On the Stereochemistry of the Robinson–Schöpf Reaction. A Stereospecific Total Synthesis of the Ladybug Defense Alkaloids Precoccinelline and Coccinelline

Robert V. Stevens* and Albert W. M. Lee

Contribution from the Department of Chemistry, University of California, Los Angeles, California 90024. *Received May 18, 1979*

Abstract: A stereospecific total synthesis of the ladybug defensive alkaloids coccinelline (**1**) and precoccinelline (**2**) is presented. A key step in this synthesis involves a Robinson–Schöpf type of condensation between amine dialdehyde equivalent **32** and acetone dicarboxylic ester to afford **37.** A rationale for this stereochemical course is presented.

There are some 4300 known species of the ladybug family (*Coccinellidae*). Many are known to play a beneficial ecological role in controlling populations of harmful insects such as aphids, mealy bugs, and scale insects. A particularly dramatic example of their value to man occurred in California in the late 1800's. At that time the cottony cushion insect (*Icerya purchasi*) was accidently introduced into this state from Australia. These voracious pests multiplied rapidly in their new environment and soon killed thousands of valuable citrus trees. Orchardists stood by helplessly until entomologists enlisted a reddish ladybug (*Rodolia cardinolis*) from the invader's homeland. Within 2 years these friendly allies had conquered the threat. The total cost for this service was about $1,500!—an investment which saved an industry worth well over a hundred million dollars today.[1]

Ladybugs have few natural enemies. This can be attributed, in part, to a highly developed and remarkable defense mechanism. When molested or disturbed they emit droplets of a fluid from the joints. This process, known as "reflex bleeding", serves as an efficient deterrent to would-be predators. In 1971 Tursch and his collaborators were the first to report on the chemical constitution of this fluid.[2] They were able to isolate from 1600 common European ladybugs (*Coccinella septempunctata*) 135 mg of a white crystalline substance ($C_{13}H_{23}NO$) which efficiently repelled ants (*M. rubra*). The structure of this substance, termed coccinelline, was soon established as **1** by a single-crystal X-ray diffraction study.[3] After this initial breakthrough, this Belgian team investigated other species of European ladybugs. Further pioneering studies were forthcoming from the Ayer group who examined various species of ladybugs indigenous to western Canada. To date, eight alkaloids have been isolated. Their structures and some important chemical interconversions are shown in Diagram I.[4]

In contemplating the synthesis of these substances it should be noted that the methyl group occupies the thermodynamically more stable equatorial position in each of the alkaloids. Inspection of the preferred conformation of each of the perhydro[9*b*]azaphenalene bases, precoccinelline (**2**), myrrhine (**4**), and hippodamine (**6**), suggests that myrrhine is the thermodynamically most stable and that precoccinelline and hippodamine should be of comparable stability. These conclusions are supported by the synthetic studies of Ayer[5] wherein **10** (Diagram II) was prepared stereoselectively from *sym*-collidine. When exposed to 2 equiv of *p*-toluenesulfonic acid in hot toluene, water is extruded to generate intermediate **11.** Inspection of the conformation (**11b**) of this intermediate reveals two possible modes for subsequent ring closure. Attack from the top face of the molecule would generate the thermodynamically less stable precoccinelline stereochemistry (**12**) was not observed. Instead ketone **13** (corresponding to the thermodynamically favored myrrhine stereochemistry) was the sole product isolated in high yield. Ayer reasoned that the conditions employed in this reaction were sufficiently drastic

