

Synthesis of the Octahydro-8b-azaacenaphthylene Ring System, A Portion of the Dimeric Coccinellid Alkaloids

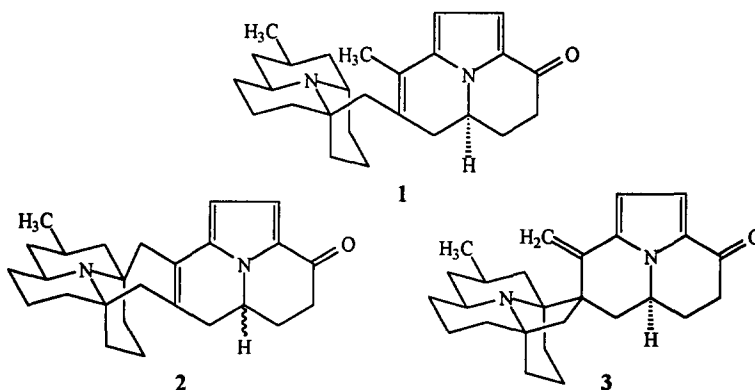
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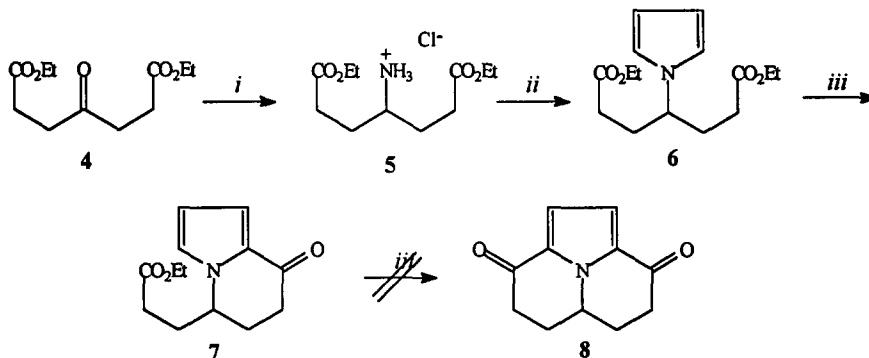
Abstract: The "dimeric" coccinellid alkaloids exochomine (1), chilocorine A (2), and chilocorine B (3) represent a challenging set of synthetic targets. An interesting structural feature of these alkaloids is the novel 3,4-disubstituted octahydro-8b-azaacenaphthylene ring system. Representatives of this ring system have been synthesized and functionalized for possible use in a synthetic approach to these alkaloids. Copyright © 1996 Elsevier Science Ltd

The "dimeric" coccinellid alkaloids, typified by exochomine¹ (1), are structurally complex defensive compounds present in the blood of certain ladybird species. The saturated, tricyclic portion of 1 corresponds to the 2-methylperhydro-9b-azaphenalene ring system, a common motif in many coccinellid alkaloids². The highly conjugated tricyclic portion of 1 is closely related to 3,4-dimethyloctahydro-8b-azaacenaphthylene, a ring system which may represent an as yet undiscovered family of non-basic, tricyclic coccinellid secondary metabolites. Exochomine (1), the heptacyclic chilocorine A³ (2), and the spirocyclic chilocorine B⁴ (3), constitute a challenging set of synthetic targets. We report now on the synthesis of several representatives of the azaacenaphthylene ring system with functionalization appropriate for future use in coupling to a suitable azaphenalene partner.



Our approach required amine hydrochloride 5, which was obtained⁵ in 44% yield from the commercially available (Aldrich) diethyl 4-oxopimelate (4) using the reductive amination technique described by Borch⁶ (Scheme 1). The moderate yield is comparable to that obtained in similar examples. Using Jefford's approach⁷, treatment of 5 with 2,5-dimethoxytetrahydrofuran and sodium acetate in hot glacial acetic acid with subsequent flash chromatographic purification gave pure pyrrole 6 in 83% yield. Reaction of 6 with boron tribromide as a Lewis acid catalyst afforded acyl pyrrole 7 in 92% yield. Not unexpectedly, a second equivalent

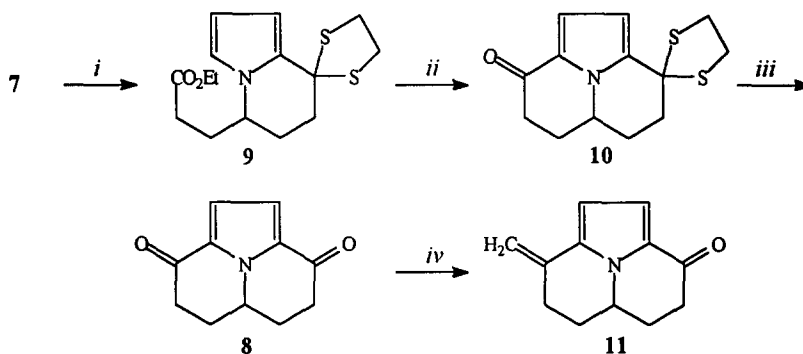
of boron tribromide failed to give the diketone **8**, since the acyl pyrrole **7** is too deactivated to undergo an electrophilic acylation.



Reaction Conditions : *i*. a. NH_4OAc , NaCNBH_3 , MeOH, HOAc, pH 5; b. HCl (g), ether; *ii*. 2,5-dimethoxytetrahydrofuran, NaOAc, HOAc, *iii*. BBR_3 (1M in CH_2Cl_2), CH_2Cl_2 .

