

Stereoselective synthesis of *trans*-fused iridoid lactones and their identification in the parasitoid wasp *Alloxysta victrix*, Part II: Iridomyrmecins

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Full Research Paper

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Abstract

Following our earlier approach to the synthesis of dihydronepetalactones, all eight stereoisomers of *trans*-fused iridomyrmecins were synthesized starting from the enantiomers of limonene. Combined gas chromatography and mass spectrometry including enantioselective gas chromatography revealed that volatiles released by the endohyperparasitoid wasp *Alloxysta victrix* contain (4*S*,4*aR*,7*S*,7*aR*)-iridomyrmecin of 95–97% ee and stereochemically pure (4*S*,4*aS*,7*R*,7*aS*)-iridomyrmecin as a minor component.

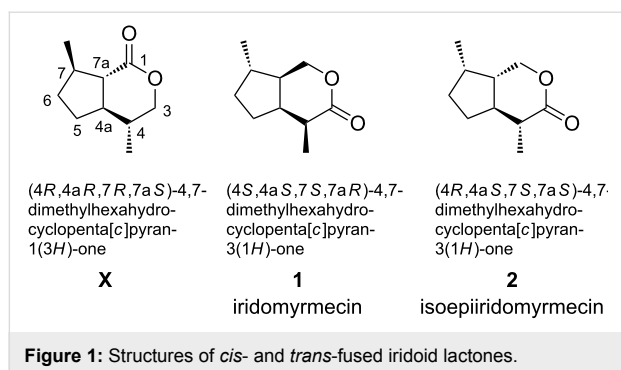
Introduction

In the course of our studies on volatile signals of the endohyperparasitoid wasp, *Alloxysta victrix*, we identified several acyclic terpenoids and the *trans*-fused (4*S*,4*aR*,7*R*,7*aS*)-dihydronepetalactone (**X**) as volatile components of cephalic secretions released by this species (Figure 1) [1,2]. However, gas chromatograms showed the presence of two additional major volatiles **Y** and **Z** which, according to their mass spectra, were suggested to be *trans*-fused iridomyrmecins [3,4]. Since no synthetic reference compounds were available, all eight *trans*-fused iridomyrmecins had to be prepared. To complete the synthesis

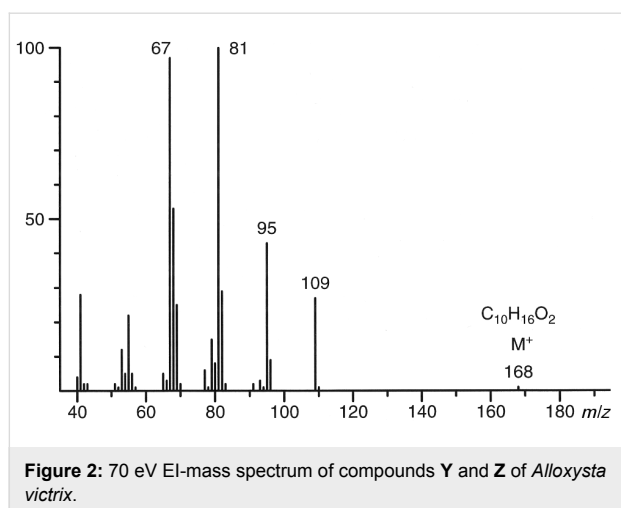
of this suite, we started from optically active limonene following a strategy similar to our route leading to *trans*-fused dihydronepetalactones [1]. The realization of this task and the unambiguous structure assignment of the natural products **Y** and **Z** is subject of the present paper.

Results and Discussion

Upon coupled gas chromatography/mass spectrometry (GC/MS), two major components, **Y** and **Z**, of the volatile secretions of both sexes of *Alloxysta victrix* (although in much



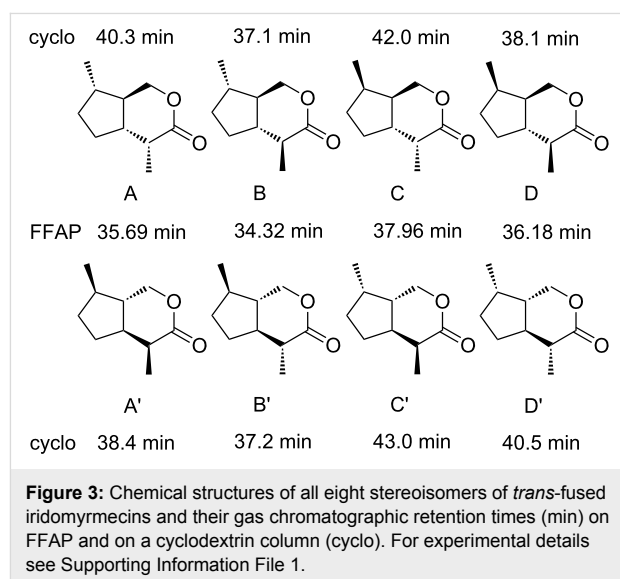
higher amounts in males) gave almost identical 70 eV EI-mass spectra (Figure 2); somewhat resembling that of the *trans*-fused dihydronepetalactone that we had already found in the insects [1]. Gas chromatography coupled with chemical ionization mass spectrometry (GC/CIMS) proved the molecular mass of the target compounds to be $[M]^+ = 168$, while high resolution mass spectrometry (GC/HRMS) showed their atomic composition to be $C_{10}H_{16}O_2$, confirming the compounds to be isomers of dihydronepetalactone. Though the fragmentation pattern showed some similarities to that of the *cis*-fused iridomyrmecin (**1**), a comparison with mass spectral data published for the *trans*-fused isoepiiridomyrmecin (**2**) suggested that the substances **Y** and **Z** are *trans*-fused iridomyrmecins. While the plotted mass spectrum of **1** showed m/z 95 as the base peak and similar abundances of about 55% for m/z 67, m/z 81 and m/z 109 [3], the data of **2** refer to m/z 81 as the base peak and m/z 95 and m/z 109 to reach 48% and 33%, respectively [4]; this is more close to the spectra of **Y** and **Z** (Figure 2).



