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STEREOSELECTIVE TOTAL SYNTHESIS OF THE LADYBUG DEFENSIVE AGENTS COCCINELLIN AND PRECOCCINELLIN

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Summary: The stereoselective total synthesis of the lady bug defensive agents coccinellin and precoccinellin is described starting from perhydroboraphenalene.

The N-oxide coccinellin (1) and its free base precoccinellin (2) were isolated from the European ladybug Coccinella septempunctata by Tursch and coworkers.[1,2] Coccinellin apparently serves the beetle as a chemical defensive agent, as it exerts a repelling effect on the ant Myrmica rubra (at 0.001 M in water) and the quail Coturnix coturnix, tastes very bitter to Homo sapiens, and has a very high natural abundance (1.5% of the insect's dry weight), thus protecting the ladybug from consumption by potential predators.[3] Coccinellin, precoccinellin, and a number of structurally related alkaloids have been found to be present in other ladybug species, occurrence generally being associated with aposematic coloration.[2,3,4,5] Biosynthetically 1 and 2 arise by a polyacetate pathway performed by the beetle itself,[4] while Ayer and Furuichi have synthesized 1 and 2 starting from 2,6-lutidine.[6] We report an alternative, stereoselective synthesis of 1 and 2 starting from the readily available[7] perhydroboraphenalene 3.

The highly stereoselective conversion of 3 to the enamine 4 has been described previously.[8,9] Failing in all attempts to directly functionalize the enamine 4 at the γ-position (marked *), we turned to the eneammonium salt 5,[10] mp 161-162°C, prepared by addition of CH_3OSO_2F to 4 (ether, -78° to 25°, 86%). Treatment of 5 with lithium diisopropylamide (1.5 equi, THF, -78°to -20°) resulted in virtually complete isomerization to a single stereoisomer of the allylic ammonium salt 6,[10a,11] mp 206-208°C, presumably via the intermediate ylide. At higher temperatures, Hofmann elimination became the predominant reaction pathway. So far, we have been unable to trap the ylide with methyl iodide and presume it to be present in only low concentration under these reaction conditions. Saunders and Gold have reported a similar isomerization (aq. NaOH, reflux) and also deuterium incorporation rate studies with several less complex eneammonium and allylic ammonium salts.[12] Specific cleavage at the methyl group of 6 was achieved with LiSEt in DMF[13] to afford the allylic amine 7[10] (82% from 5). The overall transformation of 4 to 7 constitutes the contrathermodynamic isomerization of an enamine to an allylic amine. Regiospecific functionalization of the double bond was accomplished[14] by stereoselective epoxidation (1.1 equi CF_3CO_2H, then CF_3CO_3H, CH_2Cl_2)[15] from the less hindered face to give 8[10] followed by reductive opening with lithium in ethylenediamine[16] to form exclusively the axial[17] alcohol 9,[10] mp 148-150°C (42% from 7). Oxidation (Jones reagent, HOAc, special workup[8]) then gave the ketone 10,[10] mp 81-82°C (81%), previously prepared and converted to 1 and 2 by Ayer and Furuichi.[6] In our hands reaction of 10 with both CH_3MgI and CH_3Li[6] was incomplete (presumably due to enolization), so we converted 10 to the exocyclic methylene compound 11[10] (83%) via a Wittig reaction. Hydrogenation (H_2, Pd/C, EtOH) of 11 gave a 3:2 mixture of 2 and its methyl group stereosisomer respectively. However, hydrogenation of the sterically more demanding 12[6,10a] prepared by isomerization of 11 with p-TSA (3 equi, xylene, reflux, 87%) gave 2 (picrate[10] mp 195-197°C) with greater than 97% stereoselectivity (90% yield). Comparison of MS, IR, and PMR spectra of synthetic 2 with those[18] of authentic material established the identity of synthetic and natural precoccinellin (2). Reaction of 2 with m-chloroperbenzoic acid[6] gave coccinellin (1), mp 204°C (decomp), identical to natural material by comparison of IR, PMR, and CMR spectra.[18] The hydrochloride of 1, mp 215-219°C (decomp), was identical (mp, PMR, IR) to an authentic sample.[18]