Diagram I

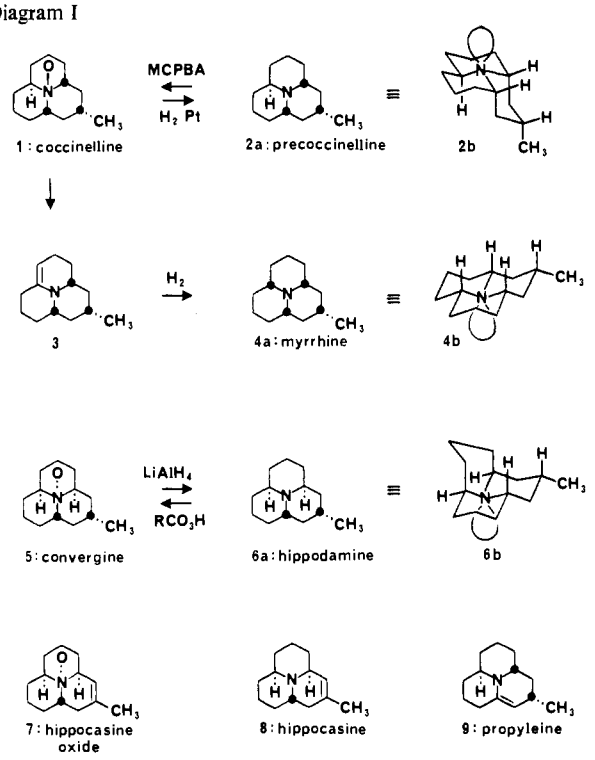

Diagram II

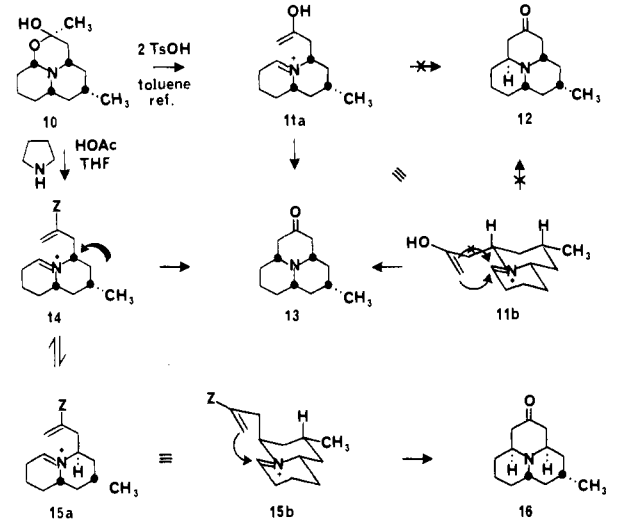

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Diagram III

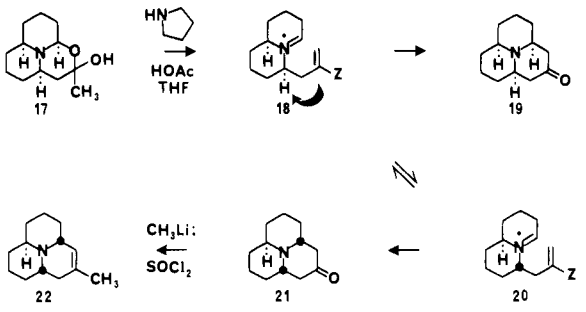
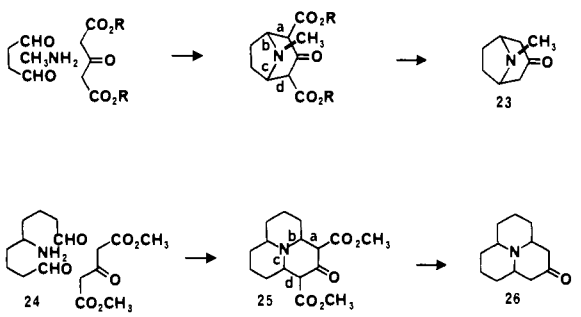


