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A Divergent Approach to the Diastereoselective Synthesis of Several Ant-Associated Iridoids

Joel S. Beckett, James D. Beckett, and John E. Hofferberth*

Department of Chemistry, Kenyon College, Gambier, Ohio 43022

hofferberthj@kenyon.edu

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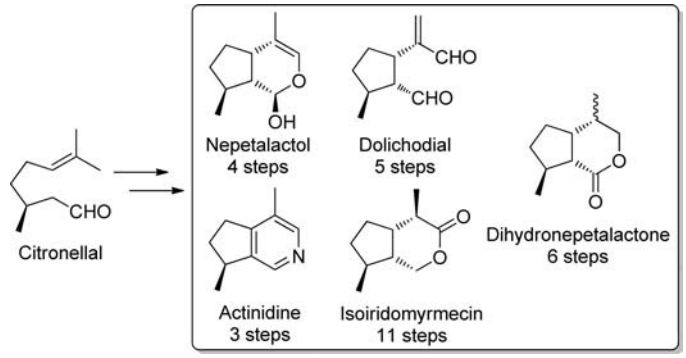
ABSTRACT



The ant-associated iridoids nepetalactol, actinidine, dolichodial, isoiridomyrmecin, and dihydronepetalactone were prepared from citronellal using a divergent approach. Key features include a three-step synthesis of the individual antipodes of actinidine by a novel tandem cycloaddition/pyridine formation and a facile diastereoselective synthesis of both enantiomers of dolichodial.

The iridoids have long been recognized as important insect semiochemicals[1] and have recently attracted attention because of their potential use as control agents for pest species.[2] We became interested in the preparation of ant-associated iridoids because of their putative role as signaling molecules in unique mutualisms between ants of the genus *Iridomyrmex* and certain Australian butterflies.[3] In these species-specific mutualisms, the juvenile stages of the butterfly (egg, pupae, and larvae) require the constant protection of ant guards for survival. In return, the butterfly larvae secrete nutritious food rewards to the ants to recruit and maintain ant guards as they mature. A female butterfly must lay eggs on appropriate food plants that are occupied by a specific species of ant-associate to allow for the survival of her offspring. The discrimination between ant species by the female butterfly, and thus the selection of egg-laying site, is thought to be mediated by semiochemicals produced by the ants, although the nature of these volatile cues has been previously unexplored.[3a]

Here we detail the preparation of macroscopic quantities of several iridoids (**1**−**5**, Scheme 1) associated with the *Iridomyrmex*[4] to allow for comparison with natural ant extracts and the advance of biological assays. While many of the target molecules considered here (**1**−**5**) have been prepared by others using varied synthetic strategies,[2,5] the goal of this work was the identification of a divergent

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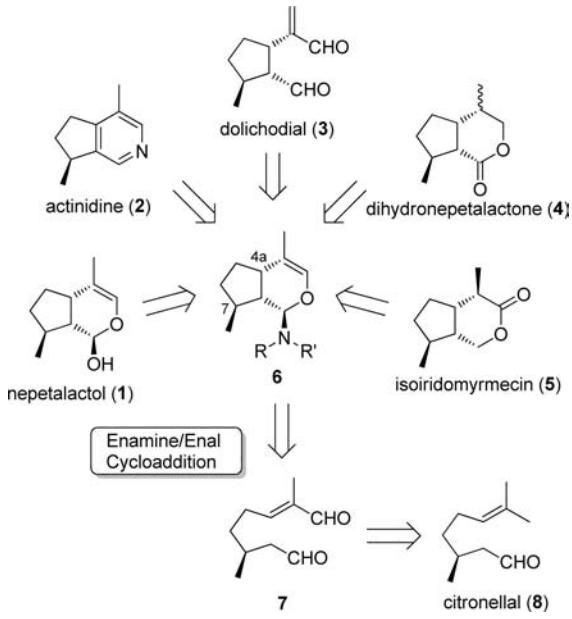
Scheme 1. Retrosynthetic Analysis

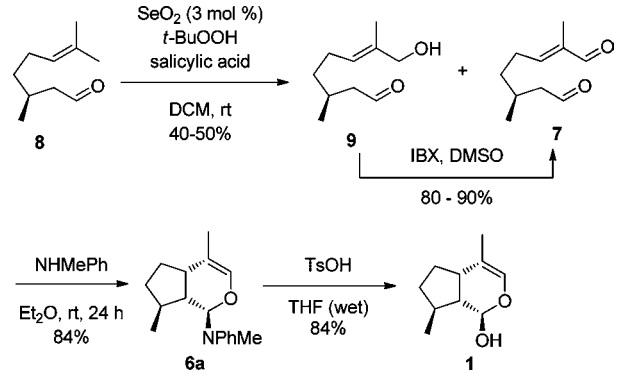


chemical synthesis that makes use of a common intermediate or key synthetic transformation to access all of the targets.

