

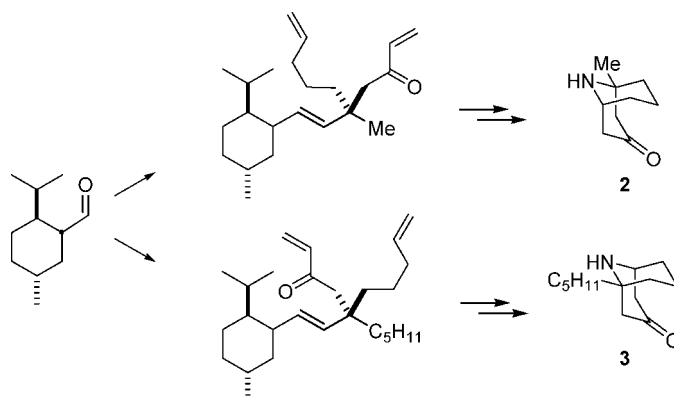
Stereoselective Synthesis of (+)-Euphococcinine and (–)-Adaline

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We describe the syntheses of (+)-euphococcinine and (–)-adalinine, two naturally occurring alkaloids containing a quaternary carbon bearing a nitrogen atom. Key features of the syntheses are a 3,3-sigmatropic rearrangement to give an all-carbon quaternary center, a ring-closing alkene metathesis to give an 8-membered ring, and the use of a single enantiomer of *p*-menthane-3-carboxaldehyde to make two natural alkaloids of opposite configuration.

Introduction

Many natural alkaloids contain quaternary centers bearing a nitrogen atom, and in particular, the defensive secretion of *Coccinellid* contain such alkaloids as exochomine (1),¹ euphococcinine (2),² adaline (3),³ and adalinine (4)⁴ (Figure 1). Euphococcinine (2) and adaline (3) are members of the 9-azabicyclo[3.3.1]nonane family and are both potent feeding deterrents to spiders and ants, part of the chemical defensive arsenal of *Coccinellid* beetles.⁵ According to biosynthetic studies,⁶ they are polyacetate in origin. Syntheses of these two alkaloids as both a racemic⁷ or a nonracemic mixture⁸ have been reported.

One of the main challenges in their synthesis is the formation of the quaternary center bearing nitrogen with control over the absolute stereochemistry. There are a number of methods to achieve this, including sigmatropic rearrangements,⁹ addition of organometallic reagents on imine,¹⁰ and Curtius rearrangement¹¹ from chiral carboxylic acids, among others.¹² In that regard, allylic alcohol 7, derived from the stereoselective addition of a vinylmetal 6 to *p*-menthane-3-carboxaldehyde 5, has proven a useful chiral scaffold on which to perform rearrangements and displacement reactions to introduce a new C–C,^{11b} C–N,^{13,11a,b} or C–S¹⁴ bond in the product 8 (Scheme

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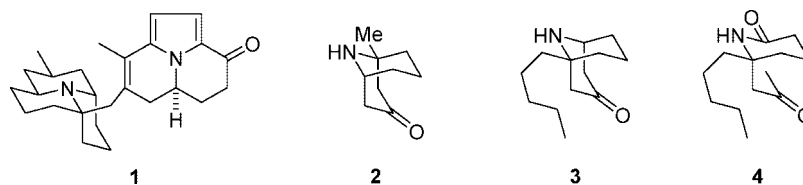
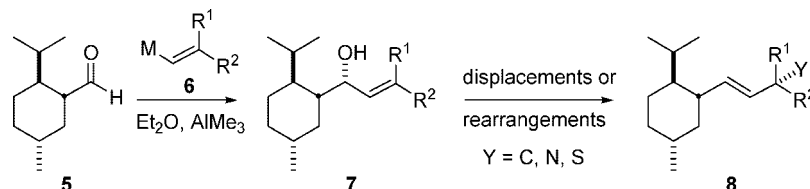
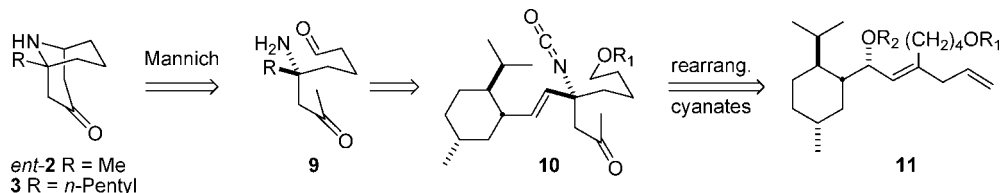


FIGURE 1. Three defensive alkaloids contained in the blood of *Coccinellid* species.

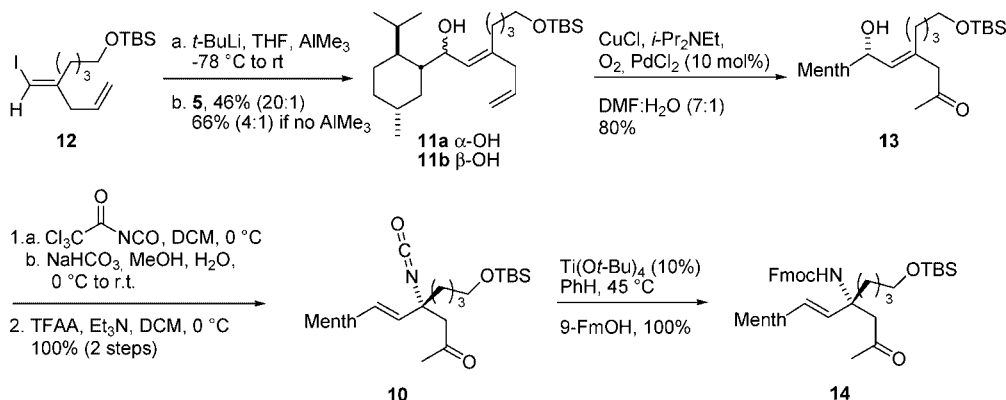
SCHEME 1. *p*-Menthyl-3-carboxaldehyde **5** as a Chiral Scaffold for the Synthesis of Quaternary Carbons



