Tetrahedron Vol. 38, No. 13, pp. 1959 to 1963, 1982
Printed in Great Britain.

0040-4020/82/131959-05$03.00/0
Pergamon Press Ltd.

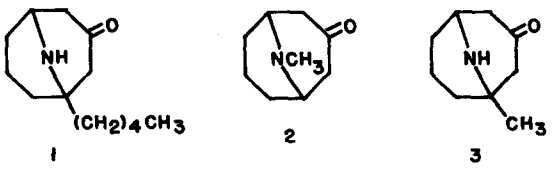
ASYMMETRIC SYNTHESES OF THE LADYBUG ALKALOID ADALINE AND 1-METHYL-9-AZABICYCLO [3.3.1]NONAN-3-ONE

RICHARD K. HILL and LOUIS A. RENBAUM
Chemistry Department, University of Georgia, Athens, GA 30602, U.S.A.

(*Received in U.S.A.* 20 *July* 1981)

Abstract—The double Michael addition of benzylamine to 3-alkyl-2,7-cyclooctadienones, followed by hydrogenolysis, affords bridgehead substituted 9-azabicyclo[3.3.1]nonan-3-ones. Use of (+)-α-methylbenzylamine in the addition leads to mixtures of diastereomeric adducts in unequal amounts. Although the degree of asymmetric induction is low (10–20% ee), the diastereomers can be easily separated, affording pure enantiomeric forms of the ladybug alkaloid adaline **1** and the *Euphorbia* alkaloid **3**.

Initial reports of a chemical defense mechanism in the European ladybug *Adalia bipunctata L.* appeared in 1961,[1] and in 1973 Tursch and his colleagues reported the isolation and proof of structure of the defensive alkaloid, adaline (**1**), from this and related species.[2] The azabicyclononane skeleton of adaline differs from the structures of other defensive secretions of the *Coccinellidae*,[3] but had previously been observed in nature in the familiar pomegranate alkaloid pseudopelletierine (**2**) and the 1-methyl derivative (**3**), found in the Australian coastal plant *Euphorbia atoto* Forst.[4]



The small amount of adaline isolated from ladybugs (35 mg from 800 specimens) emphasizes the desirability of a practical total synthesis. One obvious approach is the Robinson–Schöpf reaction, used to synthesize pseudopelletierine in almost 70% yield.[5] This method has been applied to the preparation of racemic **3**[6] and also racemic adaline,[7] although in the latter case the yield dropped to 17%. An elegant route to racemic adaline using an intramolecular nitrone cyclo-addition[8] has been achieved by Gössinger and Witkop, affording adaline in 30% overall yield in eight steps from N-hydroxy-piperidine.[9]

An attractive alternative approach is the conjugate addition of primary amines to a cross-conjugated cyclic dienone. First suggested by Robinson,[10] this route was put into practice by Horak[11] and Bottini[12] in syntheses of tropinone and pseudopelletierine. Other examples have been provided by Kashman[13] and Macdonald and Dolan have shown in a recent synthesis of pseudopelletierine that the requisite dienones can be constructed by carbene ring expansions.[14]

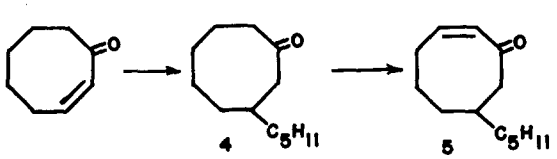
We report here the efficient total synthesis of the ladybug alkaloid **1** and the *Euphorbia* alkaloid **3** by this conjugate addition approach, using organocopper and selenium chemistry to prepare the starting cyclooctadienones, as well as a novel application of asymmetric synthesis which allows the preparation of both **1** and **3** in enantiomerically pure forms.

Initial efforts centered on the route shown in Scheme 1. Cuprous iodide-catalyzed conjugate addition[15] of n-amylmagnesium bromide to 2-cyclooctenone led smoothly to 3-n-amylcyclooctanone in 81% yield. Bromination[16] of the ketal of **4** did not proceed further than monobromination at C-8, apparently because of steric hindrance, and dehydrobromination afforded 3-n-amyl-7-cyclooctenone **5**. When repeated attempts to trap the kinetic enolate of **5** with phenylselenium bromide led to mixtures, this route was abandoned.

