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Total Synthesis of (+)-19-Deoxyicetexone, (−)-Icetexone, and (+)-5-*Epi*-icetexone[†,‡]

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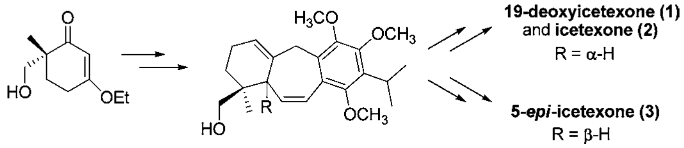
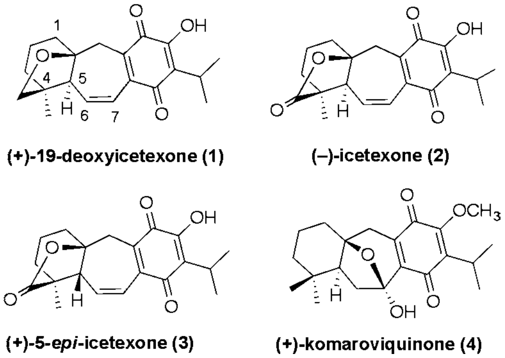
ABSTRACT



The first asymmetric total syntheses of 19-deoxyicetexone, icetexone, and 5-*epi*-icetexone was achieved from epimeric tricyclic dienes.

Many structurally novel and biologically active abietane-diterpenoids have been isolated from the extracts of shrubs and plants of the genus Salvia grown in Mexico, Asia, and Europe.[1,2] We have synthesized several icetexanes using an intramolecular Friedel−Crafts,[3,4] or cyclialkylation, strategy[5] to efficiently assemble the carbocyclic skeleton. Herein, we report the first asymmetric syntheses of 19-deoxyicetexone (**1**),[6] icetexone (**2**),[7] and 5-*epi*-icetexone (**3**) (Figure 1).[8]



(+)-19-deoxyicetexone (1) **(−)-icetexone (2)**

(+)-5-*epi*-icetexone (3) **(+)-komaroviquinone (4)**

Figure 1. Resentative icetexane diterpenoids.

Three key observations influenced our overall synthetic strategy for the icetexones. During our synthesis of (±)-komaroviquinone (**4**),[4a] we investigated if a Barton-like oxidation[9] of alcohol **5** would selectively functionalize the C(19) methyl group (cf. **6**) and thus provide access to the icetexones (Scheme 1). Despite a nearly linear relationship between the initially formed oxygen radical **i** and the proximal C(19) hydrogen atom (cf. **i**),[10] treatment of alcohol **5** with lead tetraacetate and iodine instead gave aldehyde **7**, through a fragmentation process.[11] This result required us to introduce a hydroxyl group at C(19) earlier in our synthetic

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[‡] This paper is dedicated to the memory of Dr. Anthony "Tony" Shuker, 1965−2009.

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(2) 5-*Epi*-icetexone (**3**), exhibits a strong antiproliferative effect on the parasite *Trypanosoma cruzi*, the causative agent in Chagas' disease; see: Sanchez, A. M.; Jimenez-Ortiz, V.; Sartor, T.; Tonn, C. E.; Garcia, E. E.; Nieto, M.; Burgos, M. H.; Sosa, M. A. *Acta Trop.* **2006**, *98*, 118–124.

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(4) Synthesis of (±)-**4**: (a) Majetich, G.; Li, Y.; Zou, G. *Heterocycles* **2007**, *73*, 217–225. Synthesis of (+)-**4**: (b) Majetich, G.; Yu, J.; Li, Y. *Heterocycles* **2007**, *73*, 227–235.