Diagram IV

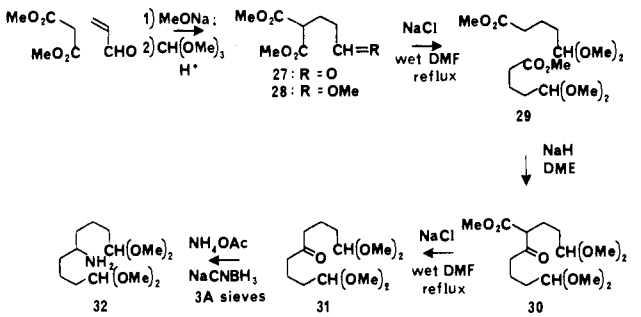


to inhibit any chance of obtaining the precoccinelline stereochemistry. Accordingly, other milder methods were investigated. When **10** was heated with pyrrolidine and acetic acid in tetrahydrofuran, two ketones were isolated. One proved to be the same ketone (**13**) obtained from the previous experiment. However, the second stereoisomeric ketone proved *not* to be **12** but rather **16.** The latter substance [which lead ultimately to hippodamine (**6**)] arose fron an (unexpected) epimerization of **14** at the center indicated to provide **15.** Although this equilibrium would be expected to be unfavorable, inspection of conformation **15b** reveals that, when the side chain is axial, it is ideally disposed for facile ring closure. All efforts to effect the conversion of **10** to the elusive precoccinelline ketone **12** failed.

At this stage the Canadian group astutely realized that the unexpected epimerization of **14** mentioned above might constitute a method for securing the elusive precoccinelline stereochemistry. Accordingly, hemiketal **17** was prepared in good overall yield from 2,6-lutidine.[5b] When this substance was subjected to the conditions described above, two isomeric ketones were isolated in equal amounts. One of these, **19,** possessed the expected all-cis stereochemistry and provided another route to myrrhine (**4**). The other, **21,** arose from the now desirable epimerization of **18** to afford intermediate **20.** As in the **14** to **15** case, this otherwise unfavorable equilibrium provides an intermediate with ideal geometry for facile ring closure. The synthesis of precoccinelline was completed by conversion of **21** to the air-sensitive olefin **22** followed by catalytic hydrogeneation.

Our interest in the synthesis of these alkaloids (especially the challenging coccinelline stereochemistry) arose from a consideration of the classic Robinson-Schöpf synthesis of tropinone (**23**).[6] Even by contemporary standards, this reaction constitutes a remarkably efficient method of bond construction. No fewer than four new bonds (a–d) are established in a single process—a fact not ignored by Nature itself in the biosynthesis of the tropane alkaloids! We had no doubt that this efficient methodology could be used to generate the perhydro[9*b*]-azaphenalene ring system found in the ladybug alkaloids. Thus, reaction of amine dialdehyde **24** (or an equivalent thereof) with acetone dicarboxylic ester could be predicted with confidence to produce the perhydro[9*b*]azaphenalene **25** and thereafter tricyclic ketone **26.** As appealing as this prospect was, further

Diagram V



analysis revealed a number of very serious potential dangers. To begin with, no less than five chiral centers are produced in this reaction from achiral starting materials! This brought us face to face with the first fundamental question, mainly, what is the stereochemistry of the Robinson-Schöpf reaction? Curiously, after all these years, this question has never really been answered. A second crucial aspect of the same basic question concerns the reaction conditions. If we select as our target coccinelline, then the results of Ayer discussed above clearly require a kinetically controlled and nonreversible reaction. Although removal of the two esters in the transformation of **25** to **26** reduces to three the number of chiral centers, these readily epimerizable centers might interfere with isolation and purification procedures. Also, the conditions required to remove these groups must be selected carefully to avoid potentially menacing retro-Mannich or retro-Michael reactions which might scramble the remaining asymmetric centers. With these thoughts and challenges in mind we turned our attention to the synthesis of the requisite amino dialdehyde **24.**

Amino dialdehyde **24** was prepared (as its dimethyl acetal **32**) by the route shown in Diagram V. Thus, reaction of malonic ester with acrolein afforded **27** which was protected as its dimethyl acetal, **28.** Decarbomethoxylation under neutral conditions[7] provided ester **29.** The latter substance had been prepared previously[8] by an alternative route which was not as convenient as the method described here. Self-Claisen condensation of **29** afforded β-ketoester **30** which was decarbomethoxylated as described above[7] to give ketone **31.** Reductive amination of **31** was effected by the method of Borch.[9] It should be noted that the employment of 3A molecular sieves was decisive in achieving a high yield of **32.** With adequate supplies of **32** in hand we turned our attention to the crucial step.