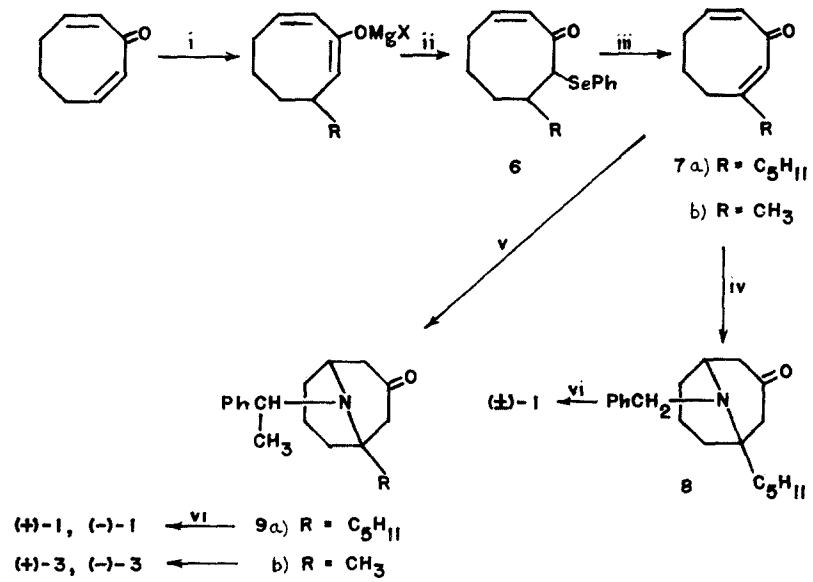
The successful, and more efficient, route is outlined in Scheme 2. Conjugate addition of n-amylmagnesium bromide or methylmagnesium iodide to 2,7-cyclooctadienone, followed by trapping the magnesium enolate with phenylselenium bromide, gave adducts **6**. These were not isolated but instead directly oxidized to the substituted dienones **7** via selenoxide elimination.[17] The overall yield in this three-step, one-pot sequence was 50–64%.

Although addition of ammonia gave dimeric or polymeric material,[13a] benzylamine added smoothly to dienone **7a** to give the crystalline bridged adduct **8**, isolated in 77% yield; the reaction was monitored by NMR and was complete after ten hours at room temperature. Hydrogenolysis of the benzyl group afforded racemic adaline, whose IR and NMR spectra were identical with those of the natural material. The overall yield of adaline from 2,7-cyclooctadienone was 39%.

The success of this double Michael addition provided an opportunity to test a novel example of asymmetric induction. The use of a chiral derivative of benzylamine should result in a mixture of diastereomeric adducts, presumably in unequal amounts, whose hydrogenolysis would provide the optically active alkaloid. Previous examples of this relatively rare type of asymmetric synthesis include the addition of (*R*)-or ((*S*)-α-methylbenzyl-



Scheme 1.



Scheme 2. Reagents: (i) RMgX, CuI, (ii) PhSeBr, (iii) H_2O_2, pyr, (iv) $PhCH_2NH_2$, (v) (+)-$PhCH(CH_3)NH_2$, (vi) H_2, Pd, $HClO_4$.

amine to crotonic, maleic, and fumaric acids and their esters.[18] Although the degree of asymmetric induction in these cases is low (5–15% ee), separation of the adducts followed by hydrogenolysis gave amino acids of high optical purity.

In the event, addition of (*R*)-(+)-α-methylbenzylamine to dienone **7a** gave a mixture of adducts **9a** in a 3:2 ratio. This mixture could be separated by a combination of low-temperature crystallization and chromatography into a solid diastereomer, m.p. 72–74°, and a liquid diastereomer. Catalytic hydrogenolysis of the solid isomer gave natural (-) adaline, $[\alpha]_D$ -11°, while hydrogenolysis of the liquid isomer afforded the enantiomer, $[\alpha]_D$ +12°. These rotations agree, within experimental error, with that reported for the natural pheromone, supporting the conclusion that the enantiomers are essentially optically pure.

(-) Adaline has been assigned the (1*R*,5*S*) configuration on the basis of the positive Cotton effect in its ORD spectrum.[7] Consequently the configurations of the diastereomeric Michael adducts can be assigned as shown in Fig. 1. The low degree of asymmetric induction (~ 20% e.e.) reflects the absence of a decisive preference for any of the possible transition state arrangements. Nevertheless the easy separation of the adducts allows the preparation of both pure enantiomers of adaline.