Iridomyrmecin (**1**) was first isolated from ants (Figure 1) [5] and along with some other volatile iridoids it has since been reported to be a potent insecticide and antibiotic from several natural sources [6]. Due to their challenging molecular

structures and their interesting physiological properties, iridomyrmecins are attractive targets in stereoselective synthesis.

Similar to dihydronepetalactones, the iridomyrmecin skeleton shows four contiguous stereogenic centers giving rise to four *trans*-fused stereoisomers **A–D** and four corresponding enantiomers **A'–D'** (Figure 3, **D'** is identical to **2** in Figure 1). The presence of the four chiral centers complicates a stereoselective synthesis despite the small size of the molecule. Several methods have been published for the preparation of optically active *cis*-fused bicyclic iridoid lactones [7–10], whereas only a few syntheses of *trans*-fused ring systems have been reported [11]. Starting from enantiomerically pure (*R*)-pulegone, mixtures of (7*R*)-configured diastereomers **A'** and **B'** as well as **C** and **D** have been synthesized by Wolinsky [12]. The set of stereochemically pure (7*S*)-configured, *trans*-fused iridomyrmecins **A**, **B**, **C'**, and **D'** has been prepared by Trave [13]. Though Wolinsky's route may generally be used for the synthesis of all eight stereoisomers of *trans*-fused iridomyrmecins, it suffers from several major disadvantages such as high costs of (*S*)-pulegone and difficult separations of diastereomeric mixtures.



Starting from the cheaply available pure enantiomers of limonene, we had reported a novel stereoselective route towards *trans*-fused dihydronepetalactones [1] which we now extended to the synthesis of all eight stereoisomers of *trans*-fused iridomyrmecins. Subsequently, the volatile components **Y** and **Z** – present in *Alloxysta victrix* – were confirmed to be *trans*-fused iridomyrmecins, and their absolute configurations could be determined by comparison of their analytical data with those of all eight synthetic stereoisomers.

Synthesis of *trans*-fused iridomyrmecins

Our approach to the eight *trans*-fused iridomyrmecins starting from the enantiomers of limonene followed our general route for the synthesis of *trans*-fused dihydronepetalactones (Figure 4) [1].

Starting from pure (*R*)-limonene (**3**), the key intermediate **4** was prepared as described previously [1] and was used for both the synthesis of *trans,trans* and *cis,trans* (these designations refer to the relative configurations between the methyl group at C-7 and the substitution pattern at C-7a and C-4a, respectively) configured iridomyrmecins. Key steps were two stereoselective hydrogenations: A transfer hydrogenation for a formal “*anti*” delivery

of hydrogen [14,15], as represented in **5**, and the use of Crabtree’s catalyst in a directed hydrogenation for a “*syn*” addition of hydrogen as represented in **6** [16–18]. Subsequent to the hydrogenation step, the synthesis of *trans*-fused iridomyrmecins could be completed after some standard functional group modifications. The synthesis of the corresponding enantiomers followed the same way, starting from (*S*)-limonene (**3'**).

Synthesis of *trans*-fused iridomyrmecins **A** and **B**

The aldehyde **8**, derived from (*R*)-limonene (**3**), served as the key intermediate for the synthesis of the *trans*-fused iridomyrmecins **A** and **B** (Scheme 1). As shown in the stereo-

