Total Synthesis of the Coccinellid Alkaloid (±)-Adalinine Utilizing a Nitrenium Ion Cyclization

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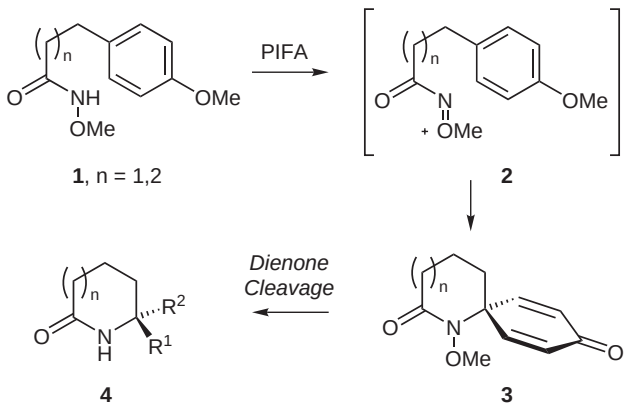
Abstract: The total synthesis of (±)-adalinine, a piperidine alkaloid from the European two-spotted ladybird *Adalia bipunctata*, is reported. Central to this undertaking are (i) the use of an *N*-alkoxy-*N*-acylnitrenium ion-induced spirocyclization to rapidly access the 6,6′-disubstituted piperidinone ring of the natural product and (ii) exploitation of the cyclohexa-2,5-dienone system generated in this process as a latent 1,6-ketoaldehyde.

Key words: adalinine, piperidine alkaloid, nitrenium ions, dearomatization, polyvalent iodine

Nitrenium ions are highly reactive intermediates, which contain a divalent, positively charged nitrogen atom. Although historically the primary motivation for studying nitrenium ions has been their proposed role in the carcinogenesis initiated by nitro and amino-aromatic compounds, they have also garnered attention from a synthetic standpoint.[1] Despite this interest however, the application of nitrenium ions to complex target-directed synthesis has hitherto been limited,[2] in part, by the harsh conditions often required for their generation and the complication of multiple reaction pathways which can result in modest yields.[3] In this context, *N*-alkoxy-*N*-acylnitrenium ions of general structure **2** (Scheme 1) are notable since they efficiently undergo azaspirocyclization to form 1-azaspiro-[4.5]decane and -[5.5]undecane systems **3** in excellent yield.[4] Furthermore, they can be generated under mild conditions by the treatment of *O*-alkylhydroxamates **1** with iodine(III) reagents.[2a,g]



Scheme 1 Nitrenium ion spirocyclization-dienone cleavage: A novel route to α,α-disubstituted *N*-heterocycles.

Having recently reported the first application of this reaction to the synthesis of 1-azaspiro[4.5]decane-based natural products,[5] we became attracted to the possibility that cleavage of one, or more, of the C-C bonds in the cyclohexa-2,5-dienone ring present in **3** would also provide an expeditious means of accessing a range of α,α-disubstituted pyrolidinone and piperidinone derivatives **4**, including the natural product adalinine (**5**, Figure 1).

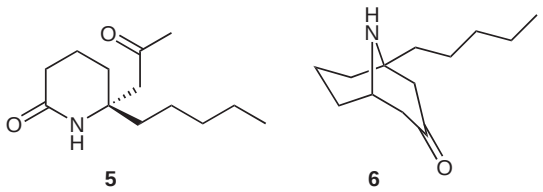


Figure 1 Adalinine (**5**) and adaline (**6**): Coccinellid alkaloids isolated from *Adalia bipunctata*.

The piperidine nucleus is a ubiquitous structural motif present in a diverse range of naturally occurring alkaloids and synthetic compounds, many of which are imbued with important biological activities.[6] Adalinine (**5**) is an alkaloid which was isolated from the hindquarters of the European two-spotted ladybird beetle, *Adalia bipunctata*, in 1996.[7] Although the biological activity of **5** has not been disclosed, biosynthetic studies have revealed that this piperidinone derivative is a biogenetic precursor of the homotropane alkaloid adaline (**6**),[8] which, when excreted by the ladybird beetle, acts as an antifeedant against insects and invertebrate predators.[9] The presence of an asymmetric nitrogen-bearing quaternary stereocenter in **5** coupled with the interest in the development of methods for the formation of such moieties has precipitated considerable synthetic interest in this natural product.[10] Herein, we report the total synthesis of **5** utilizing an *N*-acylnitrenium ion spirocyclization.

As illustrated in Scheme 2, we envisioned that **5** would be accessible through chemoselective homologation of 1,6-ketoaldehyde **7** which in turn could be accessed from **8** through a sequence involving oxidative cleavage of the C(8′)-C(9′) bond. This spirolactam could then be prepared through cyclization of the nitrenium ion generated from amide **9**.

