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Synthesis of 9-Propyl-10-azacyclododecan-12-olide

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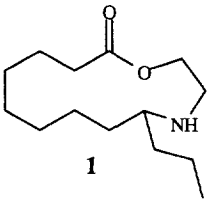
Abstract: 9-Propyl-10-azacyclododecan-12-olide, a minor component of the defensive secretion of the Mexican bean beetle *(Epilachna varivestis)* was synthesized via a reductive amination of methyl 9-ketododecanoate (**3**) followed by lactonization. This azamacrolide proved deterrent to ants, but was significantly less active than the pupal defensive secretion itself.

Some of the most intriguing alkaloids isolated from coccinellid beetles are the azamacrolides, identified in 1993 by Attygalle and coworkers.[1] This family of macrocyclic lactones was found in the oil secreted from glandular hairs covering *Epilachna varivestis* pupae. Observations of foraging ants (*Leptothorax longispinosus*) encountering these pupae indicated that the secretion was defensive. Gas-chromatographic analysis of the secreted oil showed five volatile components, each of which was identified by a combination of NMR studies, mass specral data, and infrared spectroscopy.[1]

The component present in the defensive secretion in the smallest amount was identified as 9-propyl-10-azacyclododecan-12-olide (**1**), a fully-saturated thirteen-membered lactone which also contains a secondary amine α to a stereogenic center. Due to the small amount of this material in the pupal secretion (0.2%), the structure of **1** was based only on a comparison of its GC-MS fragmentation with that of the major component (90.9%), epilachnene (**2**), whose structure was firmly established.[1] Because of its structural simplicity, **1** was



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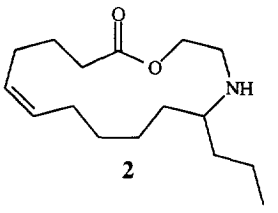

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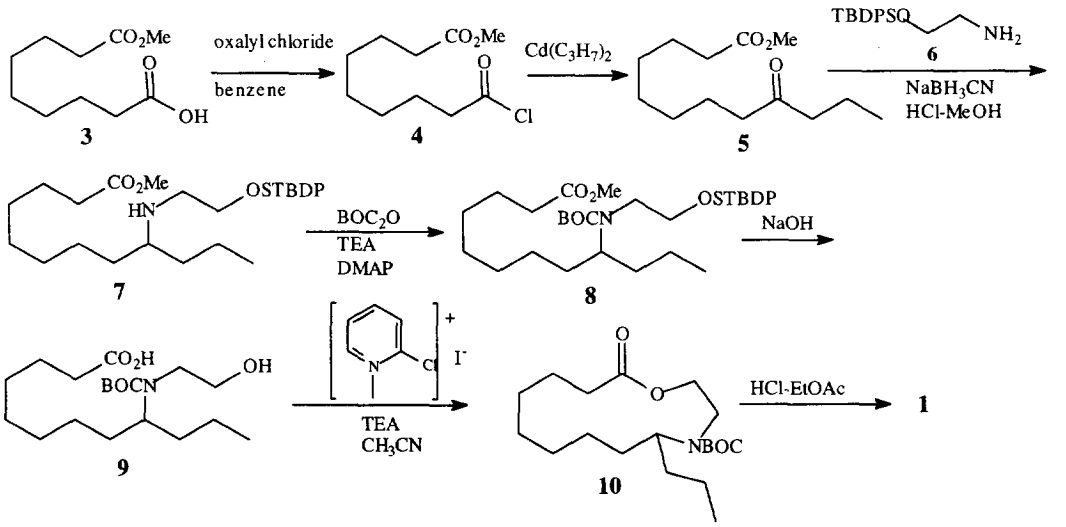
chosen as an initial synthetic target, and our approach involved introduction of the amino functionality by reductive amination and lactonization to form the macrocyclic ring. While this work was in progress, the first synthesis of (±)-9-propyl-10-azacyclododecan-12-olide was completed by Rao *et al.* [2] Gribble and Silva have also completed an imaginative synthesis of this macrocycle, and their work is detailed in the accompanying Letter.[3]

Treatment of a refluxing benzene solution of commercially available azaleic acid monomethyl ester **3** with excess oxalyl chloride cleanly afforded acid chloride **4**, which was purified by vacuum distillation.[4] This acid chloride was then converted to ketoester **5** (72% after distillation) using Cason's organocadmium methodology.[5,6] Employing standard reductive amination conditions (pH 5.5, excess amine),[7,8] ketoester **5** was treated with 1-*t*-butyldiphenylsiloxy-2-aminoethane (**6**), prepared from ethanolamine and *t*-butyldimethylsilyl chloride,[9,10] to afford amine **7** (70%). Amine **7** was transformed into the corresponding carbamate **8** by treatment with di-*t*-butyl dicarbonate, 4-(dimethylamino)pyridine, and triethylamine (82%)[11] before simultaneous base hydrolysis of the ester and silyl ether groups to give the desired hydroxyacid **9**. Protection of the amino group was necessary to prevent formation of lactam during cyclization.

Scheme 1



Mukaiyama's salt, 2-chloro-1-methylpyridinium iodide, previously used to form thirteen-member lactones under mild conditions in relatively good yield,[12] was the reagent of choice for the closing of the macrocycle. Using this reagent, protected lactone **10** was obtained as a clear oil from hydroxyacid **9** in 43%

yield, with little dimeric lactone detected.[13] With this material in hand, only deprotection was needed to complete the synthesis of the natural product. Treatment of **10** with HCl-EtOAc followed by flash chromatography afforded **1** as a clear oil in 97% yield.[14] This synthetic material was indistinguishable from the natural lactone in both gas chromatographic retention time and mass spectral fragmentation pattern and was completely characterized by ^{1}H and ^{13}C NMR spectroscopy.

Bioassays with ants (*Lepthothorax longispinosus*), carried out in accord with a previously described protocol,[15] proved 9-propyl-10-azacyclodecan-12-olide to have anti-insectan activity. The assay involves presenting individual colonies of the ant with a choice of untreated edible moth eggs, and comparable eggs treated by topical addition of test substance (10 colonies are tested per sample). *E. varivestis* pupal secretion (100-glandular hair equivalent per egg) was found to be absolutely deterrent to the ants (no eggs taken). Addition of compound **1**, at a substantial dosage (1 μg per egg), was only moderately deterrent (egg acceptibility reduced to about 40%), no more deterrent, in fact, than a markedly lesser amount (10-glandular hair equivalent) of actual secretion. Compound **1** can therefore account for only part of the activity of the natural mixture.

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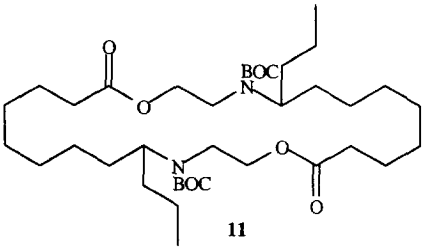
13. Employing Mukaiyama's reported conditions, initial attempts at cyclization of **8** gave only recovered starting material and dimeric product **11**, characterized by NMR and mass spectral data. Upon increasing the dilution of the reactants, the desired lactone **10** was obtained.



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