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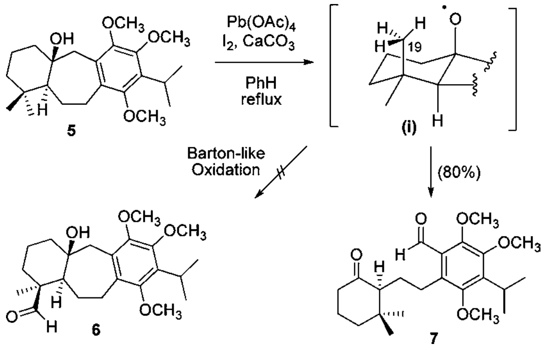
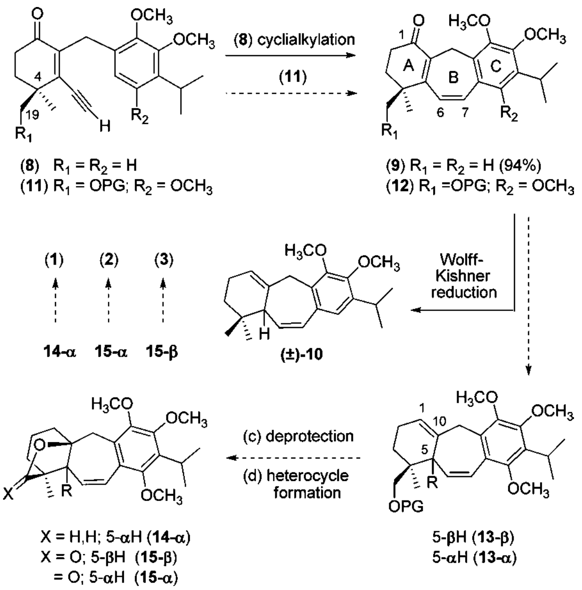
Scheme 1. Failed Strategy



Scheme 2. Prior Results and Retrosynthetic Analysis



route. Second, in our synthesis of (−)-salviasperanol,[3c] treatment of enynone **8** with excess BF$_3$-etherate and a catalytic quantity of ethanethiol gave dienone **9** in 94% yield (Scheme 2). Incorporating this observation into our icetexone strategy would allow us to efficiently introduce the C(6),C(7)-double bond. A final observation[4b] was that the Wolff−Kishner reduction of dienone **9** produces diene (±)-**10** having a double bond at C(6),C(7)[11] and a trisubstituted double bond at C(1),C(10), which would enable us to functionalize the C(10) position.[12] These observations led us to prepare enynone **11**, an analogue of **8**, with the requisite stereochemistry at C(4) and an additional methoxy substituent at C(14). Cyclization of **11** would produce dienone **12** with a C(6),C(7)-double bond and a fully substituted C-ring. We were hopeful that the asymmetric center at C(4) would influence the facial selectivity of the Wolff−Kishner reduction of the C(1) carbonyl, thereby allowing us to stereospecifically prepare dienes **13-α** and **13-*β***. Intramolecular addition of the C(19) hydroxyl group to the C(1),C(10)-double bond would generate a tetrahydrofuran ring and introduce the C(10)-stereocenter (i.e., **13-α** → **14-α**) and oxidation of the aromatic C-ring of **14-α** to a *p*-benzoquinone would complete the synthesis of **1**. Removal of the protecting group from ether **13-*β*** would afford an alcohol that would be oxidized to a carboxylic acid. Subsequent lactone formation (cf. **15-*β***) and oxidation of the C-ring would culminate in the synthesis of 5-*epi*-icetexone (**3**). Similarly, oxidation of alcohol **13-α** to a carboxylic acid, followed by lactonization (cf. **15-α**) and oxidation of the C-ring, would furnish icetexone (**2**).