The enantiomeric forms of the *Euphorbia* alkaloid **3** were also synthesized, using the same approach. Addition of (+)-α-methylbenzylamine to dienone **7b** gave a mixture, this time in almost equal amounts, of diastereomeric adducts **9b**. Chromatographic separation again afforded a solid diastereomer, m.p. 77–79°, and a liquid diastereomer. Hydrogenolysis of the solid adduct gave (-)-**3**, $[\alpha]_D$ -6.8°, while hydrogenolysis of the liquid isomer gave (+)-**3**, $[\alpha]_D$ +7.5°. The close correspondence of physical properties in the amyl and methyl series (in each case the solid Michael adduct is more polar than the liquid diastereomer and is hydrogenolyzed to the levorotatory base) strongly suggests a correspondence in configurations. This argues that the natural dextrorotatory *Euphorbia* alkaloid **3** has the (1*S*,5*R*) configuration shown in Fig. 1, the opposite of adaline.

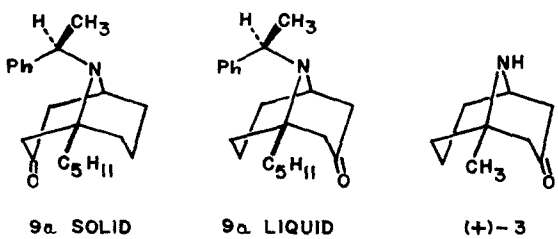
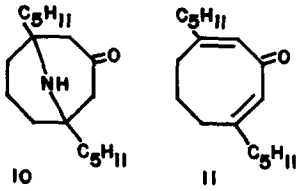


Fig. 1.

Antifeedant properties of adaline. The availability of both the natural and unnatural antipodes of the ladybug defensive alkaloid provided an opportunity to test for any gross difference in their repellent properties.[19] For this purpose imported fire ants, *Solenopsis invicta*, were chosen; they are notoriously impervious to a variety of repellents and deterrents. Two colonies of fire ants were starved for three days, then exposed to filter paper saturated with wheat-germ oil and mixed with varying concentrations of adaline. While the ants walked freely over the adaline-treated food, 87% of the ants refused to eat the wheat-germ oil containing 0.1 M adaline, and significant feeding deterrency was apparent at a concentration of 10^{-3} M. While adaline does not repel fire ants, it does appear to be a feeding deterrent. No statistical difference was found between the effects of (−) and (+)-adaline.

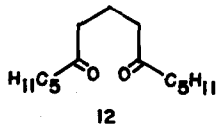
Related studies. Since the amyl substituent seems to be necessary for the strong binding to muscarinic acetylcholine receptors exhibited by dihydroadaline,[20] it was of interest to attempt the preparation of the symmetric derivative **10** containing a second amyl group at the other bridgehead. The requisite dienone **11** was prepared from dienone **7a** by the same conjugate addition-elimination sequence used to prepare **7a**. Unfortunately, the disubstituted dienone **11** was now inert to the double Michael addition; it was recovered unchanged from 72-hr

reflux with benzylamine in methanol and did not even react with ammonia in a sealed tube at 100° for one week. The Robinson–Schopf method, using diketone **12**, β-ketoglutaric acid, and ammonium chloride, also failed to yield **10**, giving instead an apparent aldol product.



10

11



12

EXPERIMENTAL

General methods. M.ps were determined in capillaries on a Thomas Hoover apparatus and are reported in °C, uncorrected. IR spectra were recorded on a Perkin Elmer 297 spectrophotometer. NMR spectra were recorded on a Varian EM-390 90 MHz instrument, using TMS as an internal standard. Mass spectra were recorded on a Finnigan 4023 GC/MS by Mr. Courtney Pape. Micro-analyses were performed by Atlantic Microlabs, Inc., Atlanta, Georgia. Diethyl ether was distilled from calcium hydride prior to use in Grignard conjugate additions, and THF was distilled from K. Low pressure liquid chromatography used Woelm type 206 silica gel, and TLC was performed on Merck plates precoated with silica gel 60 F-254.