Intermediate **32** was hydrolyzed with hydrochloric acid at pH 1. The pH of the solution was adjusted to 5.5 and buffered with a citrate-phosphate buffer. Then, a solution of acetone dicarboxylic ester in the same buffer was added dropwise at room temperature. Under these conditions *a single isomer crystallized directly from the reaction mixture in good yield.* The structure and stereochemistry of this product were established firmly from its infrared and ^{13}C NMR spectra as **37** as well as from other data. If one ignores for the moment the ester moieties, there are three possible perhydro[9*b*]azaphenalene stereoisomers (cf. **2b, 4b,** and **6b**). Of these, only that stereochemistry corresponding to myrrhine (**4a**) is capable of satisfying the stereoelectronic requirements for absorption in the 2700–2800-cm^{-1} region (Bohlmann bands).[10] The absence of such absorption in our intermediate allowed us to rule out this possibility. Since this stereochemistry corresponds to the thermodynamically most stable arrangement we could also be certain that we were dealing with a kinetically controlled process. A distinction between the remaining two possible stereoisomeric perhydro[9*b*]azaphenalenes (**2b** and **6b**) could be made from the ^{13}C NMR spectrum of our intermediate which showed only nine lines as would be expected for a meso compound. The only other structure which can satisfy both of

Diagram VI

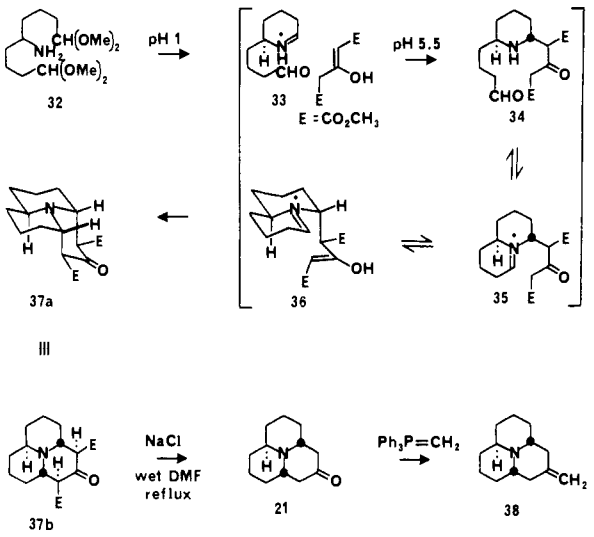
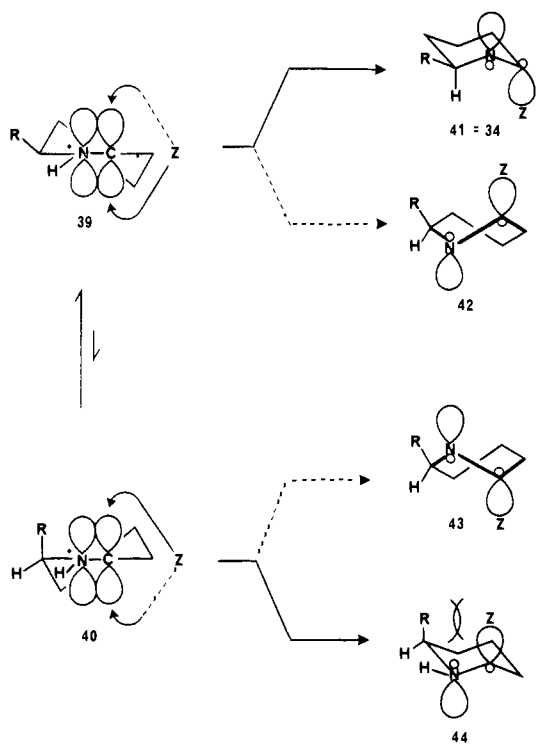


Diagram VII



these spectra would be one wherein both ester groups are down, but this possibility is readily dismissed on simple steric grounds (cf. **37a**). Decarbomethoxylation of **37** under the neutral conditions employed previously afforded the Ayer ketone **21.** In view of the technical difficulties encountered by the Canadian group in the transformation of **21** to coccinelline via **22,** we decided to examine an alternate route. Treatment of **21** with methylene triphenylphosphorane in ether provided the exocyclic olefin **38** in 82% yield. Catalytic hydrogenation of the latter compound afforded precoccinelline (**2**) which was converted to crystalline coccinelline (**1**) by oxidation with *m*-chloroperbenzoic acid.[11] Identity of the synthetic material with an authentic sample[12] was established by TLC behavior, infrared, ^{13}C NMR, and mass spectral data.