Our synthetic strategy required us to prepare a chiral 3-alkoxycyclohexenone derivative (Scheme 3). In 1999, Yamada and co-workers prepared (−)-3-ethoxy-6-hydroxymethyl-6-methylcyclohex-2-en-1-one (−)-**16** in high e.e. via an enzymatic resolution of racemic **16**;[13] hence, this optically active starting material was easy to prepare. The next step was to couple the A- and C-rings using an alkylation. However, we were concerned that (−)-**16** could undergo a retro-Aldol fragmentation faster than alkylation, so a suitable protecting group was needed to preclude this. The ideal protecting group had to be stable to both protic and Lewis acids, and the conditions for its removal had to be tolerant of olefins, ketones, and aryl methyl ethers. After careful consideration, enantiomerically enriched alcohol (−)-**16** (99% e.e.) was converted to benzyl ether **17**. In 1994 we synthesized bromide **18** from vanillin via an eight-step sequence but in only 25% overall yield.[14] Here we report that **18** can be prepared in large quantities and in >45% overall yield from carvacrol (**19**)[15] via a six-step sequence. In the first step, carvacrol was brominated in acetic acid to give a dibromide-phenol, which was then methylated to give ether **20**. Arene **20** was treated with NBS to form a benzyl bromide, which was immediately treated with sodium actetate to give acetate **21** in 70% overall yield. Treatment of dibromide **21** with excess copper(I) methoxide[16] substituted methoxy groups for the two bromines and liberated alcohol **22** via transesterification. Alcohol **22** was then converted to bromide **18** using PBr$_3$.

In 1981, Smith and co-workers alkylated 3-isobutoxy-6,6-dimethylcyclohexen-2-en-1-one with iodomethane at the α-position in 61% yield using LDA and HMPA.[17] In our hands, treatment of the enolate derived from **17** with bromide **18** using the reported conditions gave predominantly *bis*-alkylation. Fortunately, replacing HMPA with DMPU pro-

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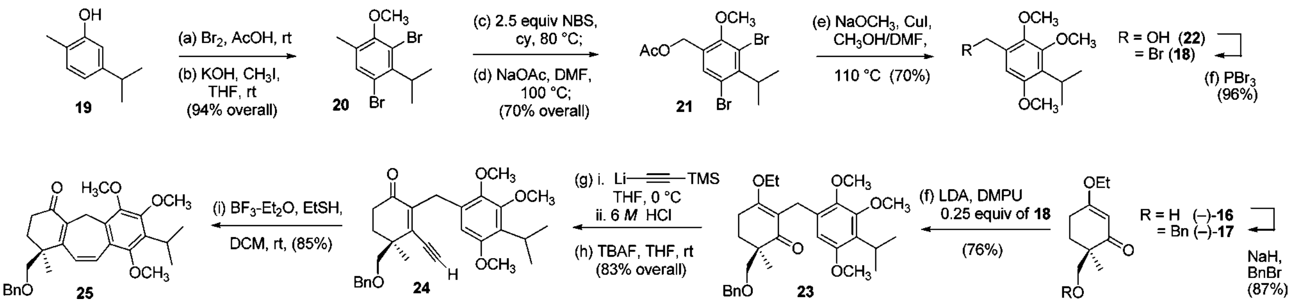
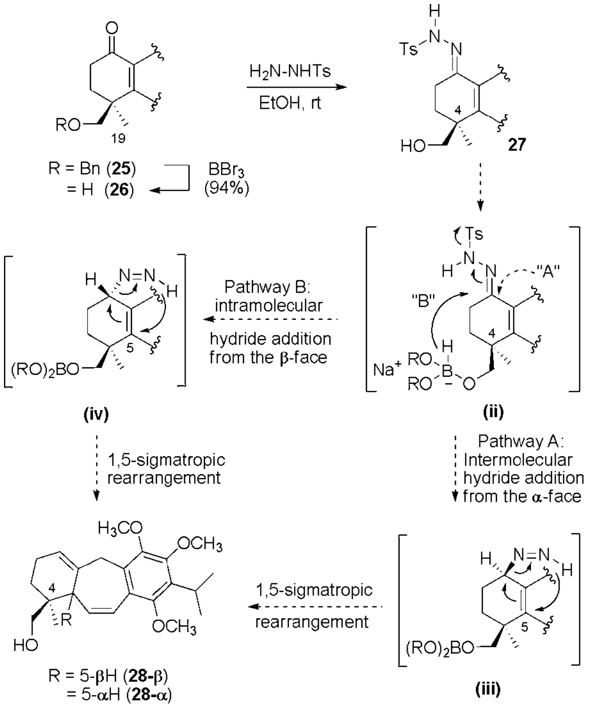
Scheme 3. Preparation of Tricycle