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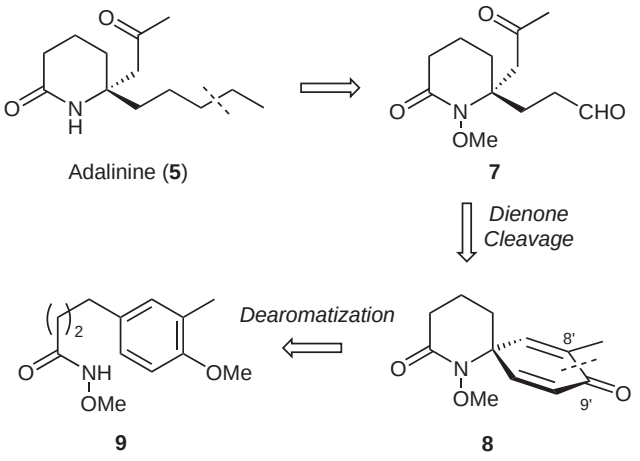
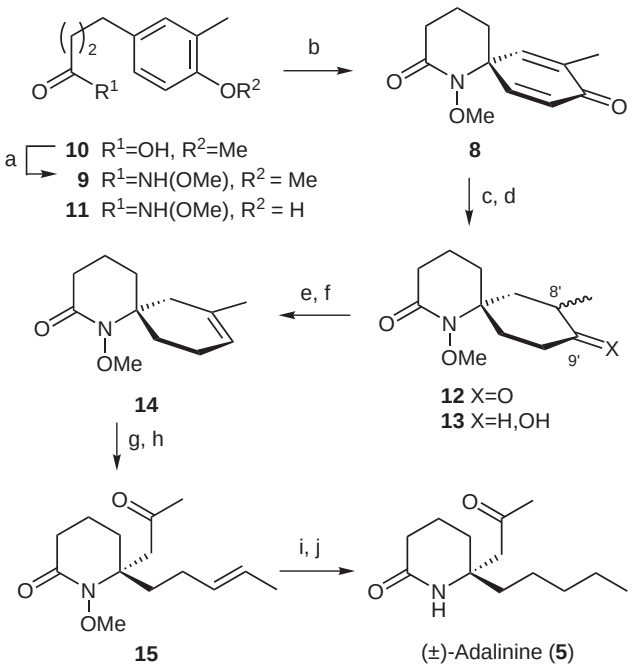


Scheme 2 Retrosynthetic analysis of adalinine.



Scheme 3 Total synthesis of (±)-adalinine. *Reagents and conditions*: (a) *i*-BuOCOCl, Et_3N, –20 °C to 0 °C; $MeONH_2$·HCl, Et_3N, 0 °C, 1 h (quant.); (b) **9**, PIFA, CH_2Cl_2–MeOH (1:1), –78 °C to 15 °C, 1.5 h then H_2O, 10 min (90%); (c) H_2 (1 atm.), PtO_2 (1%, w/w), EtOAc, 24 h (70%); (d) $NaBH_4$, MeOH, –30 °C to 0 °C (95%); (e) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 30 min (90%); (f) 100 °C, DMSO, 24 h (64%); (g) O_3/O_2, CH_2Cl_2, –78 °C, 5 min; Me_2S, r.t., 24 h (74%); (h) $CrCl_2$ (4.1 equiv), CH_3CHI_2 (1.1 equiv), DMF (1 equiv), THF, r.t., 4 h (53%); (i) H_2 (1 atm.), 10% Pd/C, EtOAc, r.t., 6 h (100%); (j) $Mo(CO)_6$, CH_3CN–H_2O (15:1), reflux, 30 h (98%).

Our synthetic route to adalinine (**5**) commenced from known carboxylic acid **10**,[11] which was converted to the corresponding mixed anhydride and coupled in situ with *O*-methylhydroxylamine, to provide *N*-methoxyamide **9** in quantitative yield (Scheme 3). Upon treatment of a solution of this compound in CH_2Cl_2 and MeOH with one equivalent of phenyliodine(III) bis(trifluoroacetate) (PIFA), azaspirocyclization proceeded smoothly to afford dienone **8** in excellent yield after in situ hydrolysis of the dimethyl acetal intermediate.[5,12] Notably, this type of azaspirocyclization can be accomplished without recourse to expensive non-nucleophilic solvents, such as trifluoroethanol and hexafluoroisopropanol. In contrast, the oxidative spirocyclization of phenolic substrates, such as amines and carboxylic acids, often requires the use of such solvents to prevent competitive intermolecular capture of the arenium intermediate.[13]