SCHEME 2. Retrosynthesis of (-)-Euphococcinine (*ent*-2) and (-)-Adaline (**3**) Partly Inspired by Their Biosyntheses



SCHEME 3. Synthesis of the Protected Chiral Amine **14** via 3,3-Sigmatropic Rearrangement of Cyanate to Isocyanate



1). It has proven particularly useful for the formation of all-carbon quaternary centers (**8**, Y = C).^{11b,15}

We therefore set out to construct the nitrogen-bearing quaternary carbons of euphococcinine and adaline considering that with two properly functionalized carbon chains as in **9**, a Mannich cyclization would conclude their respective syntheses (Scheme 2). The Mannich cyclization should be viable according to previous work^{7c,8c,f} and from biosynthetic considerations.⁶ Our initial synthetic design called for the formation of the nitrogen-bearing quaternary carbon by a cyanate to isocyanate rearrangement.^{13a}

Results and Discussion

Vinyl iodide **12** was constructed using Sato's allyltitanation¹⁶ from 5-hexyn-1-ol (see the Supporting Information for its synthesis) and was transformed into the corresponding vinyl-lithium, which was added to *p*-menthane-3-carboxaldehyde **5** to afford a 20:1 ratio of allylic alcohols **11a** and **11b**, which were easily separated (Scheme 3). The terminal alkene in **11a** was oxidized using the Wacker protocol to give methyl ketone **13**. Activation of the allylic alcohol into a carbamate was

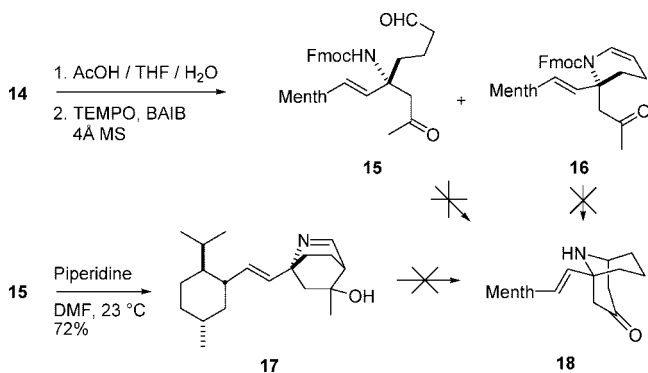
followed by its dehydration and the resulting cyanate rearranged instantly at ambient temperature through a 3,3-sigmatropic rearrangement into isocyanate **10**. We had trouble establishing the % de of this particular isocyanate (see the Supporting Information), but since this initial route proved unfruitful (vide infra) it was not pursued further. However, all quaternary

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SCHEME 4. Attempted Mannich Cyclization of Compounds 15–17



isocyanates previously prepared in this way were isolated in >99% de.^{13a} Isocyanate **10** was transformed into the Fmoc carbamate **14** using $\text{Ti}(\text{O}-t\text{-Bu})_4$ as catalyst. This catalyst is especially useful with hindered isocyanates such as **10**.¹⁷ Several other Lewis or Brønsted acids were tried but failed to give a good yield of addition of fluorenylmethanol onto this congested quaternary isocyanate.

Then, the primary alcohol in **14** was deprotected and oxidized to the aldehyde (Scheme 4). A mixture of aldehyde **15** and enamine **16**, resulting from the cyclization of the carbamate on the aldehyde, was obtained. The ratio varied depending of the conditions used. Pure aldehyde **15**, pure enamine **16**, or a mixture of both, was then submitted to several different acidic or basic conditions to deprotect the amine and achieve the desired Mannich cyclizations to **18**. However, most experiments led to decomposition products. Treating aldehyde **15** with piperidine in DMF gave a 72% yield of imine alcohol **17**. This product was formed by aldol addition of the enamine formed after deprotection of the nitrogen onto the ketone. The same reaction did not proceed from **16**. The formation of **17** from **15** was perhaps to be expected when basic conditions are used because enolization of the ketone is not favored. All of our efforts to convert **17** back to the desired Mannich product **18** were in vain. Scheme 5 shows three similar Mannich reactions taken from the literature. The difference in behavior between starting materials **15–17** and **19, 21, or 23** may reside in that the intermediate iminium (**25** or **26**) derived from any one of the latter is alkylated, whereas the iminium (**25**, R = H in acidic

conditions) derived from any one of the former is not. Considering that alkylation of the nitrogen in compound **10** and dealkylation would add at least two more steps to our sequence, we were not willing to pursue this avenue.

Instead, we investigated a synthetic approach toward *Coccinellid* defensive alkaloids that used a Curtius rearrangement to introduce the nitrogen atom. To that effect, an all-carbon quaternary stereocenter bearing a carboxylic acid, as in **32**, needed to be built (Scheme 6). This could be easily achieved using chiral auxiliary **5** and cleaving it under oxidative conditions. The ketone and protected aldehyde in **31** would react form the 8-membered ring, while the carboxylic acid would be transformed into an amine that would cyclize to give **2**.

The sequence began with a lithium–halogen exchange of vinyl iodide **27**, also prepared by Sato's allyltitanation chemistry (see the Supporting Information). The resulting vinylolithium was added to *p*-menthane-3-carboxaldehyde **5** to give the corresponding alcohol **28** as the major product (Scheme 6). The allylic alcohol in **28** was activated as its phenylcarbamate (**29**) for the *syn*-selective $\text{S}_{\text{N}}2'$ addition of dialkylcuprate reagents. The addition of a lithium dimethylcuprate gave **30a** successfully, but unfortunately, the addition of a lithium di(*n*-pentyl)cuprate did not proceed at all to give **30b**, regardless of the nature of the leaving group or of the cuprate reagent. In our experience, $\text{S}_{\text{N}}2'$ displacements by cuprate reagents are quite sensitive to steric effects, and bulky cuprates often lead to no reaction or decomposition products. To compound the problem, the subsequent steps in the synthesis of euphococcinine was a Wacker oxidation of the alkene to give the methylketone **31**, and it proved problematic. This oxidation would likely not fare better with the more hindered quaternary carbon of **30b** had we been able to generate it. A slight change in the strategy was therefore called for.