The remarkable stereoselectivity observed in the **32** to **37** transformation is worthy of additional comment. It is clear from the observations of the Canadian group that intermediates such as **15b, 20,** and, in our case, **36,** are ideally disposed for facile ring closure. This favorable arrangement of nucleophilic and electrophilic centers is established in the initial step **33** to **34.** As inspection of Diagram VII reveals, there are four possible transition states wherein maximum orbital overlap is maintained with respect to the incoming nucleophile (Z) and the developing lone-electron pair on nitrogen. Two of these, **42** and **43,** require boat-like transition states and are kinetically disfavored. Of the two possible chair-like transition states (**41** = **34** and **44**) the latter suffers from an unfavorable 1,3-diaxial interaction between R and the incoming nucleophile Z. Therefore, of the four possibilities wherein maximum orbital overlap is maintained, **41** is the least objectionable and leads to the observed product (**34**).

Experimental Section

Infrared spectra were recorded on a Beckman IR 4210 infrared spectrophotometer. NMR spectra were taken on Varian T-60, Bruker 200, and Varian CFT-20 spectrometers, in dilute deuteriochloroform solutions by using tetramethylsilane as internal standard. Mass spectra were determined on a AEI-MS 9 mass spectrometer. Melting points and boiling points are uncorrected.

Methyl 5-Oxo-2-carbomethoxypentanoate (27). Freshly distilled acrolein (61 g, 1.09 M) was added dropwise over a period of 2 h to a stirred solution of dimethylmalonate (110 g, 0.83 M) and 0.1 g of sodium in 350 mL of anhydrous CH_3OH under N_2 at 5–10 °C. The mixture was stirred at room temperature for another 10 h and the solvent removed under reduced pressure. The residue was dissolved in 200 mL of benzene and washed with 150 mL of H_2O followed by 100 mL of brine and dried over Na_2SO_4. The concentrated solution was distilled to afford 90.5 g (58%) of **27** as a colorless liquid: bp 96 °C (0.4 mm); IR (film) 2840, 2730, 1730 cm^{-1}; ^1H NMR (60 MHz) δ 9.75 (br S, 1 H), 3.70 (S, 6 H), 3.40 (t, J = 4 Hz, 1 H), 2.00–2.60 (m, 4 H); mass spectrum *m/e* 188 (parent).

Methyl 2-Carbomethoxy-5,5-dimethoxypentanoate (28). Diester aldehyde **27** (75.3 g, 0.4 M), trimethyl orthoformate (45.8 g, 0.43 M), and tosic acid monohydrate (0.5 g, 2.6 mM) were dissolved in 305 mL of anhydrous CH_3OH in a flask equipped with a drying tube and stirred at room temperature for 12 h. The solution was then neutralized with 1 N $NaOCH_3$ and the solvent removed in vacuo to produce a cloudy residue which was dissolved in 250 mL of ether, washed with 50 mL of saturated $NaHCO_3$ and then 50 mL of brine, and dried over Na_2SO_4. Removal of the solvent and distillation yielded 92 g (98%) of **28** as a pale-yellow liquid: bp 79 °C (2 mm); IR ($CHCl_3$) 2835, 1740 cm^{-1}; ^1H NMR (200 MHz) δ 4.37 (t, J = 5.6 Hz, 1 H), 3.74 (s, 6 H), 3.40 (m, 1 H), 3.31 (s, 6 H), 2.20–1.40 (m, 4 H); mass spectrum *m/e* 203 (parent − CH_3O).

