group to the corresponding mesylate and displacement with sodium iodide.

At this stage, the synthesis of indanone **22** (Scheme 3), a precursor to the other coupling partner required for the construction of **9**, was pursued.[9]

Scheme 3. Synthesis of Indanone **22**



The sequence began with known benzyl alcohol **18**,[6,7] which was oxidized under Parikh−Doering conditions[10] to afford aldehyde **19**. Horner−Wadsworth−Emmons homologation of **19** afforded enoate **20**, which following hydrogenation and saponification gave acid **21**. At this stage, the carboxylic acid group was converted to the corresponding acid chloride, and an ensuing Friedel−Crafts acylation gave indanone **22**.

(5) Sanchez, A. M.; Jimenez-Ortiz, V.; Tonn, C. E.; Garcia, E. E.; Nieto, M.; Burgos, M. H.; Sosa, M. A. *Acta Trop.* **2006**, *98*, 118–124. This paper reports studies on *epi*-icetexone. However, on the basis of the structural reassignments by Majetich (ref 6), the biological studies were conducted on icetexone.

(6) Majetich, G.; Grove, J. L. *Org. Lett.* **2009**, *11*, 2904–2907.

(7) Cyclialkylation reactions for the synthesis of icetexane diterpenoids were pioneered by Majetich. For an early example, see: Majetich, G.; Zhang, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4979–4980.

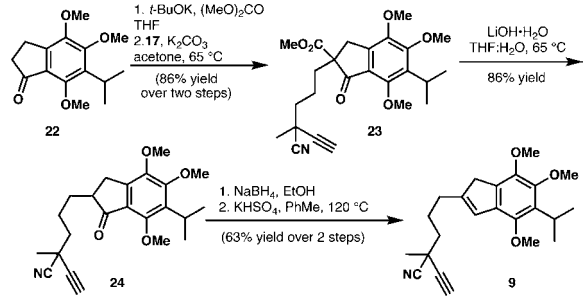
(8) In preliminary studies conducted in these laboratories, fragmentation of the seven-membered ring was observed upon generation of the presumed alkoxy-radical intermediate. This is consistent with observations made by Majetich and co-workers, see: Li, Y. Ph.D. Dissertation, University of Georgia, Athens, GA, 2006 and ref 6.

(9) The synthesis of **22** reported herein was adapted from an earlier synthesis in our laboratories, see: Simmons, E. M. Ph.D. Dissertation, University of California, Berkeley, CA, 2009.

(10) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

With indanone **22** in hand, we next investigated its conversion to indene substrate **9** as outlined in Scheme 4.

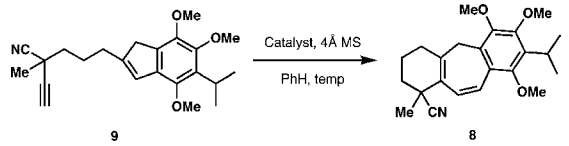
Scheme 4. Synthesis of Indene **9**



Claisen condensation of **22** and dimethyl carbonate provided a β-ketoester, which upon alkylation with **17** gave alkyne **23**. A subsequent saponification/decarboxylation sequence afforded indanone **24**. Selective reduction of the carbonyl group in the presence of the nitrile group was accomplished with $NaBH_4$ and was followed by elimination of the resulting hydroxyl group to afford indene **9**.

On the basis of our previous studies, we first investigated the cycloisomerization of alkynyl indene **9** to cycloheptadiene **8** using Ga(III) salts (entries 1−6, Table 1). We found that $GaCl_3$, $GaBr_3$, or GaI_3 worked comparably in the cycloisomerization reaction with a 0.20 equiv of catalyst loading at 40 °C in benzene (entries 1−3), resulting in ca. 40% conversion to **8** over 48 h. In the cases where GaI_3 was used to mediate the cycloisomerization, increasing the temperature to 65 (with 0.5 equiv of GaI_3; entry 4) or 80 °C (with 0.25 equiv of GaI_3; entry 5) led to complete conversion after 96 h. After a systematic investigation of various combinations of Ga(III) salts, solvents, and temperatures, an optimal set of conditions was identified (0.25 equiv of $GaCl_3$, 100 °C, 48 h; entry 6), which gave **8** in 91% isolated yield. Interestingly, the use of $PtCl_2$ or $InCl_3$, which had been previously established as catalysts for enyne cycloisomerization,[11] returned only the starting material.