3-n-Amylcyclooctanone (**4**). To a soln of amylmagnesium bromide prepared from 0.9 g Mg turnings in 30 ml dry ether and 5.3 g 1-bromopentane in 20 mL ether was added 30 mg anhyd cuprous iodide. The soln was cooled to 0° and a soln of 4.0 g 2-cyclooctenone[16] in 25 mL ether was added dropwise, keeping the temp below 5°. After the addition was complete, the soln was stirred 2 hr at room temp, then poured onto 25 mL 30% H_2SO_4 and 50 g ice. The layers were separated, the aqueous layer was extracted twice with ether, and the combined ether extracts were washed with 10% $Na_2S_2O_3$ and dried over $MgSO_4$. Distillation through a 6-in Vigreaux column afforded 4.3 g (81%) of **4**, b.p. 79–80° (0.12 mm); NMR ($CDCl_3$) δ0.85 (*t*, 3H, 1.1–2.1 (m, 17 H), 2.2–2.7 (m, 4 H); IR (neat) 2900–2850 (s), 1700 (s), 1460 cm^{-1}; mass spectrum, *m/e* (relative intensity 196 (3), 125 (20), 97 (25), 83 (30), 69 (40), 56 (80), 43 (100).

7-n-Amyl-2-cyclooctenone (**5**) (a) *From 2,7-cyclooctadienone.* To a soln of amylmagnesium bromide prepared from 0.27 Mg turnings and 1.51 g 1-bromopentane in 20 mL ether was added 5 mg cuprous iodide. The soln was cooled to 0° and a soln of 1.24 g 2,7-cyclooctadienone[16] was added dropwise, keeping the temp. at 0–5°. The mixture was stirred 1 hr at 0° and poured into 20 mL NH_4Cl aq. After separating the layers, the aqueous layer was extracted with two 10-mL portions of ether, and the combined ether layers were dried over $MgSO_4$ and concentrated. Distillation gave 1.51 g (78%) of **5**, b.p. 95–97° (0.7 mm); NMR ($CDCl_3$) δ 0.95 (t, 3H), 1.2–2.3 (m, 13 H), 2.5–2.6 (m, 4H), 5.9–6.5 (m, 2 H); IR (neat) 2940 (s), 1660 (s) cm^{-1}.

(b) *From* **4**. A mixture of 2.0 g of **4**, 0.65 g ethylene glycol, 15 mL benzene and a trace of *p*-toluenesulfonic acid was heated under reflux with a Dean-Stark trap for 12 hr, then poured into a mixture of 10 mL benzene and 30 mL water containing 0.1 g K_2CO_3. The organic layer was separated, washed with 20 mL water, dried over $MgSO_4$, and concentrated at reduced pressure to leave 2.5 g of crude ketal.

To a soln of the ketal in 20 mL ethylene glycol was added Br_2 (1.6 g) dropwise over 10 min. The mixture was stirred for 30 min, poured into 30 mL pentane and 1.0 g K_2CO_3, and 30 mL water was added a few min later. The organic layer was separated, dried over $MgSO_4$, and concentrated.

The residue was taken up in 10 mL MeOH containing 0.5 g NaOH and heated under reflux for 48 hr. The mixture was diluted with 15 mL NaCl aq and extracted with two 20-mL portions of pentane. The pentane extracts were concentrated and the residue was shaken with an equal volume of 3% H_2SO_4 for 5 min, then extracted with ether. The ether extracts were washed with brine, dried over $MgSO_4$, concentrated, and distilled to afford 0.87 g (45%) of **5**, b.p. 85–86° (0.6 mm). The NMR and IR spectra were identical with those of the product from part (a).

3-n-Amyl-2,7-cyclooctadienone (**7a**) A soln of 8.3 g 1-bromopentane in 40 mL anhyd ether was slowly added to 1.2 g Mg (with slight warming to initiate the reaction) at a rate sufficient to maintain gently reflux. After all the halide was added, the mixture was heated to reflux for 30 min, diluted with 50 mL ether, and cooled to 0° in an ice bath. Cuprous iodide (0.1 g) was added, causing the soln to turn dark. A soln of 6.1 g 2,7-cyclooctadienone (prepared by the method of Garbisch[16]) in 50 mL ether was added over 30–60 min, keeping the temp. below 5°; after addition was complete, the mixture was stirred for 30 min at 0°.

To a soln of 8.6 g diphenyl diselenide in 10 mL dry THF in a 25-mL addition funnel was added 3.95 g of Br_2. This mixture was stirred well, then added to the above stirred Grignard mixture, cooled in an ice bath, at such a rate that temp did not exceed 10°. The resulting yellow, gelatinous mixture was stirred for 10 min, poured into water, and extracted with four 100-mL portions ether. The extracts were washed twice with water, dried over $MgSO_4$, and concentrated at reduced pressure, leaving a dark oily residue of the crude **6**.