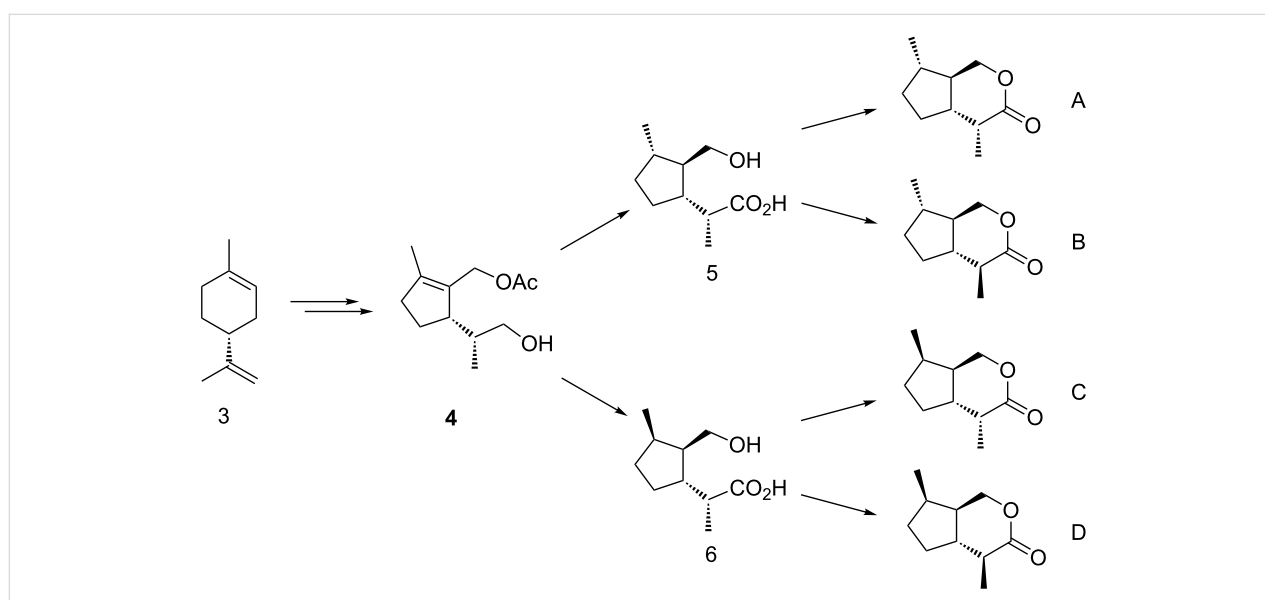
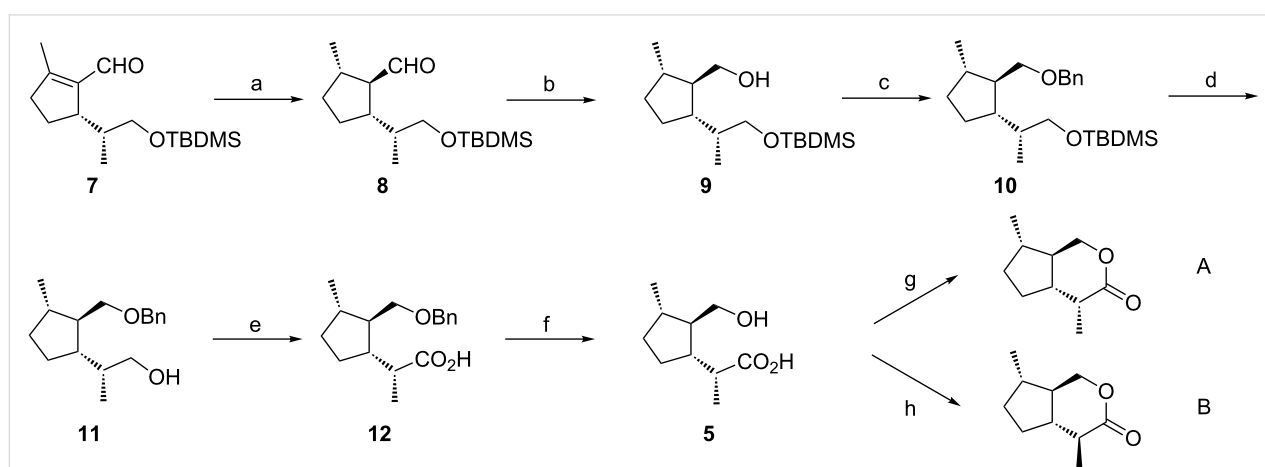


Figure 4: Strategy for the stereoselective synthesis of *trans*-fused iridomyrmecins **A–D** from (*R*)-limonene.