Having established the piperidinone ring and nitrogen-bearing quaternary center, we now directed our attention to converting **8** to advanced intermediate **7**, by way of olefin **14**. Thus, atmospheric hydrogenation of **8** in the presence of Adams catalyst (PtO_2) furnished cyclohexanone **12** as a chromatographically inseparable 4:1 mixture of C-8′ epimers (^{1}H NMR). Smaller quantities of phenol **11** (20%) and alcohol **13** (10%) were also isolated from this reaction. While **11** presumably arises through reductive rearomatization of spirodienone **8**,[14] compound **13** appears to be formed from reduction of **12**. Hydrogenation of **8** for extended periods led to an increase in the yield of alcohol **13** with a concomitant drop in the yield of **12**. Although in the context of our planned route to **14**, the direct formation of **13** from **8** was fortuitous, efforts to optimize this process failed to yield satisfactory results. Hydrogenation of the ketone proved to be impractically slow with PtO_2, while other heterogeneous catalysts, including Pd/C, $Pd(OH)_2$, and Raney nickel, favored the rearomatization process. Accordingly, ketone **12** was simply reduced with sodium borohydride in MeOH to provide **13** as a complex mixture of diastereomers. Given that the stereochemistry of the C-8′ and C-9′ stereocenters did not have a direct bearing on our synthesis, this material was carried forward and converted to the corresponding mixture of mesylate esters with MsCl and Et_3N. Upon thermolysis (100 °C) in a solution of DMSO, this mixture of compounds underwent regioselective elimination to provide trisubstituted olefin **14** together with a small amount of its disubstituted regioisomer (ca. 10%). Ozonolytic cleavage of **14**, followed by reductive workup with Me_2S provided ketoaldehyde **7** (Scheme 2) as a single compound. The remaining carbon atoms present in the natural product were then installed via chemoselective Takai ethylidenation using the *gem*-dichromium reagent generated by the reaction of 1,1-diiodoethane with chromium(II) chloride.[15] Pd-catalyzed hydrogenation of **15** now served to reduce the C-6 pentenyl side chain, but failed to cleave the *N*-methoxyl substituent. Selective reduction of the N-O bond was, however, efficiently accomplished by heating the hydrogenation product with one equivalent of $Mo(CO)_6$ in aqueous acetonitrile.[16] Although slow; this reaction proceeded smoothly to provide (±)-adalinine (**5**) in excellent yield. The spectroscopic and physical data (^{1}H NMR, ^{13}C NMR, MS) of this synthetic material were identical to those previously reported.[17]

In summary, we report a total synthesis of the ladybird alkaloid adalinine (**5**), which proceeds in ten steps and with a 13% overall yield. The central features of this work

include i) construction the 6,6′-disubstituted piperidinone ring using an *N*-alkoxy-*N*-acylnitrenium ion-induced spirocyclization and ii) exploitation of the cyclohexa-2,5-dienone generated in this transformation as a latent 1,6-dicarbonyl. Further application of the nitrenium ion spirocyclization-dienone cleavage strategy outlined herein is now underway in this laboratory. Our progress will be reported in due course.

Acknowledgment

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(12) **Experimental Procedure for Preparation of Dienone 8:** To a suspension of phenyliodine(III) bis(trifluoroacetate) (PIFA) (2.290 g, 5.16 mmol) in MeOH (10 mL), at –78 °C, was added a cold (–78 °C) solution of *N*-methoxyamide **9** (1.020 g, 4.30 mmol) in CH_2Cl_2 (10 mL) via cannula. The reaction mixture was then allowed to warm to 15 °C (internal temperature) over 1.5 h whereupon H_2O (10 mL) was added and the cooling bath removed. After stirring for 10 min, the organic and aqueous phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure and the residue purified by flash chromatography over silica gel (EtOAc/hexanes, 1:1) to provide **8** (855 mg, 90%) as a colorless oil. Recrystallization from EtOAc/hexanes yielded **8** as white crystals: Mp 97–99 °C. R_f = 0.35 (EtOAc). FT-IR(film): ν_{max} = 2933(br), 1674, 1642, 1445, 1376, 1071, 939, 823 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.89 (dd, *J* = 10.0, 3.2 Hz, 1 H) 6.70–6.68 (m, 1 H), 6.32 (d, *J* = 10.0 Hz, 1 H), 3.72 (s, 3 H), 2.59 (t, *J* = 2.6 Hz, 2 H), 2.07–1.99 (m, 2 H), 1.96–1.90 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.3, 168.4, 148.6, 143.9, 136.7, 129.9, 64.5, 64.0, 35.8, 33.3, 18.4, 15.9. HRMS-EI calcd for $C_{12}H_{15}NO_3Na$ $[M + Na]^+$: 244.0950. Found: 244.0940. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.21; H, 6.84; N, 6.34.

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(17) **Data for Synthetic (±)-Adalinine (5):** Colorless oil; R_f = 0.23 (EtOAc); FT-IR(film): ν_{max} = 3380, 3206, 2930, 2862, 1712, 1657, 1458, 1402, 1363 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.62 (br s, 1 H), 2.70 (d, *J* = 17.8 Hz, 1 H), 2.64 (d, *J* = 17.8 Hz, 1 H), 2.33–2.27 (m, 2 H), 2.14 (s, 3 H), 1.83–1.54 (m, 6 H), 1.31–1.21 (m, 6 H), 0.88 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.5, 171.7, 56.4, 51.5, 39.4, 32.1, 32.0, 31.6, 31.4, 24.1, 22.7, 17.4, 14.2. HRMS-EI calcd for $C_{13}H_{23}NO_2Na$ $[M + Na]^+$: 248.1610. Found: 248.1616.