In this altered strategy, the carboxylic acid **32** would be a precursor to the alkaloids via a Curtius rearrangement. However, we would make two modifications: first, find a more general reaction to generate the quaternary carbon (see **34a** → **33**, Scheme 7) to avoid the problematic $\text{S}_{\text{N}}2'$ displacement by a cuprate reagent; second, the 8-membered ring in **32** would be formed using a ring-closing metathesis (RCM) from enone **33**, thus circumventing the need for an allyltitanation/Wacker oxidation sequence.¹⁸

Initially, we were intrigued by the possibility that the bulky *p*-menthyl fragment of our chiral auxiliary could be made to direct a nucleophilic addition of malonates on a π -allylpalladium complex prepared from alcohols like **34a**. There are numerous examples of the stereoselective formation of tertiary centers using π -allylpalladium complexes.¹⁹ Examples of the formation of quaternary centers using this methodology are far less numerous.^{20,21} Some chiral ligands²² or directing groups²³ were developed to favor the addition of the nucleophile on the more

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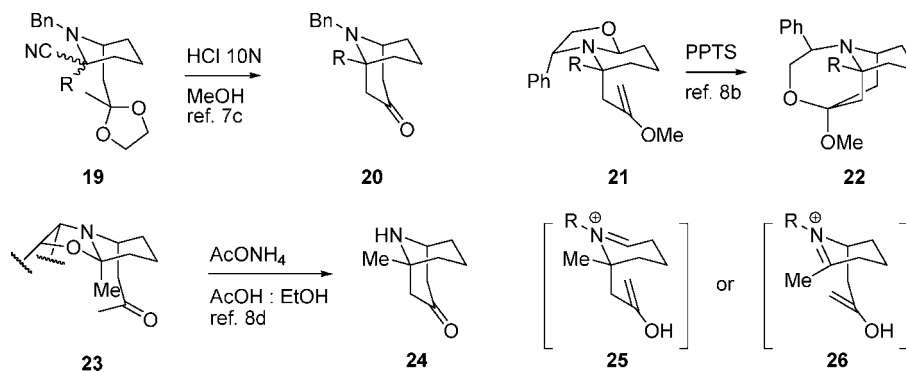
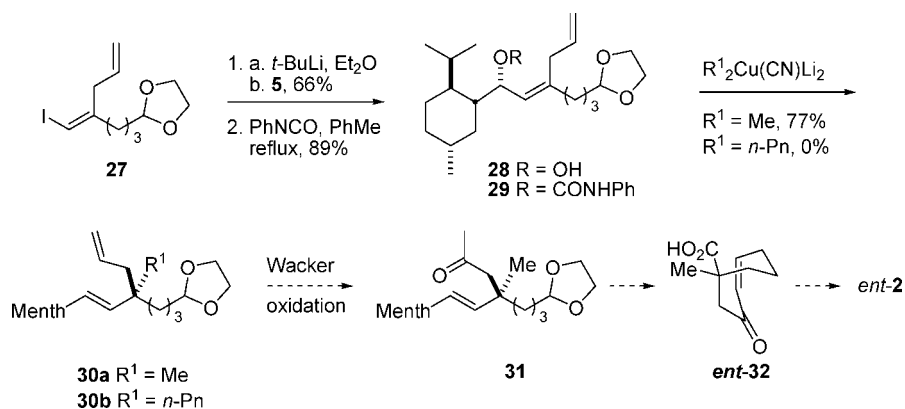
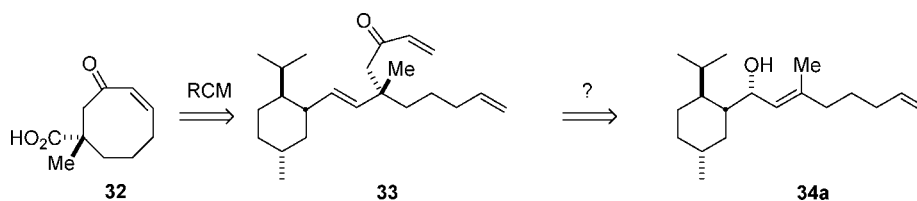
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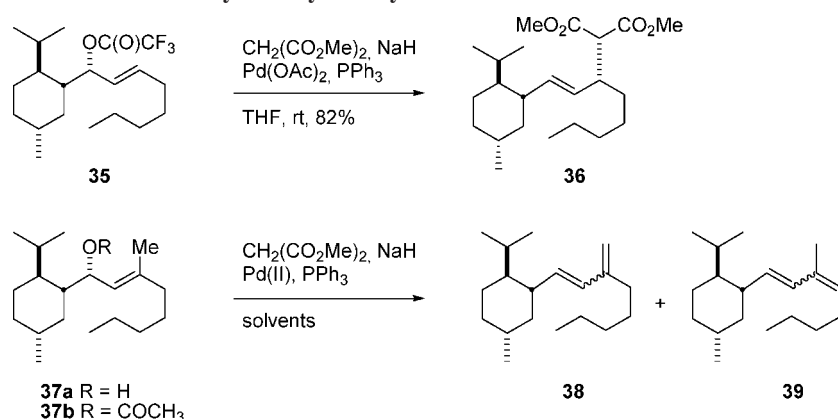
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SCHEME 5. Three Different but Similar Mannich Cyclizations Taken from the Literature

SCHEME 6. Formation of a Quaternary Center via a *Syn*-Directed S_N2' Cuprate AdditionSCHEME 7. Altered Strategy to the *Coccinellid* Alkaloids

SCHEME 8. Results of the Palladium-Catalyzed Allylic Alkylation of 35 and 37



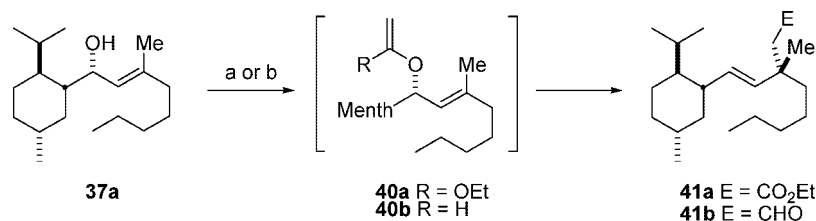
hindered end of the π -allyl complex, and we felt our chiral auxiliary should be sufficiently bulky to favor one regioisomer.