The intramolecular enamine/enal cycloaddition first described by Schreiber[6] has long been recognized as a valuable entry into the iridoid carbon skeleton.[5v,7] Importantly, the high diastereoselectivity of this process allows for the parlay of the single stereocenter in readily available citronellal (**8**) into both stereochemically stable positions (C4a, C7) of the resulting bicycloadduct (**6**). Additionally, the dihydropyran resident in **6** is well suited for chemical differentiation between the masked aldehyde functionalities. These attributes coupled with the concise nature of the chemistry leading to **6** motivated us to use it as the key point of divergence in our synthetic strategy.

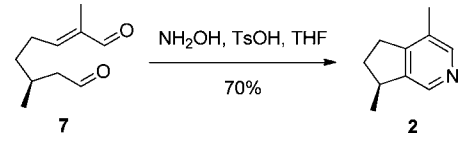
Preparation of the substrate for enamine/enal cycloaddition (**7**) from racemic citronellal was based on literature precedent[6,8] with modification (Scheme 2). In our hands, the allylic oxidation of citronellal with catalytic SeO_2 proceeded with high regioselectivity to produce mixtures rich in the aldol **9**. Direct conversion of citronellal to the desired endial (**7**) was not possible even after extended reaction times. Recourse was made to the oxidation of mixtures of **7** and **9** using stoichiometric IBX to give the cycloaddition substrate (**7**). As reported by Schreiber,[6] exposure of **7** to *N*-methylaniline for extended reaction times (>10 h) results in a highly diastereoselective intramolecular cycloaddition. It was clear from ^{1}H NMR analysis of cycloadduct (**6a**) that the diastereoselectivity of the reaction was >50:1. Hydrolysis of **6a** with TsOH in wet THF proceeded smoothly to provide nepetalactol (**1**, C1 α/β, 1:10).

Scheme 2. Synthesis of Nepetalactol (**1**)



The strategy for the conversion of **6a** into actinidine (**2**) was inspired by reports that 1,5-dialdehydes form pyridines when reacted with hydroxylamine.[9] Treatment of **6a**, a masked 1,5-dialdehyde, with hydroxylamine and TsOH in THF produced **2** in 69% isolated yield. Motivated by this transformation, the ability of hydroxylamine to induce both cycloaddition and pyridine formation was examined (Scheme 3). In the event, **7** is converted directly into actinidine (**2**) in

Scheme 3. Synthesis of Actinidine (**2**)



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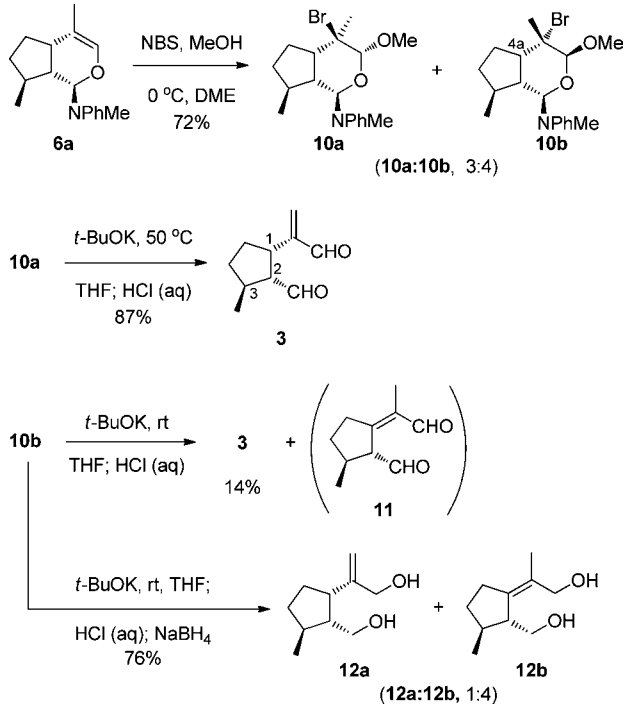
70% isolated yield under these reaction conditions. Using this tandem cycloaddition/pyridine formation, actinidine (**2**) was prepared in three synthetic operations from citroneallal in 28% overall yield. This methodology was applied to prepare the individual antipodes of actinidine from enantiomerically enriched citronellal without event.