duced a 76% yield of **23**. 1,2-Addition of the anion of trimethylsilyl acetylene to ketone **23**, followed by mild acid hydrolysis and subsequent deprotection with TBAF,[18] produced enynone **24** in 83% overall yield. Although benzyl and methyl aryl ethers can be deprotected with Lewis acid catalysts and thiols,[19] we found that treatment of enyone **24** with two equivalents of BF_3-Et_2O and a catalytic amount of EtSH in dilute DCM left the protecting groups intact and produced tricycle **25** in 85% yield. The next step was the selective deprotection of the benzyl ether. Unfortunately, the C(6),C(7)-double bond was readily reduced upon brief exposure to a stoichiometric quantity of sodium or lithium metal dissolved in ammonia, including calcium metal which is known to selectively cleave benzyl ethers in the presence of olefins (Scheme 4).[20] Instead, treatment of **25** with BBr_3 at −78 °C gave **26** in excellent yield. The formation of tosylhydrazone **27** from **26** was equally facile. The addition of one equivalent of a borohydride reducing agent to **27** forms complex (**ii**). We were curious if this complex would block the *β*-face so that the addition of a second equivalent of the reducing agent would add intermolecularly from the α-face to generate diazene **iii**, which would rearrange to afford diene **28-*β***. In theory, complex (**ii**) can deliver a hydride intramolecularly exclusively from the *β*-face to form allylic diazene (**iv**), which would rearrange to form diene **28-α**. In practice, reduction of tosylhydrazone **27** with two equivalents of catecholborane[21a,b] afforded a 1:4 diastereomeric mixture of **28-α**:**28-*β*** in 70% yield whereas the use of sodium triacetoxyborohydride (STAB-H)[21c] gave a 1:1 mixture of dienes **28-α**:**28-*β*** in 84% yield. Despite considerable effort, we were unable to improve the selectivity of these reductions.

Scheme 4. Synthesis of Dienes **28-α** and **28-*β***



With dienes **28-α/*β*** in hand, we focused on the formation of the heterocyclic rings present in **1**, **2**, and **3**. During our (+)-komaroviquinone synthesis, we noted that the C(1), C(10)-double bond reacts rapidly to form a bromohydrin. This observation suggested that the tetrahydrofuran ring of 19-deoxyicetexone could be introduced via an iodocyclization/deiododination procedure (Scheme 5). Indeed, treatment of diene **28-α** with iodine in the presence of a weak base led to the rapid formation of iodofuran **29**, establishing the C(10) stereocenter. Radical deiododination using standard conditions gave tetrahydrofuran **30** in 94% yield. Deprotection of the C(11) and C(12) methoxy groups was achieved using excess sodium ethanethiolate in hot DMF.[22] Catechol **31** was oxidized to *o*-benzoquinone (**v**) using CAN; presumably trace acid present in the reaction mixture causes *in situ* hydrolysis of the C(14) methoxy group, a vinylogous ester, followed by isomerization of the *o*-quinone to 19-deoxyicetexone (**1**) in 66% overall yield. Spectral and optical rotation data for our synthetic material matched the data reported for **1**, which confirms our stereochemical assignments for dienes **28-α/*β***. This conclusion was also verified by X-ray analysis.