This turned out to be true, and after several leaving groups and reaction conditions were screened, the trifluoroacetate **35** was transformed into a single regioisomer **36** in 82% yield (>96% de, as determined by ^1H NMR) as shown in Scheme 8. However, the formation of a quaternary stereocenter was what really interested us, and initial attempts using acetate as the

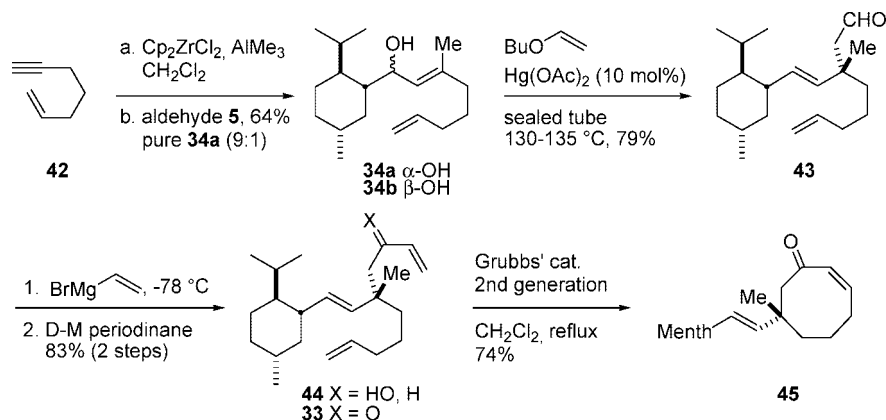
leaving group left the starting material **37b** unreacted. Unfortunately, all other leaving groups and/or reaction conditions that were attempted led to decomposition or elimination products **38** and **39**. This was also true of the Pd-catalyzed decarboxylative allylic alkylation.²⁴

The Claisen rearrangement was an attractive alternative to form a quaternary carbon center, but there are scant examples of this reported in the literature and they mostly involve rigid

SCHEME 9. Formation of a Quaternary Center via a 3,3-Sigmatropic Rearrangement



- a. MeC(OEt)₃, EtCO₂H, 135–140 °C, 62% of **41a**
 b. BuOCH=CH₂, Hg(OAc)₂ (10 mol%), sealed tube, 130–135 °C, 72% of **41b**

SCHEME 10. Synthesis and RCM of Enone **33**

cyclic molecules.²⁵ Regardless of the variant used (Claisen–Ireland, Carroll, Johnson–Claisen, etc.), the chirality transfer in these rearrangements is usually high.²⁶ The acetate **37b** and ketoester derivatives **37f** and **37g** were submitted to basic conditions, in the presence or absence of a silylating agent (Claisen–Ireland or Carroll variants), but only starting material and/or the corresponding dienes **38** and **39** were obtained in either case. However, the use of the Johnson orthoester Claisen modification on alcohol **37a** led to a 62% yield of the desired ester **41a** (Scheme 9). Meanwhile, heating **37a** with a Hg(II) catalyst²⁷ in a sealed tube afforded a 72% yield of the aldehyde **41b** as well as a small amount (10%) of vinyl ether **40b**. The use of palladium salts²⁸ to effect the sequence gave only 36% yield of the same aldehyde. The diastereomeric excess of **41b**

was determined to be >96% by ¹H NMR spectral comparison with an authentic sample of its diastereomer. We were now ready to apply this methodology toward the total synthesis of both *Coccinelid* alkaloids.

The terminal alkyne **42** was prepared according to a reported procedure²⁹ from 5-bromopentene (Scheme 10). Then, a Zr-catalyzed carboalumination gave the corresponding vinylalane that was directly added on *p*-menthane-3-carboxaldehyde **5** to give allylic alcohols **34a** and **34b** in a 9:1 ratio. After chromatographic separation, alcohol **34a** was isolated in 67% yield (>99% de, determined by GC). Then, the Claisen rearrangement on **34a** gave 79% of the desired aldehyde **43** (>96% de, determined by ¹H NMR). Vinylmagnesium bromide was added to aldehyde **43** to give a mixture of two diastereoisomeric allylic alcohols **44**, which were then oxidized to the enone **33**.

We figured that three products could potentially be formed during the RCM of enone **33**: the desired 8-membered ring **45** (Scheme 10), as well as the 5-membered ring **46** or the 6-membered ring **47** (Figure 2). Initiation at the enone alkene is unlikely,³⁰ and according to previous work in our laboratory, 6-membered rings are not formed when an all-carbon quaternary

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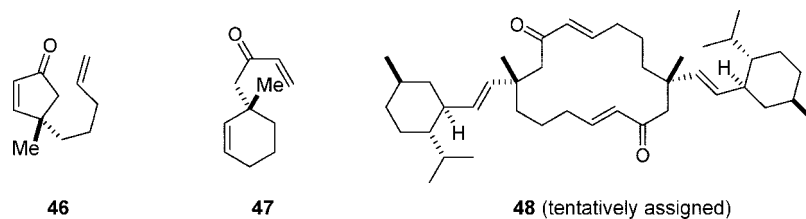
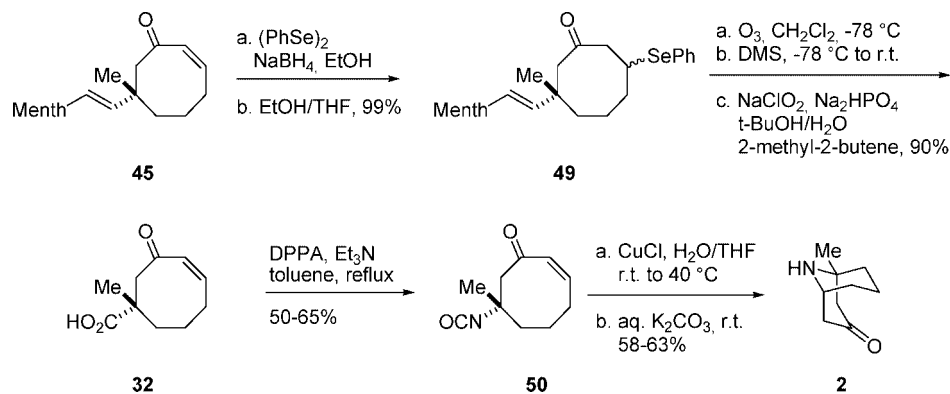


FIGURE 2. Three possible products from the RCM of **33**.