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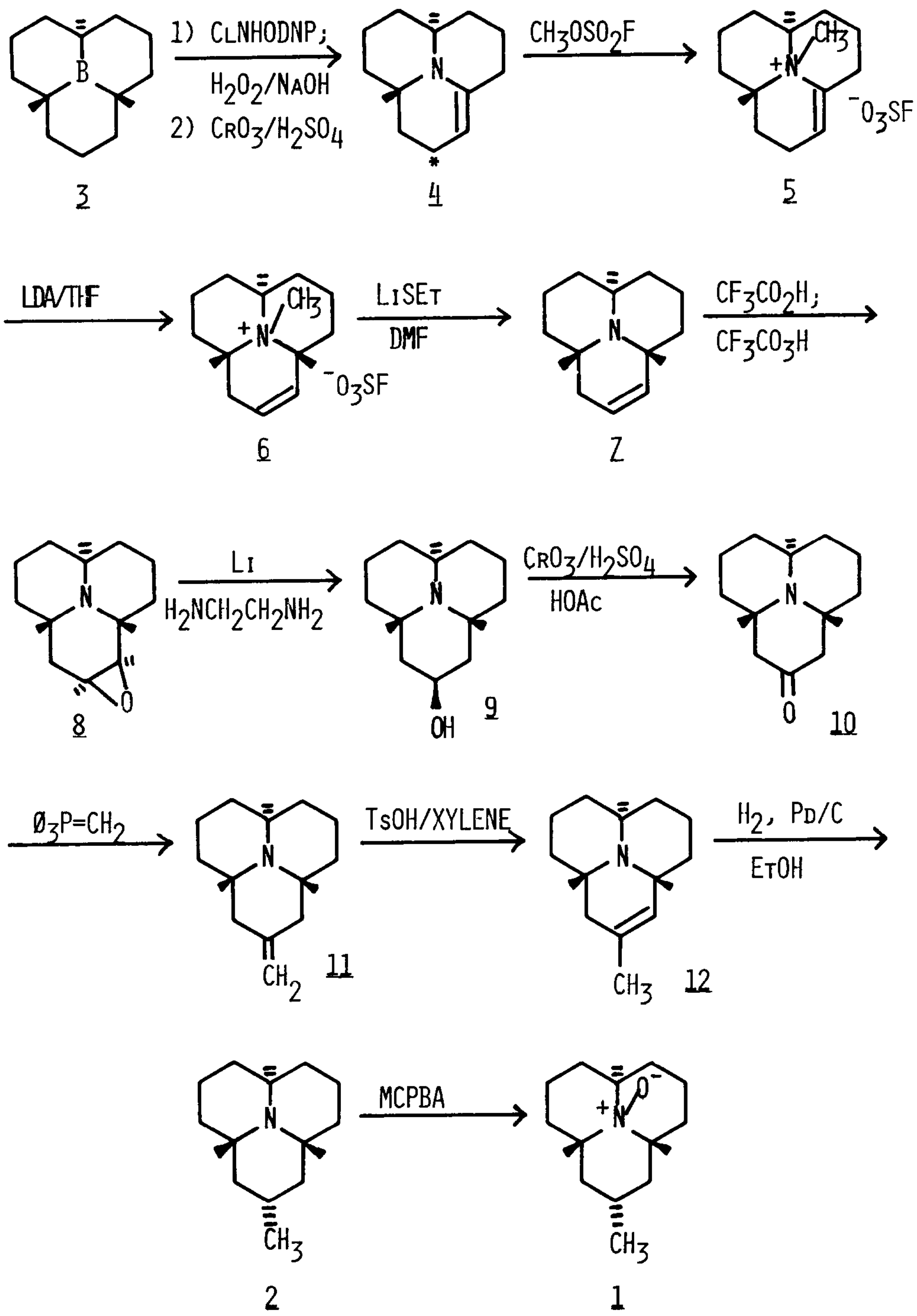
3
1) ClNHODNP; H2O2/NaOH
2) CrO3/H2SO4
4
CH3OSO2F
5
+N CH3
-O3SF
LDA/THF
6
LiSEt
DMF
7
CF3CO2H; CF3CO3H
8
Li
H2NCH2CH2NH2
9
OH
CrO3/H2SO4
HOAc
10
O
Ø3P=CH2
11
CH2
TsOH/XYLENE
12
CH3
H2, Pd/C
EtOH
2
MCPBA
1
+N O-

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10. (a) Satisfactory spectral data (IR, PMR, MS) were obtained for this compound; (b) C,H,N combustion analysis was within 0.3%; (c) melting points are corrected.
11. The stereochemistry of the methyl group of both 5 and 6 is not known with certainty at the present time.
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14. Hydroboration/oxidation gave predominantly the undesired regioisomer; oxymercuration attempts gave very little reaction.
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18. We thank Prof. B. Tursch and Dr. J. C. Braekman for spectra and a sample of coccinellin·HCl.

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