Attention was next turned to the preparation of dolichodial (**3**, Scheme 4). Exposure of **6a** to NBS in the presence of

Scheme 4. Synthesis of Dolichodial (**3**)



methanol resulted in the regioselecive and stereospecific formation of the bromo acetals **10a** and **10b**. The product ratio (**10a**/**10b**, 3:4) is consistent with electrophilic attack occurring more readily from the concave face of the bicyclic starting material (**6a**). This facial selectivity can be rationalized by considering the steric impact of the aniline residue on the convex side of **6a**. It proved important to slowly add a solution of the electrophile (NBS, 1.1 equiv) to the cold reaction mixture (0 °C) to avoid the addition of bromine to the aromatic ring of the aniline residue. Even when great care is exercised, a small proportion of the corresponding dibromide (<10%) is evident in the ^{1}H NMR spectrum of the purified products.

Bimolecular elimination of **10a** and **10b** is governed by well-established stereoelectronic principles.[10] In the case of **10a**, only the protons on the vicinal methyl group are capable of adopting an antiperiplanar orientation relative to the bromine. Exposure of **10a** to *t*-BuOK at 50 °C in THF over 4 h results in the formation of a single elimination product with the desired exo-oriented double bond. While scrutiny of the crude product mixture by ^{1}H NMR revealed the exclusive formation of the expected intermediate, this intermediate proved to be unstable to silica gel chromatography. The addition of an acidic step (1 N HCl) in the workup resulted in complete hydrolysis of the masked aldehydes and gave rise to a single diastereomer of dolichodial (**3**) in 87% yield. The relative stereochemistry of **3** was established (1*S*,2*R*,3*S*, racemic) by NOESY correlations and comparison to published spectra.[11]

In contrast to **10a**, exposure of **10b** to *t*-BuOK in THF results in rapid elimination (<5 min) even at ambient temperature. Vicinal protons on both the pendant methyl group and C4a are capable of adopting an antiperiplanar orientation relative to the bromine. As anticipated, ^{1}H NMR analysis of the reaction mixture revealed the presence of two distinct elimination products. After acidic workup, two pairs of diagnostic aldehyde signals, putatively corresponding to **3** and the undesired endocyclic elimination product **11**, were evident in the ^{1}H NMR spectrum (C_6D_6 δ 9.01 (d, $J = 1.8$ Hz, 1H), 9.12 (s, 0.4H), 9.25 (d, $J = 2.3$ Hz, 0.4H), 9.66 (s, 1H)). However, purification of the crude mixture by silica gel chromatography provided only **3** in modest yield (14%). In order to indirectly establish the presence of **11**, the reaction was repeated and the crude reaction mixture was reduced with $NaBH_4$ prior to purification to give a mixture of **12a** and **12b** in a 1:4 ratio. The dominance of **12b** in the product mixture is consistent with the preferred deprotonation occurring at C4a resulting in formation of the endocyclic double bond.

Notably, the elimination of **10a** and **10b** resulted in the preparation of a single diastereomer of **3** without epimerization at C2 to form anisomorphal. In sum, dolichodial (**3**) was prepared in five synthetic operations from citronellal in 13% overall yield. This synthesis was repeated using enantiomerically enriched citronellal to prepare both antipodes of **3** without event. To the best of our knowledge, this is the first reported synthesis of the "unnatural" enantiomer (1*S*,2*R*,3*S*) of dolichodial (**3**).