SCHEME 11. Formation of Isocyanate **50** and (+)-Euphococcinine **2**



center is present at this position.³¹ Hence, the eight-membered ring **45** should be the major product even though it is not entropically favored.³² Grubbs' first generation catalyst gave only recovered starting material. With the Grubbs' catalyst of second generation, in refluxing dichloromethane, cyclic enone **45** was obtained in 74% yield (Scheme 10). Despite conducting the reaction under high dilution (5 mM) and/or with slow addition of the substrate, what we believe is the 16-membered ring **48** was always isolated in 3–5% yield (Figure 2). When conducted in refluxing 1,2-dichloroethane, up to 5% of the 5-membered ring **46** has been isolated but no trace was detected in dichloromethane.

Selective ozonolysis of the chiral auxiliary in **45** with ozone in the presence of the enone proved impossible.³³ The enone is more electron-poor than the internal alkene but is also a lot less sterically hindered. There are reported examples in the literature where it is possible to selectively cleave an isolated alkene in the presence of an enone when pyridine is used as a cosolvent³⁴ or when indicators³⁵ are used. Both methods were tried, but without doubt the most reactive alkene toward ozone was the enone. Other methods of oxidative cleavage using large metal oxides would likely lead to the same result. We therefore decided to temporarily mask the enone by

adding phenylselenol to it and obtained selenide **49** in quantitative yield (Scheme 11). When **49** was submitted to ozonolysis, the selenide was oxidized to the selenoxide but did not undergo elimination before the internal alkene was cleaved. However, after reductive workup of the ozonide and increasing the temperature, the selenoxide underwent a smooth elimination and carboxylic acid **32** in 90% was obtained.

The Curtius rearrangement occurred with complete retention of stereochemistry at the migrating center, as expected.^{11b,36} Using diphenylphosphoryl azide (DPPA)³⁷ as source of azide, isocyanate **50** was obtained in 50–65% (Scheme 11). However, this reaction must be monitored closely because long reaction times lead to the known elimination product **51** (Figure 3). Higher temperatures (refluxing xylene for example) afford more of the byproduct **51**.

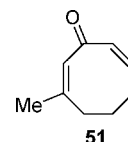


FIGURE 3. Byproduct formed during the Curtius rearrangement.

The standard conditions to hydrolyze isocyanates are usually quite acidic and seemed incompatible with a sensitive β -isocyanato ketone **51**.³⁸ There exist reductive³⁹ conditions, but they seemed unsuitable for a substrate containing an enone. Therefore, we first elected a round-about way and protected the

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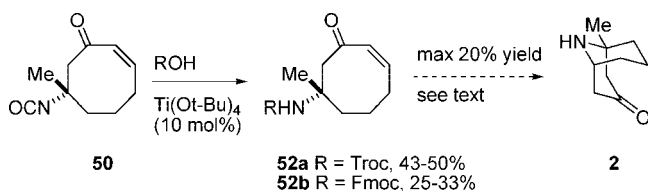
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SCHEME 12. Protection of Isocyanate 50 into a Carbamate and Subsequent Deprotection


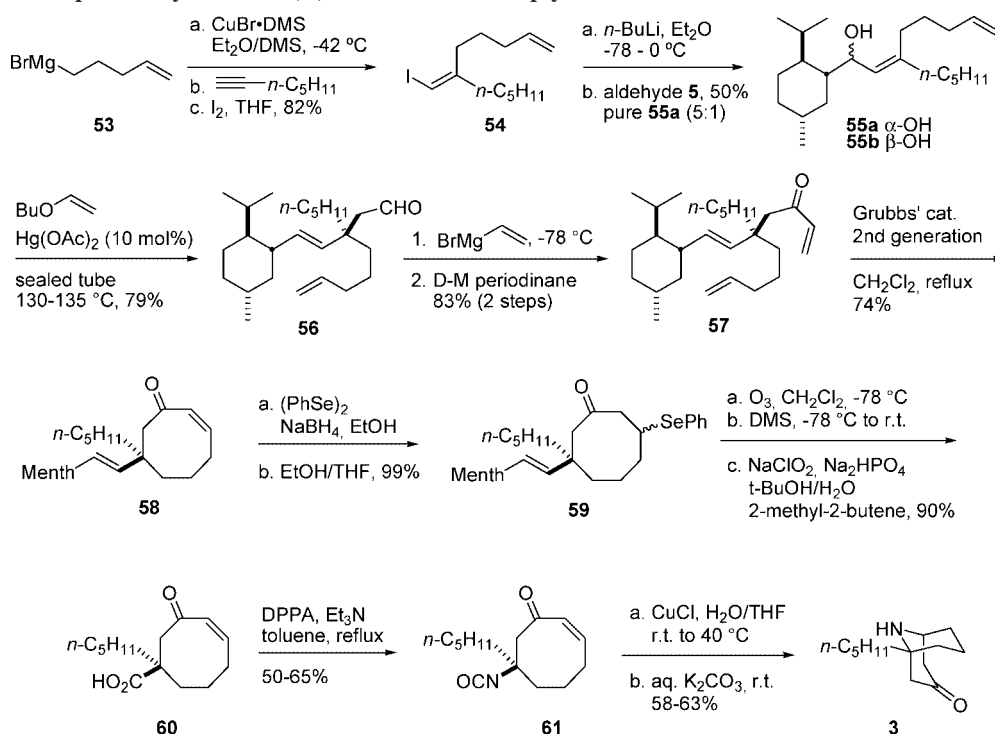
isocyanate into a Troc or Fmoc carbamate, which we planned on removing under milder conditions to access the free amine and allow the intramolecular cyclizations to **2**. These protections were effected in modest yield using our catalyst $\text{Ti(O-}t\text{-Bu)}_4$ (Scheme 12).¹⁷ Under typical reductive deprotection conditions to remove the Troc protecting group (zinc dust), a mixture of unidentified compounds was obtained, though partial reduction of the enone was obvious. Removal of the Fmoc protecting group under basic conditions, using piperidine or TBAF, did not fare better and gave a mixture of unknown products. Possibly, addition of piperidine in a Michael fashion to the enone caused problems. When the reaction was conducted in deuterated solvents with the more hindered base DMAP, it was possible to detect by $^1\text{H NMR}$ the formation of euphococcinine and the latter was isolated in 20% yield.

