Stereodivergent Total Syntheses of Precoccinelline, Hippodamine, Coccinelline, and Convergine†

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ABSTRACT

A stereodivergent approach toward total syntheses of Coccinellidae defensive alkaloids is described. These syntheses feature a highly diastereoselective intramolecular aza-[3+3] annulation strategy, which represents a de novo approach to this family of natural products.

Ladybird beetles (Coccinellidae) play an important role in controlling populations of agricultural pests such as aphids, mealy bugs, and scale insects, and to protect themselves from their natural predators such as ants and quails, they utilize a reflex bleeding mechanism.1 When scarred or disturbed, they release an orange fluid from their joints that contains a mixture of defensive alkaloids.2 In 1971, Tursch and co-workers3a first isolated precoccinelline 1 from this fluid along with a crystalline substance, which was confirmed as the N-oxide of 1 or as coccinelline 2 by X-ray analysis.3b Isolations of hippodamine3c,d 3, its N-oxide convergine3c,d 4, and the thermodynamically most stable all syn isomer myrrhine3c 5 were reported later. Alkaloids 1 and 3 represent the two other possible stereoisomers of the 2-methylperhydro-9b-azaphenalene system with the methyl group being equatorial. Interestingly, N-oxide of myrrhine 5 does not occur naturally.

1 Dedicated to Professor Jeffrey D. Winkler on the occasion of his 50th birthday.


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in Ayer’s syntheses,5a and in all syntheses of these alkaloids except for one,4a the equatorial methyl group is being introduced in the latter steps of the sequence. Herein, we report a de novo approach to precocine line 1 and hippocadine 3 and their respective N-oxides 2 and 4, featuring a highly stereoselective intramolecular aza-[3 + 3] annulation.7–10


Retrosynthetically, as shown in Scheme 1, we envisioned that both 1 and 3 could be derived from the same aza-tricyclic intermediate A upon hydrogenation of the double bonds and removal of the carboxymethyl group. The key tricycle A can be prepared via an intramolecular aza-[3 + 3] annulation of vinyllogous urethane 6,10 which should be accessible in several steps from cis-1,3-disubstituted lactam 7 with bromide 9 and glutarimide 8 as the essential starting points.

Our synthesis commenced with alkylation of TBDPS-protected propargyl alcohol 1011,12 employing excess 1,3-dibromopropane followed by Lindlar hydrogenation that led to bromide 9 in 59% overall yield (Scheme 2). Lactam 7 was prepared via reductive alkylation13 of 4-methyl glutarimide 8.14 The Grignard reagent generated from bromide 9 was added to the Mg salt 8a formed in situ from glutarimide 8 and 1.0 equiv of CH3MgCl, and after stirring overnight at room temperature, NaBH3CN and AcOH were added to reduce the intermediate hemi-aminal (see 11a). The reduction proceeded stereoselectively and afforded lactam 7 in 75% overall yield exclusively as the 1,3-syn isomer. This is likely a result of an axial approach of hydride to the conformation shown for N-acyliminium ion 11b.

Converting 7 to the corresponding thiolaactam using Lawesson’s reagent15 followed by alkylation with α-bromo methyl acetate gave thiol ether 12 in 90% yield over two steps (Scheme 3). Eschenmoser sulfide contraction16 of 12 proceeded smoothly and led to the protected Z-vinylogous

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**Scheme 1.** Retrosynthetic Analysis

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1: precocine line

intramolecular aza-[3 + 3] annulation

4: E = COR

5: hippocadine

3: N-oxide

2: N-oxide

1: intermediate A upon hydrogenation of the double bonds and removal of the carboxymethyl group. The key tricycle A can be prepared via an intramolecular aza-[3 + 3] annulation of vinyllogous urethane 6,10 which should be accessible in several steps from cis-1,3-disubstituted lactam 7 with bromide 9 and glutarimide 8 as the essential starting points.