Methyl 5,5-Dimethoxypentanoate (29). A mixture of diester acetal **28** (104 g, 0.44 M), NaCl (26 g, 0.44 M), and water (16 mL, 0.89 M) was refluxed in 400 mL of dimethylformamide under N_2 for 35 h. Then, the cooled reaction mixture was diluted with 400 mL of H_2O and extracted with 4 × 200 mL portions of ligroin (bp 35–60 °C). The combined extracts were washed with brine and dried over Na_2SO_4. Concentration and distillation in vacuo provided 54 g (69%) of **29** as a colorless liquid: bp 68 °C (1.3 mm), [lit. bp 70–72 °C (2.3 mm)]; IR (film) 2830, 1735 cm^{-1}; ^1H NMR (60 MHz) δ 4.38 (t, J = 5 Hz, 1 H), 3.65 (s, 3 H), 3.30 (s, 6 H), 2.35 (m, 2 H), 1.80–1.55 (m, 4 H); mass spectrum *m/e* 145 (parent − OCH_3).

Ketoester Acetal (30). Sodium hydride (5.55 g, 0.23 M) was suspended in 200 mL of dry 1,2-dimethoxyethane (DME) under N_2. The stirred suspension was brought to reflux and monoester acetal **29** (32.3 g, 0.18 M) in 100 mL of DME was added dropwise over a period of 2 h. The mixture was then refluxed an additional 15 h. The mixture was then cooled in an ice bath and the excess NaH decomposed by careful addition of water. The solution was then neutralized with 30% aqueous acetic acid and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were then washed with saturated $NaHCO_3$ and dried over Na_2SO_4. Removal of the solvent in vacuo provided 27.7 g (96%) of crude **30** which was sufficiently pure to use directly in the next step. A sample was purified by distillation: bp 155 °C (0.25 mm); IR (film) 2840, 1718, 1740 cm^{-1}; ^1H NMR (200 MHz), δ 4.34 (t, J = 5.4 Hz, 2 H), 3.72 (s, 3 H), 3.45 (m, 1 H), 3.31 (s, 12 H), 2.55 (m, 2 H), 1.70 (m, 8 H); mass spectrum *m/e* 258 (parent − $2OCH_3$).

Diacetal Ketone (31). The crude ketoester acetal **30** (27.7 g) was decarbomethoxylated via the NaCl-H_2O-DMF procedure described above to afford 16.1 g (67% overall from **29**) of distilled **31**: bp 124

°C (0.4 mm); IR ($CHCl_3$) 2840, 1710 cm^{-1}; ^1H NMR (200 MHz), 4.34 (m, 2 H), 3.31 (s, 12 H), 2.43 (m, 4 H), 1.60 (m, 8 H); mass spectrum *m/e* 231 (parent − OCH_3).

Diacetalamine (32). Ammonium acetate (44 g, 0.57 M, dried under vacuum at room temperature) and diacetal ketone **31** (15 g, 0.057 M) were dissolved in 200 mL of anhydrous methanol. Sodium cyanoborohydride (3.6 g, 0.057 M) and 10 g of 3A molecular sieves were added and the mixture was stirred under N_2 at room temperature for 24 h. The molecular sieves were filtered off, and the filtrate was concentrated under reduced pressure. The residue was taken up in 40 mL of H_2O and the pH adjusted to >9 with 10% NaOH. The solution was extracted with $CHCl_3$ (3 × 50 mL), and the extracts were dried over Na_2SO_4. Removal of the solvent gave 14.9 g (99%) of pure **32**: bp 120 °C (0.25 mm); IR (film) 3450, 2830 cm^{-1}; ^1H NMR (200 MHz), δ 5.05 (br s, 2 H, exchangable with D_2O), 4.40 (m, 2 H), 3.33 (s, 12 H), 3.10 (m, 1 H), 1.20–1.75 (m, 12 H); mass spectrum *m/e* 232 (parent − OCH_3).