This crude selenide was taken up in 150 mL CH_2Cl_2 and 12.2 mL pyridine was added. Then a soln of 13.6 mL of 30% H_2O_2 in 12 mL water was added dropwise, keeping the temp between 30–35°; warming was necessary to initiate the reaction. After addition was complete, the mixture was stirred 30 min at room temp and poured slowly into a mixture of 75 mL CH_2Cl_2 and 90 mL sat $NaHCO_3$ aq. After extracting this mixture with 100 mL CH_2Cl_2, the extracts were washed with 200 mL 10% HCl, then with 200 mL of brine, dried ($MgSO_4$), and concentrated. The yellow oily dienone was eluted quickly through a 12-in column of 60–200 mesh silical gel with hexane, then subjected to low pressure liquid chromatography[21] (5 psi) on silica gel using hexane–ethyl acetate (19:10) as eluant. The dienone (5.6–6.2 g, 58–64%) was purified further by Kugelrohr distillation, b.p. 51–52° (0.01 mm). NMR ($CDCl_3$) δ 0.95 (t, 3H), 1.1–1.9 (m, 8H), 2.1–2.6 (m, 6H), 6.2–6.5 (m, 3H); IR (neat) 3020, 2940 (s), 2860, 1610 (s), 1618 (s), 1460, 1390, 1280, 1160, 875 (s) cm^{-1}; mass spectrum *m/e* (relative intensity) 193 (42), 192 (20), 164 (10), 150 (8), 135 (14), 121 (19), 107 (26), 93 (30), 91 (35), 81 (100), 79 (45), 77 (30), 67 (28), 53 (70), 41 (78).

N-Benzyl-1-n-amyl-9-azabicyclo[3.3.1]*nonan-3-one* (*N-benzyladaline*, **8**): A soln of 2.9 g of benzylamine in 10 mL MeOH was added to a soln of 2.9 g **7a** in 25 mL MeOH. The mixture was stirred 12 hr at room temp, concentrated at reduced pressure, and the residue was taken up in 50 mL ether and extracted with four 50-mL portions 10% HCl. The acidic extracts were washed twice with ether, then brought to pH 9–11 with NaOH aq and extracted with two 100 mL portions ether. The ether extracts were dried over $MgSO_4$ and concentrated at reduced pressure. The residue was taken up in hexane and quickly eluted through a 6 in column of silica gel (60–200 mesh) with hexanes–ethyl acetate (9:1) to remove dark polar impurities. After concentration of the eluate, the residue was precipitated several times at −78° from an ether-hexane (1:20) soln to afford 3.45 g (77%) of colorless base, mp 53–55°, R_f 0.18 (hexanes-ethyl acetate, 9:1). NMR ($CDCl_3$) δ 0.95 (t, 3H), 1.1–1.9 (m, 14H), 2.0–2.8 (m, 4H), 3.1–3.3 (m, 1H), 3.8 (AB quartet, J = 15 Hz, 2H), 7.2–7.5 (m, 5H); IR (neat) 3078, 3057, 3019, 2930 (s), 2850, 1700 (s), 1490, 1225, 903 (s), 725 (s) cm^{-1}; mass spectrum, *m/e* (relative intensity) 299 (15), 256 (20), 243 (25), 91 (100), 55 (20), 41 (40). (Found: C, 80.16; H, 9.75; N, 4.66. Calc. for $C_{20}H_{29}NO$: C, 80.27; H, 9.70; N, 4.68%).

1-n-Amyl-9-azabicyclo[3.3.1]*nonan-3-one*, (±)-*adaline* **1**. A mixture of 0.65 g of **8**, 130 mg 5% Pd/C, one drop 60% perchloric acid, and 20 mL MeOH was hydrogenated at atmospheric pressure at 25° for 48 hr; 52.5 mL H_2 was taken up. The mixture was filtered through celite and the filtrate was concentrated at reduced pressure. The residue was taken up in 5 mL of 20% NaOH aq, saturated with salt, and extracted with three 10-mL portions ether. The extracts were dried over $MgSO_4$, concentrated, and distilled in a Kugelrohr apparatus (100°, 0.05 mm) to

afford 0.40 g (88%) of (±)-adaline as a colorless oil. NMR ($CDCl_3$) δ 0.9 (t, J = 3 Hz, 3H), 1.1–1.9 (m, 14H), 2.1–2.7 (m, 4H), 3.8 (m, 1H); IR (neat); 3300 (m), 2920 (s), 2850 (m), 1700 (s), 1460 (m), 1200 (s), 1045 (m), 615 (m) cm^{-1}; mass spectrum, *m/e* (relative intensity) 210 (30), 166 (20), 153 (50), 96 (100), 43 (95). The NMR and IR spectra were identical with those of natural adaline kindly provided by Dr. B. Tursch.