Table 1. Cycloisomerization of **9**

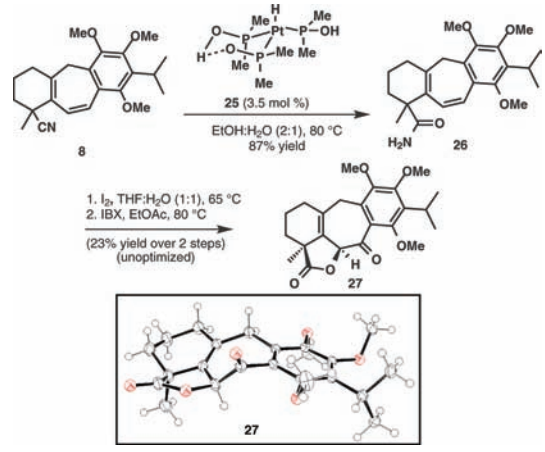


entry	catalyst	equiv	temp (°C)	time (h)	% conversion[a]
1	$GaCl_3$	0.2	40	48	41
2	$GaBr_3$	0.2	40	48	43
3	GaI_3	0.2	40	48	38
4	GaI_3	0.5	65	96	100
5	GaI_3	0.25	80	96	100
6	$GaCl_3$	0.25	100[b]	48	100
7	$PtCl_2$	0.2	40	72	NR
8	$InCl_3$	0.2	40	120	NR

[a] Conversion of **9** based on ^1H NMR of crude reaction product following standard workup. [b] Reaction was run in toluene.

With benzannulated cycloheptadiene **8** in hand, our attention turned to the functionalization of the conjugated diene moiety. We first investigated the hydrolysis of the nitrile functional group. In this regard, we found that the transformation was best effected using Ghaffar and Parkins' platinum catalyst (**25**, Scheme 5),[12] which was uniquely effective in giving primary amide **26** in 87% yield. Subjecting **26** to standard iodolactonization conditions, followed by IBX oxidation, led to the isolation of lactone **27**, the structure of which was confirmed by X-ray crystallography (see ORTEP representation in Scheme 5). Although **27** was undesired with respect to our efforts toward icetexone and *epi*-icetexone, it provides a potential entry to the synthesis of anastomosine (**4**) and related natural products.

Scheme 5. Initial Iodolactonization Studies

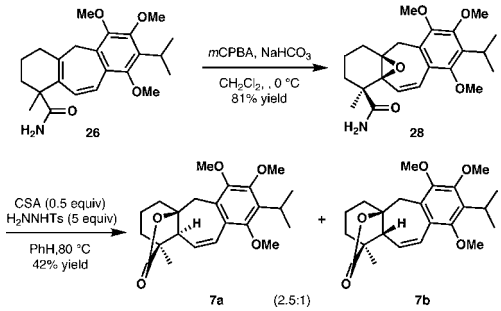


Following careful optimization studies, we established a route, as outlined in Scheme 6, that leads to the late-stage intermediates **7a** and **7b** for the synthesis of icetexone and *epi*-icetexone, respectively. The sequence begins with the diastereoselective epoxidation of cycloheptadiene **26** to afford **28** in 81% yield. Treatment of **28** with camphorsulfonic acid and tosylhydrazide in benzene at 80 °C gave a 2.5:1 mixture of **7a** and **7b** in a combined 42% yield. In this key reductive condensation event, the permethylated hydroquinone precursors to icetexone and *epi*-icetexone are formed in a single pot cascade transformation.

(11) For recent examples, see: (a) Simmons, E. M.; Hardin, A. R.; Guo, X.; Sarpong, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6650–6653. (b) Miyanohana, Y.; Chatani, N. *Org. Lett.* **2006**, *8*, 2155–2158.

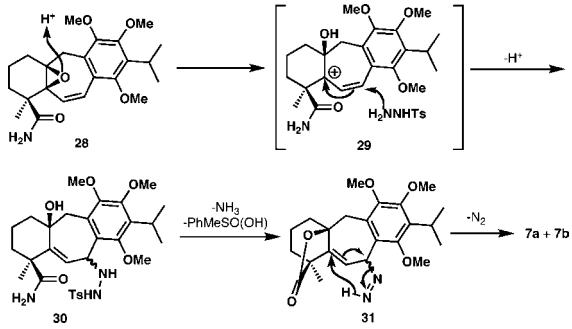
(12) (a) Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett.* **1995**, *36*, 8657–8660. (b) Ghaffar, T.; Parkins, A. W. *J. Mol. Catal. A* **2000**, *160*, 249–261.