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**Scheme 2.** Synthesis of Lactam 7

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1. n-Buli, THF, and then

Br Br (5 equiv)

72 h, rt

2. 1 atm H2, 5% Pd/BaSO4

quinoline, pet. ether

PO H

OTBDPS

OTBDPS

10

9: P = TBDPS

8a

11b

acid

H (‘‘axial’’)

H

N

ClMpt

N

ClMpt

‘‘axial’’

H

H

OTBDPS

7 (75% overall) or 9: 1
urethane 13. Subsequent deprotection of the TBDPS group with TBAF furnished allyl alcohol 14. It is noteworthy that the described sequence was suitable for multigram scale synthesis of alcohol 14 with an 82% overall yield starting from lactam 7.

Pyr\(\text{SO}_3\) oxidation\(^\text{17}\) of allyl alcohol 14 led to the corresponding enal 15 as a 7:1 cis/trans isomeric mixture (Scheme 4). Enal 15 was subjected to the aza-[3 + 3] annulation conditions employing piperidinium trifluoroacetate in EtOAc. The desired cycloadduct 16 was obtained as a single diastereomer in 51% yield, and its anti relative stereochemistry at the ring junction was established using nOe’s (see the box in Scheme 4) and by X-ray of a later intermediate. The observed stereoselectivity is in good agreement with our previous experience.\(^\text{10b}\)

Because of the precarious nature of 16, we found it more convenient to hydrogenate the reaction mixture over Pd(OH)\(_2\): after the annihilation.\(^\text{10c}\) The one-pot protocol allowed us to access the more stable aza-tricycle 17 with a consistent 43% overall yield from 15. It is noteworthy that aza-tricycle 17 contains three of the four stereogenic centers required for precoccinelline 1 and hippodamine 3.

With aza-tricycle 17 in hand, we hydrogenated the internal double bond employing Adam’s catalyst\(^\text{18}\) (Scheme 5).

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Although esters 18a,b could be separated by a tedious alumina gel column, it was found that they could be readily resolved via a selective alkaline hydrolysis of the equatorial ester 18a (Scheme 5). Upon treatment of the crude hydrogenation mixture with 1.7 M aq KOH, unreacted axial ester 18b was recovered by simple extraction in 36% overall yield from 17. Upon acidification of the aqueous phase, acid 19a was isolated in 49% yield with its assigned relative stereochemistry being supported by nOe’s. The structure of 18b was unambiguously assigned by X-ray analysis of its corresponding picrate salt (Figure 1).

To complete the total synthesis of precoccinelline 1, acid 19a was subjected to Barton’s decarboxylation conditions (Scheme 6). The desired alkaloid was isolated in 43% overall yield with all physical data matching the reported literature data. Subsequent oxidation of precoccinelline 1 with m-CPBA provided coccinelline 2 in excellent yield.

The synthesis of hippodamine 3 turned out to be more challenging, as all attempts to directly hydrolyze ester 18a failed. This can be attributed to the inaccessibility of the hindered axial ester group in 18b. We attempted to epimerize the axial ester to the more stable equatorial one using K<sub>2</sub>CO<sub>3</sub>/MeOH and DBU/toluene protocols, but neither condition was suitable with complete recovery of the starting material.

Ultimately, we found that treatment of ester 18b with KHMSD<sub>2</sub> at −78 °C with subsequent quenching of the reaction mixture with MeOH at 0 °C led to the desired equatorial ester 18c with 86% yield (Scheme 7). Hydrolysis of 18c was successful using 1.7 M aq KOH at 50 °C, leading to carboxylic acid 19b in 44% yield. Subsequently, hippodamine 3 was obtained in 43% overall yield after decarboxylation of 19b under Barton’s conditions. Successive oxidation of 3 with m-CPBA afforded convergine 4 in 88% yield. Both natural products matched the literature spectroscopic data.

We have described here total syntheses of precoccinelline and hippodamine (overall yields from glutarimide are 4.8% and 1.3%, respectively) and their respective N-oxides coccinelline and convergine (overall yields from glutarimide are 4.6% and 1.2%, respectively), featuring a stereoselective intramolecular aza-[3 + 3] annulation strategy, an interesting Eschenmoser sulfide contraction, and a stereodivergent hydrogenation. This work provides a novel approach toward the 2-methyl-perhydro-9b-azaphenalene family of alkaloids.

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**Supporting Information Available:** Experimental and ¹H NMR spectral data and characterizations for all new compounds as well as X-ray structural data. This material is available free of charge via the Internet at http://pubs.acs.org.

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