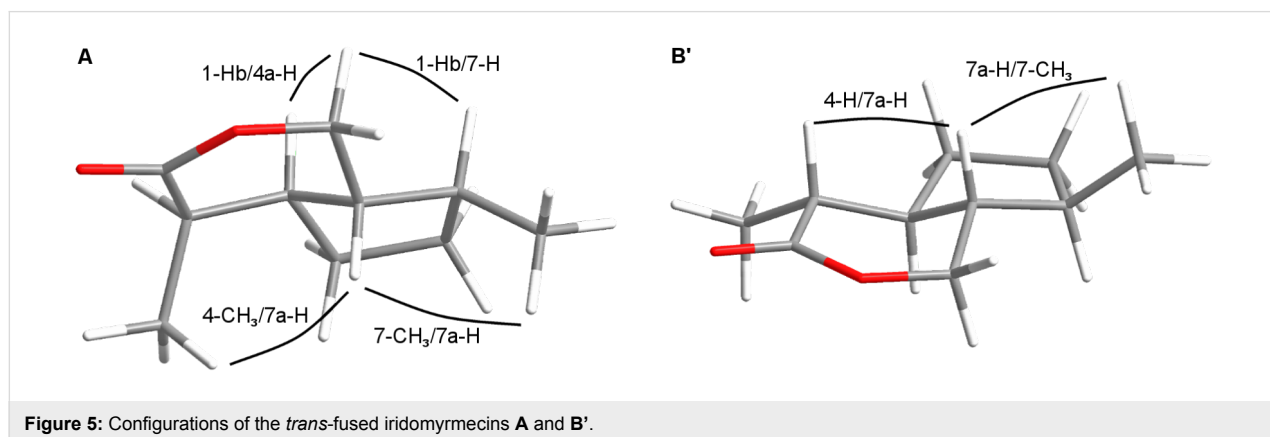
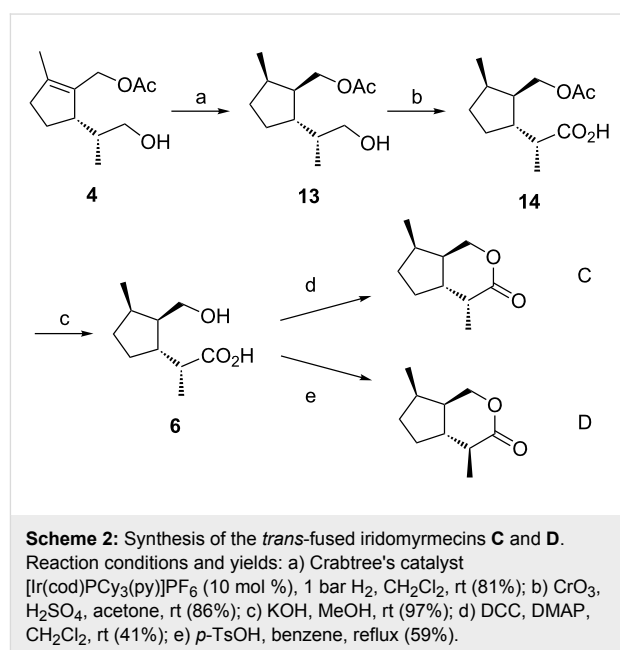
Scheme 1: Synthesis of the *trans*-fused iridomyrmecins **A** and **B**. Reaction conditions and yields: a) ammonium formate, Pd/C, MeOH, reflux (48%); b) NaBH₄, MeOH, H₂O, rt (79%); c) NaH, BnBr, THF, reflux (96%); d) HF, CH₃CN, rt (71%); e) CrO₃, H₂SO₄, acetone, rt (99%); f) Pd/C, 40 bar H₂, THF, rt (100%); g) DCC, DMAP, CH₂Cl₂, rt (66%); h) *p*-TsOH, benzene, reflux (56%).

selective synthesis of *trans*-fused dihydronepetalactones [1], this key intermediate could be obtained via a highly diastereoselective transfer hydrogenation of the known [19] trisubstituted cyclopentene **7** with ammonium formate over palladium [1,14,15]. Starting from the aldehyde **8**, the relative configuration of which had been confirmed by NOE experiments [1], the synthesis of **A** and **B** was completed in six additional steps.

First, the aldehyde **8** was reduced with sodium borohydride, and the resulting alcohol **9** was protected as the benzyl ether to form **10**. Deprotection of the TBDMS ether was carried out with HF in acetonitrile to yield the mono-protected diol **11**. Using Jones reagent, the free hydroxy group of **11** was oxidized to the carboxylic acid **12**, and the benzyl ether was cleaved upon catalytic hydrogenation over Pd/C to produce the hydroxy acid **5**. The latter served as the immediate precursor for the formation of either of the two diastereomeric iridomyrmecins **A** and **B**: Careful cyclization using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in dichloromethane at rt afforded iridomyrmecin **A**. In contrast, treatment of **5** with catalytic amounts of *p*-toluenesulfonic acid in benzene under reflux conditions for 12 h resulted in a complete epimerization at the CH-acidic C-4 position, exclusively yielding the thermodynamically more stable iridomyrmecin **B**. All reaction steps were also carried out starting from enantiomerically pure (*S*)-limonene affording *trans*-fused iridomyrmecins **A'** and **B'**. Relative configurations of iridomyrmecins **A**, **A'** and **B**, **B'** were confirmed by NOESY experiments. In **A** (Figure 5, **A**) decisive NOEs could be observed between 1-H_b and 4a-H as well as between 1-H_b and 7-H which showed 4a-H and 7-H to be located at the same side of the molecule. In addition, NOEs between 4-CH₃ and 7a-H as well as between 7-CH₃ and 7a-H proved the two methyl groups to be located at the same side of the molecule. In contrast, as shown in Figure 5, **B'**, NOEs between 4-H and 7a-H as well as between 7-CH₃ and 7a-H, prove that in **B'** the two methyl groups are situated at opposite sides of the molecule.