In light of those failures, we decided to investigate the direct hydrolysis of the isocyanate, despite our earlier concerns. When the isocyanate was placed in aqueous HCl, a frequently used acid to accelerate the hydrolysis of isocyanates,⁴⁰ followed by a basic treatment, (+)-euphococcinine **2** was isolated in 35–40%. We were pleased by this result but looked to improving the yield of reaction. $\text{Ti(O-}t\text{-Bu)}_4$ ¹⁷ and CuCl ⁴¹ are two Lewis acids used to facilitate the addition of alcohol on isocyanates, but the former cannot be used with water because of its rapid reaction to form titanium oxide.¹⁷ To the best of our knowledge, copper

chloride has never been used to hydrolyze isocyanate and despite its low solubility in water and THF, it gave quite acceptable yields of (+)-euphococcinine **2**, after treatment with base (Scheme 11). Spectral data were identical to the one reported for the natural (+)-euphococcinine.^{2,7a,8b-f}

A similar sequence of reactions was used for the synthesis of natural (–)-adaline. Note that the absolute configuration of natural adaline is opposite that of natural euphococcinine, yet we need not change chiral auxiliary for its synthesis. Vinyl iodide **54** was obtained via a carbocupration of 1-heptyne (Scheme 13).⁴² The vinyl iodide was always slightly contaminated with the dimer resulting from a homocoupling but the latter did not interfere with the subsequent reaction and was removed thereafter. After a lithium–halogen exchange, the corresponding vinyl lithium was added to the *p*-menthane-3-carboxaldehyde **5** to give the allylic alcohol **55a** in 50% pure yield (ratio **55a**:**55b** 5:1) (>96% de, determined by $^1\text{H NMR}$). We feared that the more sterically demanding quaternary carbon might lower the yields of the subsequent steps, but that turned out to be incorrect and (–)-adaline was obtained after the same sequence of reaction as described for the synthesis of (+)-euphococcinine with similar yields (Scheme 13). The final hydrolysis of the isocyanate to give (–)-adaline **3** proceeded in 69% yield. Spectral data (^1H and $^{13}\text{C NMR}$, IR, MS, and optical rotation) were identical to those reported for the natural (–)-adaline.^{3,7a,8a,b,f}

In summary, *p*-menthane-3-carboxaldehyde **5** was used for the formation of quaternary centers using a 3,3-sigmatropic rearrangement. The total syntheses of two alkaloids containing a quaternary amine carbon, namely (+)-euphococcinine **2** and (–)-adaline **3**, were achieved in only 10 steps each, with overall yields of 7.6% and 6.3% and average yields per step of 77% and 76%, respectively. Both syntheses began with simple starting materials. The same chiral auxiliary was effectively used to make those two antipodal alkaloids.