Scheme 6. Synthesis of Icetexone and *epi*-Icetexone Precursors **7a** and **7b**



Tetracycles **7a** and **7b** may arise via the postulated sequence outlined in Scheme 7. The transformation com-

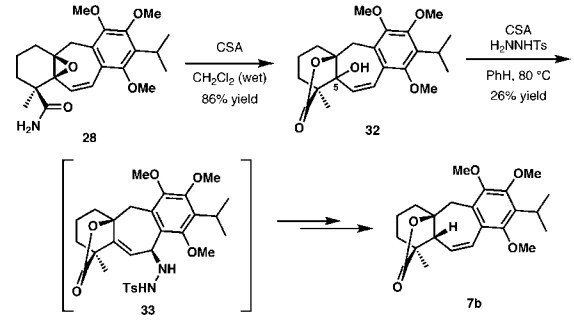
Scheme 7. Proposed Mechanism for the Formation of **7a** and **7b** from **28**



mences with protonation of the epoxide group of **28** and subsequent opening to afford allylic cation **29**, which is trapped by tosylhydrazide to afford **30**. This trapping step ultimately determines the ratio of **7a** to **7b** that is obtained (vide infra).[13] From **30**, the icetexone and *epi*-icetexone precursors **7a** and **7b** may arise via a sequence involving (A) cyclization with accompanying loss of a molecule of NH_3 to install the bridging lactone and (B) loss of *p*-toluenesulfinic acid to afford diazene **31**, which undergoes a diazene decomposition[14] with accompanying double bond transposition and loss of dinitrogen. The stereospecific nature of the diazene rearrangement leads to the observed mixture of **7a** and **7b**.

Support for the proposed formation of **7a** and **7b** from **28** was gained from the observations detailed in Scheme 8. Treating epoxide **28** with camphorsulfonic acid in wet CH_2Cl_2 yielded **32** as a single diastereomer.[15] Subjection of **32** to camphorsulfonic acid and tosylhydrazide in benzene at 80 °C for 15 h gave **7b** as the major product

Scheme 8. Synthesis of **7b**



(>10:1 dr of **7b**:**7a**). Presumably, attack of tosylhydrazide occurs with high diastereocontrol from the convex face of the rigid, polycyclic, allylic cation generated from **32** to give **33**. Following the loss of *p*-toluenesulfinic acid, stereospecific diazene rearrangement yields **7b** as the major product. Because Majetich and Grove have previously employed **7b** in the synthesis of *epi*-icetexone, this sequence completes a formal synthesis of this natural product. Furthermore, because **7a** was also applied in the synthesis of icetexone by Majetich and Grove, we have also achieved a formal synthesis of this natural product.

In conclusion, we have applied a Ga(III)-catalyzed cycloisomerization reaction to the synthesis of a benzannulated cycloheptadiene bearing a cyano group that serves as a key intermediate in the synthesis of the icetexane diterpenoids icetexone and *epi*-icetexone. The synthesis features a late-stage cascade sequence that constructs the tetracyclic core of these natural products.

Because the syntheses of compounds closely related to **17** are known in enantioenriched form,[16] the strategy outlined here should be readily applied to the enantioselective syntheses of **5** and **6**. Our current efforts are focused on this pursuit and the application of cycloheptadiene intermediates such as **8** to the synthesis of other natural products.

Acknowledgment. The authors are thankful to Ms. Ariel Yeh for assistance in the preparation of **17** and Dr. Eric Simmons (University of Illinois Urbana−Champaign) for numerous intellectual contributions. The authors are grateful to UC Berkeley, the NIH (NIGMS RO1 GM086374-01 and F31 GM089139-01), Johnson and Johnson, and Eli Lilly for generous financial support. R.S. is an Alfred P. Sloan Foundation Fellow and a Camille Dreyfus Teacher-Scholar.

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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(13) On the basis of the observed ratio of **7a** to **7b**, this trapping step likely proceeds with poor diastereocontrol.

(14) Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841–4844.

(15) The relative stereochemistry for **32** at C-5, which is inconsequential, was not established.

(16) Sawamura, M.; Hamashima, G.; Shinoto, H.; Ito, Y. *Tetrahedron Lett.* **1995**, *36*, 6479–6482.