Synthesis of *trans*-fused iridomyrmecins **C** and **D**

As shown in our previous paper on the synthesis of *trans*-fused dihydronepetalactones, the double bond of the acetate **4** could be hydrogenated with high stereocontrol to the diastereomerically pure acetate **13** [1] by using Crabtree's catalyst [16-18]. The synthesis of the iridomyrmecins **C** and **D** was completed in three additional steps (Scheme 2). The oxidation with Jones reagent yielded **14**, and subsequent saponification of the acetate group with methanolic KOH afforded the hydroxy acid **6**. Similar to the approach described above, careful lactonization with DCC and DMAP gave iridomyrmecin **C**, whereas treatment with *p*-toluenesulfonic acid in benzene under reflux conditions led to complete epimerization at C-4 and afforded iridomyrmecin **D**. All reaction steps were also carried out starting from enantiomerically pure (*S*)-limonene (**3'**) and afforded iridomyrmecins **C'** and **D'**.



Relative configurations of the iridomyrmecins **C**, **C'** and **D**, **D'** were confirmed by NOESY experiments. In **C** (Figure 6, **C**) decisive NOEs between 1-Hb and 4a-H as well as between 1-Hb and 7-CH₃ proved 4a-H and 7-CH₃ to be located at the same side of the molecule. The NOE between 4-CH₃ and 7a-H showed them to be geometrically close and the two methyl groups to be in opposite positions. In contrast, as shown in Figure 6, **D'** NOEs between 4a-H and 4-CH₃ as well as between 4a-H and 1-Hb and furthermore between 1-Hb and 7-CH₃ proved the methyl groups in **D'** to be at the same side of the molecule. This is confirmed by a NOE between 4-H and 7a-H.

In summary, we have completed the first enantioselective synthesis of all eight stereoisomers of *trans*-fused iridomyrmecins, starting from either of the cheaply available enantiomers of limonene. The acetate **4** is the decisive intermediate, and key reaction steps are two stereoselective hydrogenations: A transfer hydrogenation for a formal “*anti*” delivery of hydrogen and the use of Crabtree’s catalyst in a directed hydrogenation for a “*syn*”-addition of hydrogen. Starting from pure enantiomers of limonene [1] these novel synthetic routes provided iridomyrmecins **A**, **A'** and **B**, **B'** in 2–3% yield over 15 steps as well as iridomyrmecins **C**, **C'** and **D**, **D'** in 10–15% yield over 9 steps.

All eight stereoisomers of *trans*-fused iridomyrmecins could be separated by gas chromatography using a capillary column coated with FFAP as an achiral polar stationary phase and a second capillary coated with a 1:1 mixture of OV1701 and heptakis(6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-methyl)- β -cyclodextrin as an enantioselective stationary phase. Figure 3 shows the structures and retention times of all eight stereoisomers of *trans*-fused iridomyrmecins on both capillary column systems. Despite the small differences in retention times between **B** and **B'** on the cyclodextrin column, the enantiomers could be well distinguished under the experimental conditions.

Structure assignment of volatile components **Y** and **Z** in the parasitoid wasp *Alloxysta victrix*

Comparison of mass spectra and GC retention times of synthetic iridomyrmecins with corresponding data of the volatile substances **Y** and **Z** – which are present in pentane extracts of heads of *Alloxysta victrix* – allowed their unambiguous identification as *trans*-fused iridomyrmecins.

Coupled GC/MS analysis using FFAP as the stationary phase revealed the natural iridoid lactones **Y** and **Z** to show the same mass spectra and retention times as the two early eluting racemates of the synthetic iridomyrmecins, i.e., **B/B'** and **A/A'**, respectively (Figure 3). Enantioselective gas chromatography on heptakis(6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-methyl)- β -cyclodextrin showed that **A** and **A'** were well separated with an α -value of **A:A'** = 1.05 (Figure 3). Consequently, the structure of **Z** could be easily determined to be **A'**, namely (4*S*,4*aS*,7*R*,7*aS*)-iridomyrmecin. Under the same experimental conditions, **B** and **B'** were only poorly resolved, however, heptakis(2,6-di-*O*-methyl-3-*O*-pentyl)- β -cyclodextrin produced a good α -value of **B':B** = 1.015 [20]. As a result, **Y** was unambiguously identified to be (4*S*,4*aR*,7*S*,7*aR*)-iridomyrmecin. A careful inspection of the analytical data obtained with the cyclodextrin column revealed the presence of small amounts of (4*R*,4*aS*,7*R*,7*aS*)-iridomyrmecin **B'** in the natural extract, showing the ee of natural **B** to be ca. 95–97%. Figure 7 shows a typical gas chromatogram (obtained with FFAP as the stationary phase) of an extract of heads of male *A. victrix*. Identified structures are assigned.