SCHEME 13. Ten-Step Total Synthesis of (–)-Adaline from 1-Heptyne


Experimental Section

Allylic Alcohols 34a and 34b. Argon was bubbled through a solution Cp_2ZrCl_2 (1.53 g, 5.23 mmol) in CH_2Cl_2 (75 mL) at rt for 5 min. Then, AlMe_3 (11.1 mL, 116 mmol) was added, and the resulting mixture was stirred for 30 min. The solution was cooled to 0 °C, hept-1-en-6-yne **42**²⁹ (3.62 g, 38.5 mmol) was added dropwise, and the reaction mixture was stirred for 22 h at rt. A solution of (-)-*p*-menthane-3-carboxaldehyde **5** (3.06 g, 18.2 mmol, freshly distilled under reduced pressure) in THF (70 mL) was slowly transferred via canula at -78 °C over a period of 10 min. The reaction mixture was stirred for 17 h and allowed to warm to rt. It was then cooled to 0 °C, a saturated aqueous solution of K_2CO_3 was slowly added, and the mixture was allowed to stir until no more gas evolution was observed and a white precipitate formed. Then, a 1 N HCl aqueous solution was added to dissolve completely the precipitate. The phases were separated, and the aqueous phase was quickly extracted with three portions of Et_2O to avoid rearrangement of the alcohol. The organic layers were combined, washed with brine, dried over anhydrous MgSO_4 , and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with a mixture of Et_2O and hexanes (5:95 to 10:90) to yield alcohol **34a** as a colorless oil (3.48 g, 68%, >99% de as determined by GC analysis) as the major diastereomer and 500 mg of alcohol **34b** (9%) as the minor diastereomer. Major isomer **34a**: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 5.80 (ddt, 1H, $J = 17.3, 10.2, 6.6$ Hz), 5.33 (d, 1H, $J = 8.0$ Hz), 4.99 (dd, 1H, $J = 17.3, 1.7$ Hz), 4.94 (d, 1H, $J = 10.2$ Hz), 4.66 (d, 1H, $J = 8.0$ Hz), 2.23–2.13 (m, 1H), 2.06–1.98 (m, 4H), 1.75–1.66 (m, 3H), 1.63 (s, 3H), 1.51 (quint, 2H, $J = 7.4$ Hz), 1.39–1.23 (m, 3H), 1.03–0.80 (m, 4H), 0.93 (d, 3H, $J = 7.2$ Hz), 0.88 (d, 3H, $J = 6.6$ Hz), 0.77 (d, 3H, $J = 6.6$ Hz); $^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ (ppm) 138.7 (d), 136.5 (s), 127.1 (d), 114.5 (t), 67.6 (d), 44.8 (d), 43.1 (d), 39.1 (t), 35.1 (t), 34.0 (t), 33.3 (t), 32.7 (d), 26.9 (t), 26.3 (d), 24.2 (t), 22.8 (q), 21.6 (q), 16.4 (q), 15.5 (q); IR (film) ν (cm^{-1}) 3643–3236, 3081, 2953, 2871, 1724, 1711, 1642, 1441, 610; LRMS (m/z , relative intensity) 278 (M^+ , 5), 235 (5), 209 (5), 139 (100); HRMS calcd for $\text{C}_{19}\text{H}_{34}\text{O}$ 278.2610, found 278.2618; $[\alpha]_D^{20} = -39.5$ ($c = 0.73$, CHCl_3). Minor alcohol **34b**: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 5.76 (ddt, 1H, $J = 16.9, 10.4, 6.6$ Hz), 5.28 (d, 1H, $J = 9.9$ Hz), 4.96 (dd, 1H, $J = 16.9, 1.7$ Hz), 4.91 (d, 1H, $J = 10.4$ Hz), 4.54 (dd, 1H, $J = 9.9, 4.1$ Hz), 2.02–1.89 (m, 5H), 1.85–1.74 (m, 1H), 1.69–1.41 (m, 5H), 1.66 (s, 3H), 1.35–1.22 (m, 1H), 0.99–0.66 (m, 5H), 0.86 (d, 3H, $J = 6.1$ Hz), 0.79 (d, 3H, $J = 6.6$ Hz), 0.75 (d, 3H, $J = 6.6$ Hz); $^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ (ppm) 140.0 (s), 138.5 (d), 123.6 (d), 114.5 (t), 67.6 (d), 44.5 (d), 44.1 (d), 39.3 (t), 35.2 (t), 34.0 (t), 33.1 (t), 32.6 (d), 26.9 (t), 26.3 (d), 24.1 (t), 22.8 (q), 21.5 (q), 16.3 (q), 15.2 (q); IR (film) ν (cm^{-1}) 3567–3276, 2966, 2843, 1708, 1447; LRMS (m/z , relative intensity) 278 (M^+ , 5), 235 (5), 209 (5), 184 (10), 139 (90), 83 (100); HRMS calcd for $\text{C}_{19}\text{H}_{34}\text{O}$ 278.2610, found 278.2615; $[\alpha]_D^{20} = -18.9$ ($c = 0.55$, CHCl_3).

Aldehyde 43. In a sealed tube, a solution of alcohol **34a** (700 mg, 2.51 mmol), butyl vinyl ether (1.63 mL, 12.6 mmol), and mercury(II) acetate (115 mg, 0.360 mmol) was heated at 130–135 °C for 20 h. After being cooled to rt, the reaction mixture was diluted with brine and extracted with three portions of Et_2O . The organic layers were combined, washed with brine, dried over anhydrous MgSO_4 , and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with a mixture of Et_2O and hexanes (3:97 to 10:90) to yield

aldehyde **43** as a colorless oil (550 mg, 72%, >96% de as determined by $^1\text{H NMR}$): $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 9.69 (t, 1H, $J = 3.3$ Hz), 5.76 (ddt, 1H, $J = 17.1, 9.4, 6.6$ Hz), 5.38 (d, 1H, $J = 15.7$ Hz), 5.13 (dd, 1H, $J = 15.7, 9.4$ Hz), 4.98 (dd, 1H, $J = 17.1, 1.7$ Hz), 4.93 (d, 1H, $J = 9.4$ Hz), 2.34 (dd, 1H, $J = 14.7, 2.8$ Hz), 2.23 (dd, 1H, $J = 14.7, 3.6$ Hz), 2.00 (q, 2H, $J = 6.6$ Hz), 1.94–1.73 (m, 3H), 1.69–1.49 (m, 2H), 1.40–1.27 (m, 5H), 1.10 (s, 3H), 1.01–0.77 (m, 4H), 0.86 (d, 3H, $J = 7.2$ Hz), 0.85 (d, 3H, $J = 6.6$ Hz), 0.68 (d, 3H, $J = 6.6$ Hz); $^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ (ppm) 204.0 (d), 138.6 (d), 135.6 (d), 134.1 (d), 114.5 (t), 54.0 (t), 47.1 (d), 45.2 (d), 43.6 (t), 41.7 (t), 38.1 (s), 35.1 (t), 34.0 (t), 32.4 (d), 28.2 (d), 23.9 (t), 23.8 (q), 23.2 (t), 22.6 (q), 21.4 (q), 15.1 (q); IR (film) ν (cm^{-1}) 3081, 2940, 2852, 2737, 1726, 1642, 1456, 1381, 1364; LRMS (m/z , relative intensity) 304 (M^+ , 5), 260 ($[\text{M}-\text{C}_2\text{H}_4\text{O}]^+$, 30), 235 (25), 217 (100); HRMS calcd for $\text{C}_{21}\text{H}_{36}\text{O}$ 304.2766, found 304.2775; $[\alpha]_D^{20} = -21.6$ ($c = 1.00$, CHCl_3).