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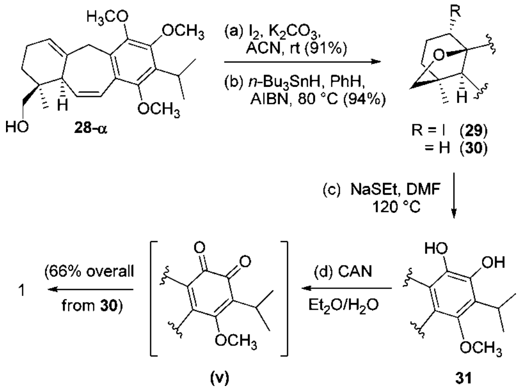
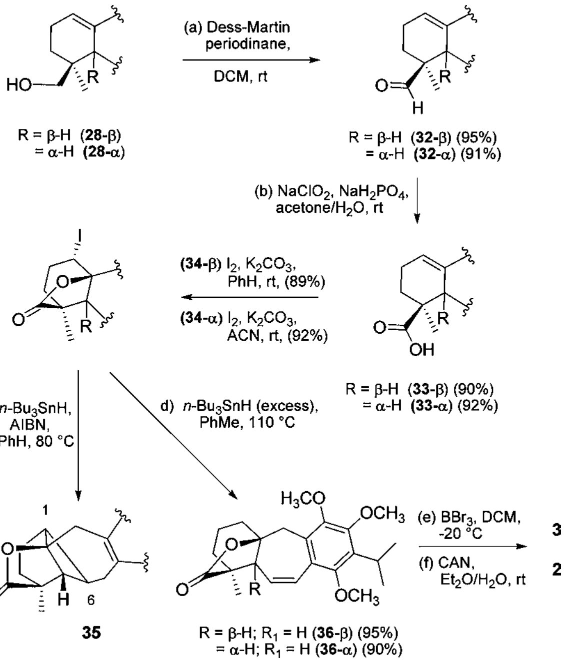
Scheme 5. Synthesis of 19-Deoxyicetexone (**1**)



Scheme 6. Syntheses of Icetexone (**2**) 5-*Epi*-icetexone (**3**)



The oxidization of alcohols **28-α**/***β*** to their corresponding carboxylic acids would allow us to introduce the lactone moiety present in icetexone and 5-*epi*-icetexone (Scheme 6). This oxidation was achieved using Dess-Martin periodinane to provide the aldehydes **32-α**/***β*** in high yields. Further oxidation to carboxylic acids **33-α**/***β*** was achieved using buffered $NaClO_2$ in acetone/water. Iodolactonization of acid **33-*β*** was carried out in benzene. Surprisingly, deiododination of lactone **34-*β*** using standard radical reduction conditions initiated by AIBN gave polycycle **35**, whereby the initially formed C(1) radical adds intramolecularly to C(6), which is in close proximity, instead of abstracting a hydrogen atom from the tri-*n*-butyltin hydride present. The use of a large excess of tri-*n*-butyltin hydride, without AIBN, suppressed this undesired side reaction and gave lactone **36-*β*** in excellent yield. Instead of using NaSEt to deprotect the C(11) and C(12) methoxy groups, treatment of lactone **36-*β*** with BBr_3 at −20 °C cleanly produced a catechol that was oxidized to the corresponding *o*-quinone; hydrolysis of the C(14) methoxy group and isomerization of the *o*-quinone to a *p*-benzoquinone gave 5-*epi*-icetexone (**3**) in good overall yield. (−)-Icetexone (**2**) was prepared from alcohol **28-α** using the same sequence of transformations and conditions, except that deiododination of **34-α** occurred using standard free radical reducing conditions because the C-5 stereochemistry precluded formation of **35**. X-ray analysis of our synthetic icetexone and 5-*epi*-icetexone confirmed our structural assignments. However, we found that the NMR, optical rotation, and melting point data reported for 5-*epi*-icetexone instead matched our synthetic icetexone, representing a discrepancy in the isolation data. Additionally, although NMR data on natural icetexone were not available, all other physical data reported for natural icetexone matched our synthetic 5-*epi*-icetexone. Thus, our synthesis and characterization of these natural products have enabled us to verify the original structural assignments, but required the reassignment of their spectral and physical data.

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Note Added after ASAP Publication. This paper was published ASAP on June 4, 2009. Scheme 4 was replaced. The revised paper was reposted June 8, 2009.

Supporting Information Available: Experimental procedures for all transformations, and spectroscopic data for all new compounds, are provided, including X-ray data for **1**,**2**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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