Structural relations between the *Alloxysta*-compounds and other insect iridoids

The iridoid lactones which are present in the cephalic secretions of *Alloxysta victrix* show an unusual *trans*-fusion. Among the compounds showing this structure, only the lactone **X** [1]

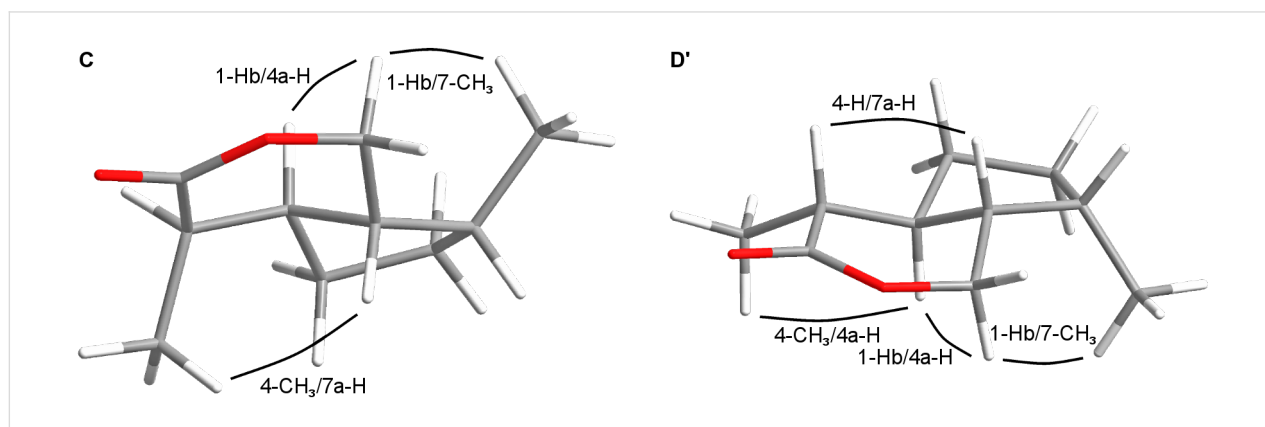


Figure 6: Configurations of the *trans*-fused iridomyrmecins **C** and **D'**.

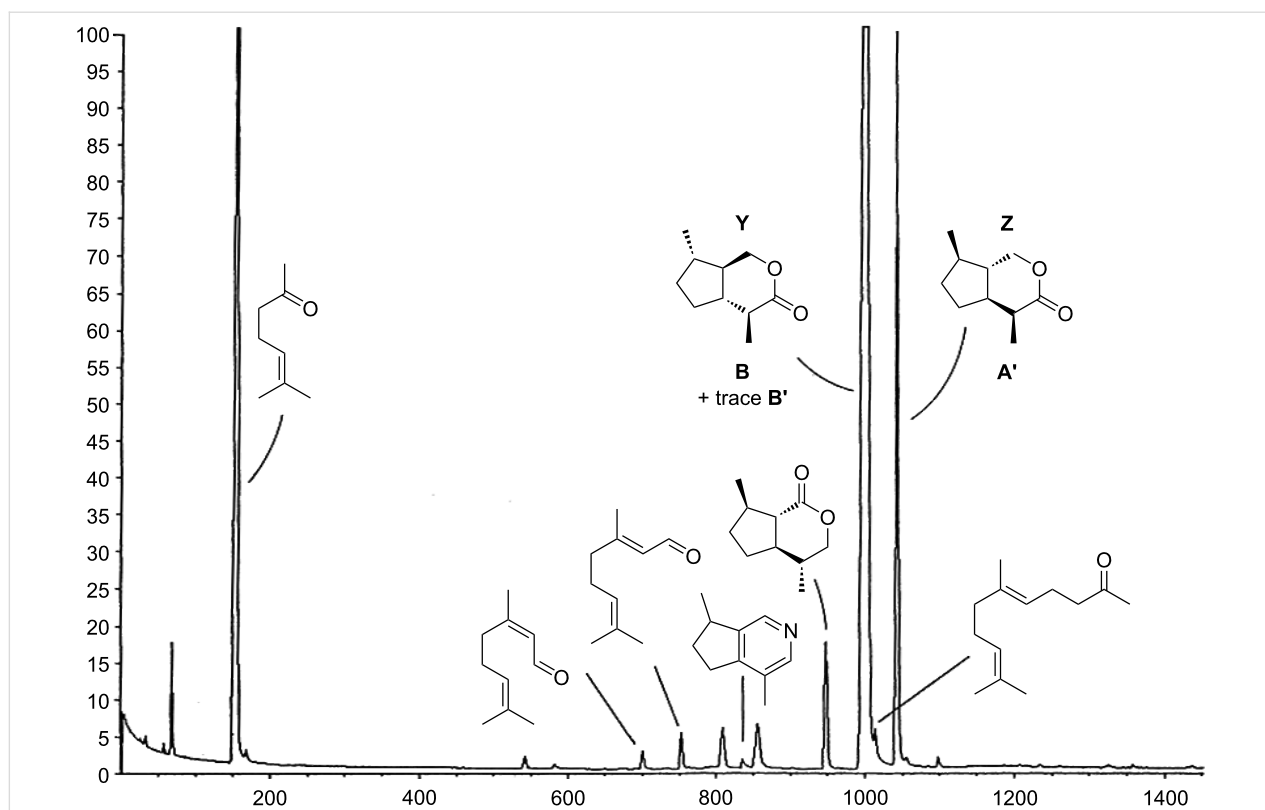


Figure 7: Volatile terpenoids in the cephalic secretion of *Alloxysta victrix*. For the identification of compounds other than Y and Z see [1].

