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The total synthesis of coccinelline and precoccinelline

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On décrit la synthèse à partir de la lutidine-2,6 des substances défensives des coccinelles soit la precoccinelline et la coccinelline.

[Traduit par le journal]

Recently we have described the synthesis from 2,4,6-collidine of the ladybug defensive substances myrrhine (1) hippodamine (2), and convergine (3) (1). The key step in the synthesis of these substances involved the cyclization of the ketoaldehyde 4a (which is isolated as the carbinolamine ketol 5a) to furnish the ketones 6aand 7a. Removal of the oxygen function from 6aprovided myrrhine (1), and from 7a, hippodamine (2). The ketone 8, a potential precursor of precoccinelline (9) and thus also of coccinelline (10), could not be obtained from 4a(1). Coccinelline (10) (2) is the major defensive substance of several species of Coccinellidae (ladybugs) (3) and thus its synthesis remained a challenge. As noted previously (1) the ketone 7b (=11), potentially available from the ketoaldehyde 4b, is an attractive precursor of precoccinelline (9). We now report the synthesis of 11 (= 7b) and its transformation to precoccinelline (9) and coccinelline (10).

The synthesis of 4b followed the same pathway as the synthesis of 4a except that 2,6-lutidine was utilized as starting material rather than 2,4,6-collidine. Treatment of the monolithium



3 N-oxide of 2



derivative of 2,6-lutidine (1 equiv.) with β -bromopropionaldehyde dimethyl acetal (1 equiv.) (4) in ether in the presence of excess 2,6-lutidine (2 equiv.) gave the acetal 12,1 bp 85-90 °C/0.3 torr, in 76% yield (based on alkylating agent). Treatment of an ether solution of 12 with phenyllithium, followed by the slow (over 4 h) addition of an ethereal solution of acetonitrile (1 equiv.) (1) provided after work-up the crude ketone 13 which was immediately transformed (ethylene glycol - benzene - p-toluenesulfonic acid) to the diacetal 14 (bp 110–120 $^{\circ}$ C/0.1 torr)¹. The overall

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¹All new compounds reported, with the exception of 16, gave satisfactory combustion analyses. Nuclear magnetic resonance, ir, and mass spectra were obtained on all new compounds and are completely consistent with the structures formulated.



yield of 14 from 12 was 48%, with 27% of 12 (as the ethylene acetal) recovered.

Reduction of 14 using sodium – isoamyl alcohol followed by careful chromatography over silicic acid gave the *cis* piperidine 15 (bp 135–140 °C/0.05 torr, hydrochloride mp 118–119 °C)¹ in 63% yield. The *trans*-isomer of 15 was isolated in 25% yield. The stereochemistry of the major product was assigned on the basis of: (1) its mode of formation (thermodynamically favored product); (2) a comparison of its cmr spectrum with that of the *trans*-isomer (cf. ref. 1); (3) trans-

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formation to the carbinolamine ketol 5*b*. Hydrolysis of 15 with 5% aqueous hydrochloric acid gave the ketol 5*b* (mp 87–88.5 °C)¹ which shows OH absorption and strong Bohlmann bands in the ir, a methyl signal at δ 1.48 (s, 3H) in the pmr and at δ 30.3 in the cmr, and thus

must have the structure and stereochemistry shown in 5b (cf. 5a, ref. 1).

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Cyclization of 5*b* (closed form of 4*b*) using pyrrolidine (1 equiv.) and acetic acid (2 equiv.) in refluxing tetrahydrofuran (1) gave a 1:1 mixture of ketones 6*b* and 7*b* (= 11) in 86% yield. The mixture of ketones was separated by chromatography over silicic acid (eluant CHCl₃– MeOH–NHMe₂, 100:10:1); 6*b* (bp 75–80 °C/ 0.2 torr)¹ shows carbonyl absorption at 1730 cm⁻¹ and strong Bohlmann bands in the ir; 7*b* (= 11) (mp 82–84 °C)¹ shows carbonyl absorption at 1710 cm⁻¹ and no Bohlmann bands.

Treatment of ketone 7b with methyllithium in ether followed by dehydration of the resulting carbinol with thionyl chloride in methylene chloride yielded the air sensitive olefin **16** (pmr, δ 1.66 (bs, 3H), 5.15 (bs, 1H)) which was hydrogenated (Pt, CH₃OH, room temperature, 1 atm) to give precoccinelline **9** (27% yield from 7b), identical (ir, pmr, ms, tlc) with an authentic sample.² Oxidation of synthetic precoccinelline with *m*-chloroperbenzoic acid in methylene chloride gave coccinelline (**10**), mp 205-210 °C (dec.), hydrochloride mp 215-220 °C (dec.), identical (mp, ir, ms, tlc) with an authentic sample.²

Treatment of ketone 6b with methyllithium followed by dehydration (SOCl₂-CH₂Cl₂) and hydrogenation gave myrrhine (1).

Acknowledgement

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