Tricyclic Ketoester (37). The diacetal amine **32** (17 g, 0.065 M) was hydrolyzed in 50 mL of dilute hydrochloric acid (pH ~1) for 1 h. The pH of the solution was then adjusted to 5.5 with 25% NaOH solution and 400 mL of citrate–phosphate buffer (pH 5.5) added. Acetone dicarboxylic acid methyl ester (11.8 g, 0.068 M) in 250 mL of the buffer was added dropwise to the well stirred solution, and stirring was continued for an additional 24 h. Fourteen grams of fine yellow crystals was collected by suction filtration and washed with water and air dried. An additional gram of crystals was obtained by adjusting the pH of the filtrate to 8 and stirring an additional 24 h. The combined yield was 75%: mp 102–103 °C (ethyl acetate/hexane); IR ($CHCl_3$) 1735 cm^{-1} (broad); ^1H NMR (200 MHz), δ 3.75 (s, 6 H), 3.55 (m, 3 H), 2.68 (m, 2 H), 1.15–2.10 (m, 12 H); ^{13}C NMR 200.8, 169.0, 60.8, 54.0, 52.1, 49.6, 33.7, 28.2, 18.7; mass spectrum calcd for 309.1576 (found 309.1585).

Tricyclic Ketone (21). A mixture of ketoester **37** (1 g, 3.23 mM), sodium chloride (0.2 g, 3.42 mM), and water (2 mL, 11.1 mM) was dissolved in 15 mL of dimethylformamide and heated at reflux under N_2 for 4 h. The solvent was removed in vacuo and the residue taken up in 10 mL of CH_2Cl_2 and filtered rapidly through a short column of neutral alumina. Final purification was achieved by chromatography on neutral alumina eluting with ethyl acetate–hexane (1:1) to afford 0.35 g (56%) of tricyclic ketone **21** as colorless crystals: mp 83 °C (lit. mp 82–84 °C); IR ($CHCl_3$) 1705 cm^{-1}; ^1H NMR (200 MHz), δ 3.50–2.50 (m, 3 H), 1.00–2.40 (m, 16 H); ^{13}C NMR 210.9, 58.8, 48.1, 40.5, 33.9, 29.9, 18.9; mass spectrum (calcd for 193.1466): 193.1469.

Tricyclic Olefin (38). Ketone **21** (0.708 g, 3.67 mM) in 10 mL of ether was added dropwise under nitrogen to a stirred solution of methylene triphenylphosphorane in ether prepared by adding 1.8 mL of 2.2 M *n*-butyllitium (3.96 mM) to 1.4 g (3.92 mM) of methyl triphenylphosphonium bromide suspended in 25 mL of anhydrous ether. The mixture was stirred at room temperature for 1 h and then heated to reflux for 0.5 h. After cooling to room temperature, 5 mL of H_2O was added and the mixture extracted with 3 × 25 mL of ether. The combined extracts were dried over Na_2SO_4. Removal of the solvent and chromatography on neutral alumina eluting with ether–cyclohexane (15:100) provided 0.577 g (82%) of **38** as a colorless oil: IR (film) 1650 cm^{-1} (weak); ^1H NMR (200 MHz), δ 4.63 (m, 2 H), 2.00–3.30 (m, 7 H); 2.00–0.80 (m, 12 H); mass spectrum *m/e* 191 (parent).

Precoccinelline (2) and Coccinelline (1). Tricyclic olefin **38** (0.577 g, 3.02 mM) was dissolved in 10 mL of anhydrous methanol and reduced over 10% Pd/C at atmospheric pressure for 8 h. The oily reduction product showed no vinyl protons and the ^1H NMR (200 MHz) showed a sharp doublet at δ 0.95 (J = 5 Hz). Without further purification, this oil was treated with 85% *m*-chloroperbenzoic acid (0.7 g, 3.45 mM) in CH_2Cl_2 at 0 °C for 8 h. The mixture was then passed through a column of basic alumina eluting with CH_2Cl_2–CH_3OH (10:1) to remove acidic materials. Finally, chromatography on neutral alumina using CH_2Cl_2–CH_3OH (100:1) provided 0.373 g (64% from 38) of white crystalline coccinelline (mp > 225 °C) identical in TLC behavior, IR (KBr), ^{13}C NMR, and mass spectrum with an authentic sample.

Acknowledgments. We are most grateful to the National Science Foundation (NSF CHE76-84340 and NSF CHE 76-05927, Instrument Grant for Bruker NMR 200) for financial support.

References and Notes

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(12) We are most grateful to Professor Ayer for providing us with a sample of natural coccinelline.