(Figure 1) and a compound with the same relative configuration [21] have been described from insects so far. In contrast to that, the *cis*-fused nepetalactone **15** and diastereomers thereof are typical components of many species of the plant genus *Nepeta* [22,23]. Along with the corresponding hemiacetal **16**, which shows (1*R*)-configuration, **15** is also a most important sex pheromone of aphids [24] (Figure 8). Nevertheless, iridoids are usually associated with defense chemistry. Whilst configurations at the stereogenic centers of **15** and related iridoid lactones in insects appear to be stereotypic, several monocyclic iridoids show further stereochemical variation. Lactol **16** and iridodial (**17**) have first been identified as defense compounds of ants [25]. More recently, **17** – which shows (*R*)-configuration at C1 of the side-chain – was found to be a male-produced aggregation pheromone of lacewings [26,27].

The *cis*-fused iridomyrmecin (**1**) and dolichodial (**18**) are constituents of the anal gland secretion of the Argentine ant *Iridomyrmex humilis* [28]. More recently, (1*S*,2*R*,3*S*)-dolichodial (**18**) has been identified as an electrophysiologically active volatile released from the rosy apple aphid *Dysaphis plantaginea* oviparae and has been discussed apart from **15** and **16** as a possible third component of the aphid sex pheromone [29]. Actually, **18** was first identified in the defensive secretions of dolichoderine ants [25]. The same substance

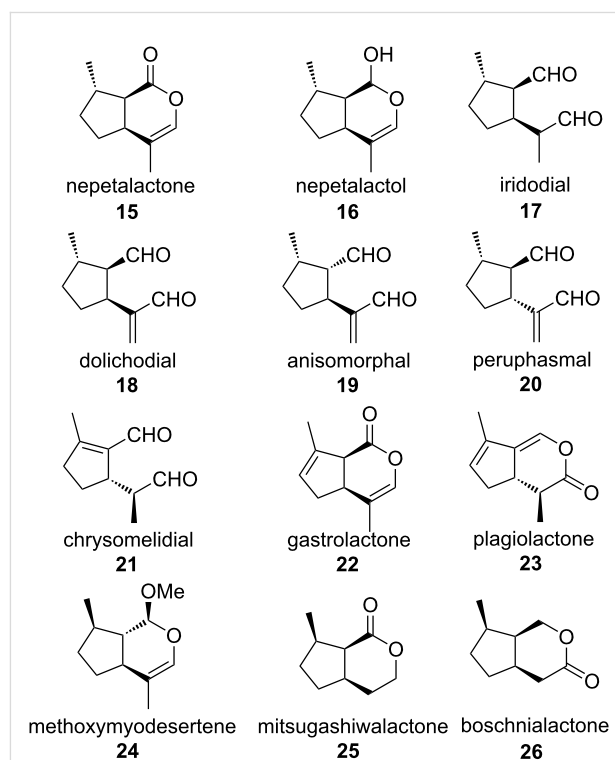


Figure 8: Structures of iridoids from insects and plants. Absolute configurations of **19** and **20** are "educated guesses".

(or its enantiomer) has been found as a defensive compound of *Nematine larvae* [30] and in adults and larvae of the thrips *Calloccithrips fuscipennis* [31]. A stereoisomer of dolichodial – anisomorphal (**19**) – is a component of the defensive secretion of the walking stick *Anisomorpha buprestoides* [32], whilst a third stereoisomer – peruphasmal (**20**) – has been identified in another walking stick, *Peruphasma schultei* [33,34]. Recent investigations show that the qualitative and quantitative composition of cyclopentanoid iridoids in the defensive secretion of *A. buprestoides* may vary with age and population. The secretion may contain all three isomers **18**, **19** and **20** which the insect can produce from glucose [35]. The absolute configurations of **19** and **20** are still unknown. It should be mentioned that along with other iridoids **18** and **19** are also components of the essential oil of some plant species [36]. A related cyclopentene derivative is chrysolimodial (**21**), a relatively widespread defense compound in larvae of phytophagous leaf beetles *Chrysomelidae* [37,38], which has been found in other insects, too. In the defensive secretion of oribatid mites it keeps the depicted (5*S*,8*S*)-configuration [39]. In some species, chrysolimodial is accompanied by the dehydronepetalactone **22** (gastro-lactone) [40] or the didehydroiridomyrmecin **23** (plagiolactone) [37]. To the best of our knowledge, the two iridomyrmecins **Y** and **Z** are new natural products, representing the first *trans*-fused iridoid lactones of this type.