The hydrochloride, prepared by adding a solution of dry HCl in ether, had m.p. 185–186°; lit.[7] m.p. 186°.

N-[(R)-1-Phenylethyl]-1-n-amyl-9-azabicyclo [3.3.1] *nonan-3 one* (**9a**). A mixture of 6.2 g of **7a** and 6.2 g (*R*)-(+)-α-methylbenzylamine in 70 mL MeOH was stirred for 12 hr at room temp and worked up as described for the preparation of **8** to give a mixture of diastereomers, R_f 0.17 and 0.25 (hexanes–ethyl acetate, 9:1). Preliminary separation was effected by taking up the residue in 45 mL hexanes and 5 mL ether, cooling to −78°, and quickly filtering the solid. The solid and the oil left from concentrating the filtrate were then separately chromatographed at 5 psi on Woelm type 206 silica gel, using hexanes–ethyl acetate (19:1), to afford 3.8 g of the solid diastereomer, R_f 0.17, and 3.2 g of the liquid diastereomer, R_f 0.25 (total yield 70%). The solid diastereomer could also be obtained pure by repeated crystallization from hexane–ether at −78°

Solid diastereomer of **9a**. m.p. 72–74°; NMR ($CDCl_3$) δ 0.85 (t, 3H), 1.2–1.8 (m, 14H), 1.5 (d, J = 6 Hz, 3 H), 2.2–2.5 (m, 4H), 3.4 (m, 1H), 4.6 (q, J = 6 Hz, 1H), 7.3–7.7 (m, 5H); IR (KBr) 2930 (s), 2860, 1700 (s), 1180, 750, 700 (s) cm^{-1}; mass spectrum, *m/e* (relative intensity) 313 (15), 166 (25), 153 (20), 105 (100), 79 (20), 41 (30). (Found: C, 80.40; H, 10.00; N, 4.52. Calc. for $C_{21}H_{31}NO$: C, 80.51; H, 9.90; N, 4.47%).

Liquid diastereomer of **9a**. NMR ($CDCl_3$) δ 0.92 (t, 3H), 1.1–1.8 (m, 14H), 1.95 (d, J = 7 Hz, 3H), 2.3 (s, 2H), 3.4 (m, 1H), 4.6 (q, J = 7 Hz, 1H), 7.2–7.7 (m, 5H); IR (neat) 2930 (s), 2860, 1700 (s), 1190, 755, 695 (s) cm^{-1}; mass spectrum, *m/e* (relative intensity) 313 (15), 166 (25), 153 (15), 105 (100), 79 (25), 41 (45).

Optical antipodes of adaline (**1**). Hydrogenolysis of the solid diastereomer of **9a** (760 mg) was carried out as described for hydrogenolysis of **8** to yield 440 mg (87%) of (−)-adaline, $[\alpha]_D$ − 11° (*c* = 2.0, $CHCl_3$), lit[2] $[\alpha]_D$ − 13° (*c* = 2.0, $CHCl_3$). The NMR, IR, and mass spectra were identical with those of racemic adaline.

The *hydrochloride* was prepared as described above, and had m.p. 203–206°, lit.[2] m.p. 204–205°.

Hydrogenolysis of the liquid diastereomer of **9a** was effected in the same manner to give 84% of (+)-adaline, $[\alpha]_D$ + 12° (*c* = 2.0, $CHCl_3$).

3-Methyl-2,7-cyclooctadienone (**7b**). The procedure for the preparation of **7a** was followed, using 7.8 g MeI in place of 1-bromo-pentane. Dienone **7b** was obtained in 50% yield; NMR ($CDCl_3$) δ1.6–2.1 (m, 2H), 2.2 (s, 3H), 2.2–2.7 (m, 7H), 6.4 (m, 3H); IR (neat) 2930 (s), 2860, 1620 (s), 1580, 1460, 1440, 1270, 1200, 820, 805 (s) cm^{-1}.