The preparation of two biologically important diastereomers of dihydronepetalactone, **4a** and **4b**, exploits the differing steric environment of the two faces of the enol resident in **6a** and **14** (Scheme 5).[5w,12] Catalytic hydrogenation (Pd/C) of **6a** occurs exclusively from the *concave* face to provide pyran **13** (C1 α/β, 1:10) after hydrolysis of the aniline residue. Steric shielding of the *convex* face of the molecule by the C1 aniline residue appears to exert a strong influence on the approach of the catalyst. Oxidation of **13** with Fetizon's Reagent proceeded smoothly to yield dihy-

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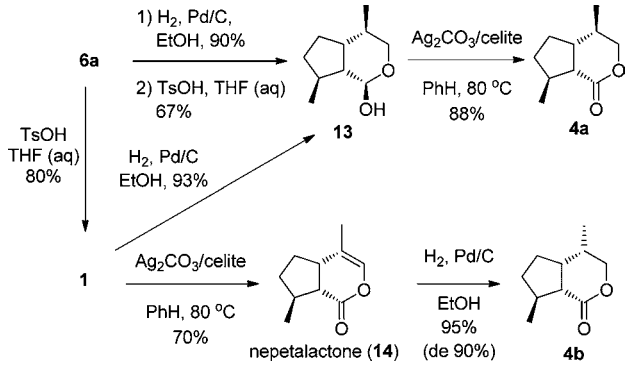
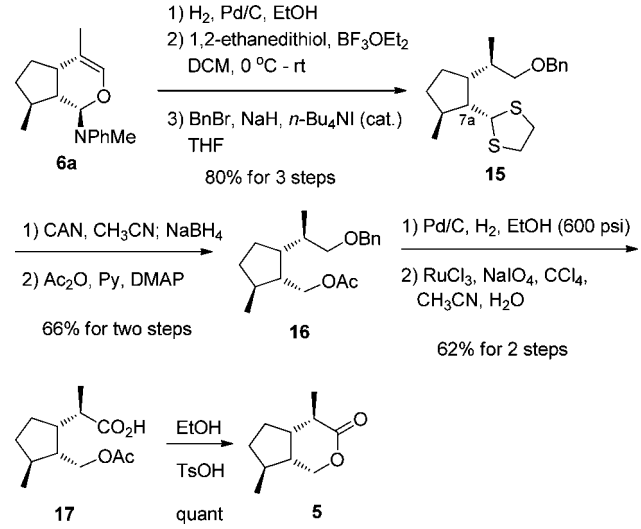
Scheme 5. Synthesis of Dihydronepetalactones **4a** and **4b**



Scheme 6. Synthesis of Isoiridomyrmecin (**5**)



dronepetalactone **4a**. As has been observed by others,[5w,12b] nepetalactol (**1**), with its anomeric hydroxyl group oriented on the *convex* face of the molecule, is also capable of directing the reducing agent to the *concave* face and produces **13** under catalytic hydrogenation conditions (Pd/C).

Nepetalactone (**14**) was prepared from **6a** using the synthesis described by Schreiber (**6a** → **1** → **14**).[6] In contrast to **6a** and **1**, hydrogenation (Pd/C) of **14** provided dihydronepetelactone **4b** as the major diastereomer (90% de).[5w,12a] This result is consistent with the primary steric influence on the approach of the catalyst to **14** being the fused cyclopentane ring although stereocontrol is not complete in this instance. In sum, two biologically significant dihydronepetalactones, **4a** and **4b**, were prepared in six synthetic steps from citronellal with an overall yield of 25% and 20%, respectively.

Access to isoiridomyrmecin (**5**) required chemical differentiation of the masked aldehydes resident in **6a** (Scheme 6). As in the preparation of **4a**, catalytic hydrogenation of **6a** established the C4 stereocenter found in **5**. Treatment of the resulting aminal with $BF_3{\cdot}OEt_2$ and 1,2-ethanedithiol converted the remaining masked aldehyde to the corresponding dithiolane, and the liberated primary alcohol was protected as a benzyl ether (**15**). In a one-pot procedure, the dithiolane was removed by treatment with CAN,[13] and the free aldehyde was reduced with $NaBH_4$ to preserve the stereochemistry at the C7a position. Subsequent acetylation of the newly formed primary alcohol gave the orthogonally protected diol **16**. Reductive removal of the benzyl protecting group followed by oxidation of the resulting primary alcohol using the conditions developed by Sharpless[14] yielded the carboxylic acid **17**. Transesterification of **17** with catalytic TsOH in ethanol provided isoiridomyrmecin (**5**) in quantitative yield.

In conclusion, we have prepared five ant-associated iridoids by a divergent approach using the readily available starting material citronellal and common reagents. Biological examination of the iridoids prepared in this program is ongoing. Additionally, we are exploring the tandem cycloaddition/pyridine formation methodology, developed during our preparation of actinidine (**2**), for its potential in preparing other molecules containing the cyclopenta[C]pyridine substructure.

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

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