Cyclooctenone 45. To a solution of Grubbs' second-generation catalyst (9 mg, 0.01 mmol) in CH_2Cl_2 (70 mL) was added a solution of the enone **33** (117 mg, 0.350 mmol) in CH_2Cl_2 (70 mL). The resulting mixture was refluxed for 1 h. It was then opened to the air and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with a mixture of Et_2O and hexanes (10:90 to 15:85) to yield enone **45** as a colorless oil (78 mg, 74%): $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 6.45 (dt, 1H, $J = 12.1, 8.5$ Hz), 6.21 (d, 1H, $J = 12.1$ Hz), 5.38 (d, 1H, $J = 15.8$ Hz), 5.15 (dd, 1H, $J = 15.8, 9.1$ Hz), 3.04 (br d, 1H, $J = 12.1$ Hz), 2.72–2.66 (m, 1H), 2.51–2.41 (m, 1H), 2.43 (br d, 1H, $J = 12.1$ Hz), 1.93–1.69 (m, 4H), 1.62–1.31 (m, 6H), 1.04 (s, 3H), 1.02–0.79 (m, 4H), 0.87 (d, 3H, $J = 6.6$ Hz), 0.86 (d, 3H, $J = 6.6$ Hz), 0.69 (d, 3H, $J = 6.6$ Hz); $^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ (ppm) 201.4 (s), 142.5 (d), 136.8 (d), 136.6 (d), 132.3 (d), 52.3 (t), 47.3 (d), 44.9 (d), 43.7 (t), 36.9 (s), 35.2 (t), 34.2 (t), 32.5 (d), 28.8 (d), 28.1 (q), 25.9 (t), 24.2 (t), 22.6 (q), 21.4 (q), 20.6 (t), 15.3 (q); IR (film) ν (cm^{-1}) 3014, 2962, 2927, 2868, 1651, 1456, 1213, 807, 772; LRMS (m/z , relative intensity) 302 (M^+ , 20), 287 ($[\text{M} - \text{CH}_3]^+$, 5), 259 (25), 137 (55), 95 (75), 81 (100); HRMS calcd for $\text{C}_{21}\text{H}_{34}\text{O}$ 302.2610, found 302.2615; $[\alpha]_D^{20} = -104.1$ ($c = 1.62$, CHCl_3).

Isocyanate 50. To a solution of carboxylic acid **32** (34.5 mg, 0.19 mmol) and triethylamine (32 μL , 0.23 mmol) in toluene (1.3 mL) was added diphenylphosphoryl azide (47 μL , 0.22 mmol), and the resulting mixture was refluxed for 90 min. A saturated aqueous solution of NH_4Cl was added, the phases were separated, and the aqueous phase was extracted with three portions of Et_2O . The organic layers were combined, washed with brine, dried over anhydrous MgSO_4 , and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with a mixture of Et_2O and hexanes (20:80) to yield isocyanate **50** as a colorless oil (22 mg, 65%): $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 6.53 (dt, 1H, $J = 12.1, 8.8$ Hz), 6.24 (d, 1H, $J = 12.1$ Hz), 3.18 (d, 1H, $J = 12.4$ Hz), 2.85 (d, 1H, $J = 12.4$ Hz), 2.82–2.75 (m, 1H), 2.63–2.53 (m, 1H), 1.94–1.57 (m, 4H), 1.43 (s, 3H); $^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ (ppm) 197.7 (s), 143.0 (d), 136.1 (d), 123.0 (s), 57.7 (s), 55.1 (t), 36.1 (t), 31.1 (q), 25.4 (t), 20.1 (t); IR (film) ν (cm^{-1}) 3026, 2980, 2953, 2868, 2269, 1659, 1651, 1487, 1452, 1306, 1240, 1220, 1134; LRMS (m/z , relative intensity) 179 (M^+ , 15), 164 (5), 151 ($[\text{M} - \text{CO}]^+$, 10), 136 (35), 108 (50), 96 (100); HRMS calculated for $\text{C}_{10}\text{H}_{13}\text{NO}_2$ 179.0946, found 179.0950; $[\alpha]_D^{20} = -62.9$ ($c = 0.52$, CHCl_3).

(+)-Euphoccoccinine 2. To a solution of the isocyanate **50** (14.6 mg, 0.0814 mmol) in a mixture of H_2O (0.6 mL) and THF (1.0 mL) was added CuCl (18 mg, 0.18 mmol). The green suspension was stirred vigorously at rt for 29 h. CuCl (26 mg, 0.26 mmol) was added, and the resulting mixture was heated to 40 °C for 2.5 h. A saturated aqueous solution of K_2CO_3 was added, and the mixture was stirred vigorously at rt for 15 h and then extracted with three portions of CH_2Cl_2 . The organic layers were combined, washed

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with brine, dried over anhydrous MgSO_4 , and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with a mixture of MeOH and CH_2Cl_2 (saturated with NH_3) (2:98 to 5:95) to yield (+)-euphococcinine **2** as a white solid (7.9 mg, 63%). All spectroscopic data correspond to those reported in the literature:^{2,8c,e} mp 34–36 °C; ^1H NMR (300 MHz, CDCl_3) δ (ppm) 3.72–3.66 (m, 1H), 2.57 (dd, 1H, $J = 16.3, 6.9$ Hz), 2.44–2.35 (m, 2H), 2.21 (d, 1H, $J = 16.3$ Hz), 1.93 (br s, 1H), 1.73–1.44 (m, 6H), 1.19 (s, 3H); ^{13}C NMR (75.5 MHz, CDCl_3) δ (ppm) 211.2 (s), 53.5 (t), 52.3 (s), 49.8 (d), 46.3 (t), 38.6 (t), 31.6 (q), 31.2 (t), 18.1 (t); IR (film) ν (cm^{-1}) 3337–3156, 2931, 2874, 1704; LRMS (m/z , relative intensity) 153 (M^+ , 40), 124 (10), 110 (100), 96 (70); HRMS calcd for $\text{C}_9\text{H}_{15}\text{NO}$ 153.1154, found 153.1161; $[\alpha]_D^{20} = +5.4$ ($c = 0.65$, MeOH).

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Supporting Information Available: Experimental procedures for all new compounds not included in the Experimental Section of this article, ^1H NMR spectra for all new compounds, and GC traces for compounds **10**, **11a**, **11b**, **12**, **34a**, **34b**, **55a**, and **55b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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