N-[(R-1-Phenylethyl]-1-methyl-9-azabicyclo[3.3.1]*nonan-3-one* (**9b**). A mixture of 3.4 g of **7b** and 4.8 g (*R*)-(+)-α-methylbenzylamine in 70 mL MeOH was stirred for 12 hr at room temp and worked up as described for the preparation of **8** and **9a**. The mixture of diastereomers was separated by low pressure (5 psi) liquid chromatography on silica gel, using hexane–ethyl acetate (19:1), to give 2.4 g of a solid, R_f 0.11 (hexanes-ethyl acetate 9:1), and 2.2 g of a liquid, R_f 0.16; the total yield was 72%.

Solid diastereomer of **9b**. m.p. 77–79; NMR ($CDCl_3$) δ 1.2 (s, 3H), 1.3–1.7 (m, 6H), 1.5 (d, J = 6 Hz, 3H), 2.2–2.7 (m, 4H), 3.6 (m, 1H), 4.55 (q, J = 6 Hz, 1H), 7.3–7.7 (m, 5H); IR (KBr) 2980, 2960, 2930, 2910, 2880, 1690 (s), 1485, 1345, 1182, 1100 (s), 1020 (s), 760 (s), 695 cm^{-1}; mass spectrum, *m/e* (relative intensity) 257 (30), 152 (15), 105 (100), 96 (30), 77 (40), 41 (50). (Found: C, 79.31; H, 9,01; N, 5.53. Calc. for $C_{17}H_{23}NO$: C, 79.37; H, 8.95; N, 5.45).

Liquid diastereomer of **9b**. NMR ($CDCl_3$) δ 1.3 (s, 3H), 1.4–1.7 (m, 6H), 1.5 (d, J = 7 Hz, 3H), 2.1–2.35 (m, 4H), 3.6 (m, 1H), 4.6 (q, J = 7 Hz, 1H), 7.3–7.7 (m, 5H); IR (neat) 3020, 2930 (s), 2860, 1000 (s), 1490, 1235 (s), 750, 720 (s), 695 (s) cm^{-1}; mass spectrum, *m/e* (relative intensity) 257 (40), 152 (20), 105 (100), 96 (25), 77 (30), 41 (45).

1-Methyl-9-azabicyclo[3.3.1]*nonan-3-one* (**3**). Hydrogenolysis of the solid diastereomer of **9b** (300 mg) was carried out as described for **8** and **9a**. The crude product was sublimed at 50° and 0.01 mm to yield 152 mg (85%) of (−)-3, m.p. 30–31°, $[\alpha]_D$ − 6.8° (*c* = 2.0, CH_3OH); NMR ($CDCl_3$) δ 1.1 (*s*, 3H), 1.3–1.7 (m, 6H), 2.0–2.7 (m, 4H), 3.65 (m, 1H); IR (neat) 3300, 2950 (s), 1700 (s), 1255, 1100, 800 cm^{-1}; mass spectrum, *m/e* (relative intensity) 153 (40), 110 (90), 96 (80), 82 (50), 68 (25), 55 (25), 42 (100).

The liquid diastereomer of **9b** was subjected to hydrogenolysis in the same manner to afford 145 mg (81%) of (+)-**3**, m.p. 30–31°, lit.[4] m.p. 30°, $[\alpha]_D$ + 7.5° (*c* = 2.0, CH_3OH), lit. $[\alpha]_D$ + 6.0° (*c* = 2.0, CH_3OH). The NMR, IR, and mass spectra were identical with those of the levorotatory enantiomer.

3,7-Di-n-amyl-2,7-cyclooctadienone (**11**) The procedure described above for preparation of **7a** was followed, substituting 9.6 g of **7a** for 2,7-cyclooctadienone. Workup gave 5.9 g (45%) of **11**, NMR ($CDCl_3$) δ 0.9 (t, 6H), 1.1–2.0 (m, 14H), 2.1–2.7 (overlapping triplets, 8H), 6.2 (s, 2H); IR (neat) 2940 (s), 1640, 1610 cm^{-1}; mass spectrum, *m/e* (relative intensity) 262 (10), 163 (20), 107 (30), 81 (40), 67 (40), 55 (60), 41 (100).