Scheme 1

Protection of the carbonyl group of **7** would be expected to eliminate the deactivation of the pyrrole ring and thereby facilitate a second ring closure. Formation of thioketal **9** in 69% yield was accomplished using a modification of a procedure of Wallace *et al.*⁸ (Scheme 2). Under the previously described conditions for ring closure, **9** was cyclized to acyl pyrrole **10** in 84% yield. This mono-protected product is a useful synthetic building block for subsequent transformations.

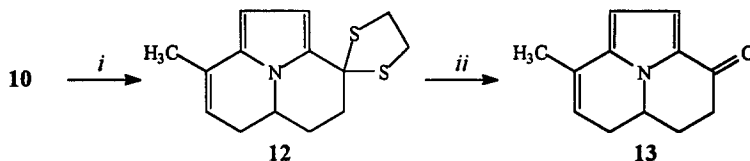


Reaction Conditions : *i*. 1,2-ethanedithiol, EtOH, aniline hydrochloride; *ii*. BBR_3 (1M in CH_2Cl_2), CH_2Cl_2 , *iii*. $\text{Tl}(\text{NO}_3)_3 \cdot 3\text{H}_2\text{O}$, MeOH, THF, 0°C ; *iv*. $\text{Ph}_3\text{P}^+\text{CH}_3\text{I}^-$, potassium *t*-butoxide, toluene.

Scheme 2

Deprotection of dithioketal **10** using thallium (III) nitrate⁹ gave diketone **8** in 65% yield. Treatment of **8** with the methylene Wittig reagent, prepared by a modification of Dauben's procedure¹⁰, gave the exocyclic methylene compound **11** (possessing the ultraviolet chromophore of **3**) in 36% yield. The isomeric endocyclic alkene **13**, corresponding to the ultraviolet chromophore of **1** and **2**, was synthesized *via* a Wittig reaction of

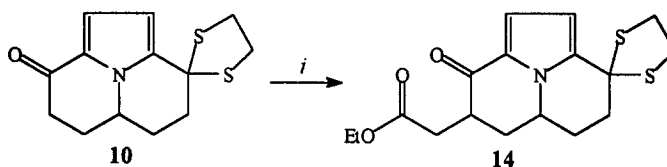
10, which was accompanied by migration of the exocyclic double bond to give **12** in 65% yield (**Scheme 3**). Removal of the thioketal protecting group as previously described gave **13** in 59% yield.



Reaction Conditions : *i.* $\text{Ph}_3\text{P}^+\text{CH}_3\text{I}$, potassium *t*-butoxide, toluene; *ii.* $\text{Tl}(\text{NO}_3)_3 \cdot 3\text{H}_2\text{O}$, MeOH, THF, 0°C .

Scheme 3

Our attention then turned to functionalizing the azaacenaphthylene ring system to produce intermediates which might have utility in the synthesis of **1** itself. In a model alkylation, **10** was treated with LDA and ethyl bromoacetate to give acyl pyrrole **14** in 33% yield (**Scheme 4**).

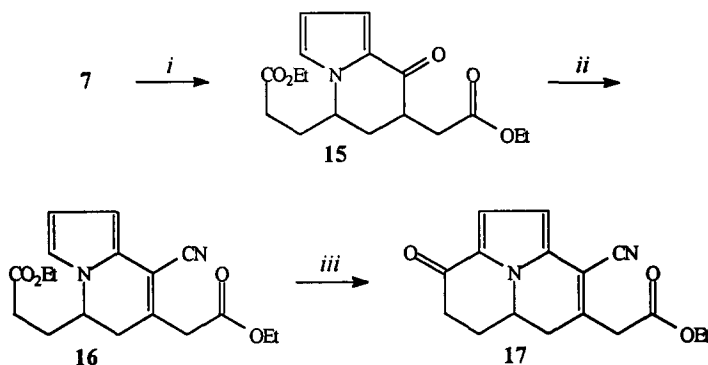


Reaction Conditions : *i.* a. LDA, THF; b. ethyl bromoacetate.

Scheme 4

Another approach to a suitably functionalized ring system involved starting with the bicyclic pyrrole **7** to avoid the thioketal protection/deprotection sequence. Acyl pyrrole **7** was treated with LDA and alkylated with ethyl bromoacetate to give an 88% yield of pyrrole **15** (**Scheme 5**). Treatment of **15** with trimethylsilyl cyanide and a catalytic amount of zinc iodide gave a trimethylsiloxy nitrile which spontaneously decomposed giving a 35% yield of the desired α, β -unsaturated nitrile **16**. Although, according to the precedent of Oda *et al.*¹¹, phosphoryl chloride and pyridine are required to effect this elimination, in this instance, the strong driving force for extending conjugation evidently facilitates this reaction. Pyrrole **16** is no longer deactivated to acylation, and boron tribromide catalyzed ring closure gave a 51% yield of acyl pyrrole **17**, with the desired functionalized azaacenaphthylene ring system.

We hope that it will prove possible to couple some of these azaacenaphthylenes with suitably functionalized azaphenalenes once these coupling partners can be conveniently prepared.



Reaction Conditions : *i.* a. LDA, THF, b. ethyl bromoacetate; *ii.* TMSCN, ZnI₂, benzene; *iii.* BBr₃, CH₂Cl₂.

Scheme 5

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