Whilst the *trans*-fused nature of the new iridoid lactones is very unusual, their stereochemical pattern (Figure 7) is even more puzzling: The configurational arrangements of the substituents in **X** and **Y** are strictly opposite, whereas the relations between **X** and **Z** are relatively close, showing inversion at C-4 only. Strangely, **Z** is not the expected C-4-epimer of **Y**, but the C-4-epimer of its enantiomer.

Apart from very few exceptions such as methoxymyodesertene (**24**) [41], the 4-*nor*-nepetalactone mitsugashiwalactone (**25**) [42] and its “*nor*-iridomyrmecin-complement” boschnialactone (**26**), [43] which all are plant volatiles, the methyl group in the typical five-membered ring of iridoids keeps its (*S*)-configuration (see also Figure 8), which is just in contrast to **X** and **Z** [44]. However, recently, two stereoisomers of iridomyrmecin showing (7*R*)-configuration have been reported to be components of the defense chemistry of the *Drosophila* parasitoid *Leptopilina heterotoma* [45].

Remarks on the biosynthesis of iridoids

Today it is generally accepted that the biosynthesis of iridoids starts from the acyclic geraniol (**27**). In a series of careful, elegant experiments it was shown that **27** is oxidized to 8-hydroxygeraniol (**28**) which is further transformed to 8-oxogeraniol (**29**) [46-48] (Figure 9).

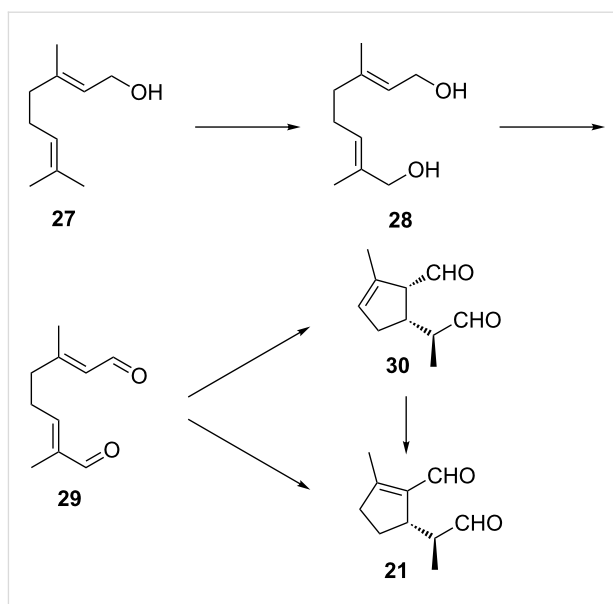


Figure 9: Biosynthetic ways to iridoids from geraniol.

During these investigations the stereochemistry of the subsequent cyclization to iridoids was found to be different in larvae of herbivorous leaf beetles and in carnivorous rove beetles. In *Phaedon cochleariae* (*Chrysomelidae*), cyclization of **29** directly affords chrysolimodial (**21**). In contrast, in *Phylonthus* sp. (*Staphylinidae*) the first step is the formation of plagiodial (**30**), which was first identified from larvae of several leaf beetle species [49,50]. Subsequently, **30** may rearrange to the thermodynamically more stable, conjugated **21**. Despite these results, there are still a lot of open questions concerning the biosynthesis of iridoids. Recently, it could be shown that leaf beetles may produce iridoid monoterpenes *de novo* [33] but they are also able to sequester glycosidically bound terpene precursors from their food plants [51-53] which is highly interesting with regards to the evolution of insect-plant relationships and insect defense chemistry. At present, nothing is known about the formation of “saturated” iridoids such as iridodial (**17**) or the iridoid lactones in *Alloxysta*. The strange stereochemical relations between these compounds may well be the result of different mechanisms in the enzymatic hydrogenation steps.

Conclusion

The new iridoid lactones have been found in the mandibular gland secretions of several *alloxystine* wasps [54] and their activity in intraspecific and interspecific communication has been discussed [55]. According to first bioassays, the new iridoids seem to play a multifunctional role in the tritrophic system of the aphid *Sitobion avenae*, its parasite, the wasp *Aphidius uzbekistanicus*, and the hyperparasitoid *Alloxysta vitrix* as they obviously sedate *Sitobion* and repel *Aphidius*.

However, additional bioassays will be needed to better understand the biological significance of the newly identified iridoid lactones. As our way from limonene to iridoids provides relatively easy access to a large variety of iridoid lactones and monocyclic iridoids, behavior experiments using synthetic compounds may shed some more light on the complex relationships between host aphids, primary parasitoids such as *Aphidius* spp., and aphid hyperparasitoids such as *Alloxyysta* spp. [56].

Supporting Information

Supporting Information File 1

Experimental details and characterization data for synthesized compounds.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-141-S1.pdf>]

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