Bioassay of adaline[19] Two colonies of *Solenopsis invicta*, each containing about 10,000 workers and a large supply of brood, were starved for three days prior to testing. The alkaloid was mixed with wheat germ oil, a food readily acceptable to *S. invicta*. Filter paper discs, 6.5 mm dia., were saturated with wheat germ oil, patted dry, and skewered to a carboard feeding tray. For each of five feeding trials, 12 discs were prepared, half (control) receiving 5 μL acetone, half receiving adaline-treated wheat germ oil in concentrations ranging from 10^{-1} to 10^{-3} molar in adaline made up in 5 μL acetone. After the bait was placed in the foraging arena, a period of 20 min was allowed to establish foraging equilibrium, then at 5-min intervals from 20 to 40 min a count was made of the number of ants with mouthparts touching the bait. Trials were run at least 6 hr apart.

The mean acceptability of the bait, expressed as a percentage of the controls, was 13 ± 13% (10^{-1} M), 61 ± 18% (10^{-2} M), and 79 ± 19% (10^{-3} M). The enantiomers of adaline gave the same results within statistical error.

Acknowledgements—This research was supported by a grant (GM 28236) from the National Institutes of Health, to whom the authors express their appreciation. We thank Dr. B. Tursch (Free University of Brussels) for supplying us with spectra of adaline for comparison, and Dr. Dennis Howard (Entomology Dept., University of Georgia), for conducting the bioassays with *S. invicta*.

REFERENCES

[1]M. Rothschild, *Trans. Roy. Entomol. Soc. London* **113**, 101 (1961).
[2]B. Tursch, J. C. Braekman, D. Daloze, C. Hootele, D. Losman, R. Karlsson and J. M. Pasteels, *Tetrahedron Letters* 201–202 (1973).
[3]W. A. Ayer, L. M. Browne, *Heterocycles* **7**, 685–707 (1977).
[4]N. K. Hart, S. R. Johns and J. A. Lamberton, *Aust. J. Chem.* **20**, 561–563 (1967).
[5]A. C. Cope, H. L. Dryden Jr., C. G. Overberger and A. A. D'Addieco, *J. Am. Chem. Soc.* **73**, 3416–3418 (1951); A. C. Cope, H. L. Dryden Jr. and C. F. Howell, *Org. Synth. Coll. Vol. IV*, 816–819 (1963).
[6]K. Alder, H. Betzing, R. Kuth and H. A. Dortmann, *Liebigs Ann. Chem.* **620**, 73–87 (1959).
[7]B. Tursch, C. Chome, J. C. Braekman and D. Daloze, *Bull. Soc. Chim. Belg.* **82**, 699–703 (1973).
[8]*Cf.* J. J. Tufariello, G. B. Mullen, J. J. Tegeler, E. J. Trybulski, S. C. Wong, S. A. Ali, *J. Am. Chem. Soc.* **101**, 2435–2442 (1979).
[9]E. Gössinger and B. Witkop, *Monatsh. Chem.* **111**, 803–811 (1980).
[10]R. Robinson, *J. Chem. Soc.* **111**, 762–768 (1917).
[11]V. Horák and P. Zuman, *Tetrahedron Letters* 746–748 (1961); V. Horák, *Collect. Czech. Chem. Commun.* **28**, 1614–1617 (1963).

[12]A. T. Bottini and J. Gal, *J. Org. Chem.* **36**, 1718–1719 (1971).
[13]Y. Kashman and E. Benary, *Ibid* **37**, 3778–3781 (1972); Y. Kashman and S. Cherkez, *Tetrahedron* **28**, 155–165, 1211–1221 (1972).
[14]T. L. Macdonald and R. Dolan, *J. Org. Chem.* **44**, 4973–4976 (1979).
[15]A. C. Cope and G. L. Woo, *J. Am. Chem.* **85**, 3601–3608 (1963).
[16]E. W. Garbisch Jr., *J. Org. Chem.* **30**, 2109–2120 (1965).
[17]H. J. Reich, J. M. Renga and I. L. Reich, *J. Am. Chem. Soc.* **97**, 5434–5447 (1975); *J. Org. Chem.* **39**, 2133–2135 (1974).
[18]These examples are reviewed in J. D. Morrison and H. S. Mosher, *Asymmetric Organic Reactions* p. 321. Prentice-Hall, Englewood Cliffs, New Jersey (1971).
[19]These tests were conducted by Dr. Dennis Howard, Department of Entomology, Univ. of Georgia.
[20]B. Witkop, Plenary Lecture, International Research Congress on Natural Products as Medicinal Agents, Strasbourg, 6–11 July (1980).
[21]A. I. Meyers, J. Slade, R. K. Smith, E. D. Mihelich, F. M. Hershenson, C. D. Liang, *J. Org. Chem.* **44**, 2247–2249 (1979).