δ 6.64 (m, 1 H), 5.34 (s, 1 H), 1.23 (d, J = 6.3 Hz, 3 H).

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Registry No. **1a**, 22020-87-7; **1b**, 141345-97-3; **1c**, 141345-98-4; **3a**, 6142-73-0; **3b**, 124571-36-4; **3c**, 54211-14-2; **4a**, 141345-99-5; **4a** 4-spiro regioisomer, 141346-01-2; **4b**, 141346-00-1; **4b** 4-spiro regioisomer, 141346-02-3; **4c**, 141346-03-4; **4d**, 141346-04-5; **4d** 4-spiro regioisomer, 141346-05-6; **4e** (isomer 1), 141346-06-7; **4e** (isomer 2), 141434-12-0; **4f**, 141346-07-8; **4f** 4-spiro regioisomer, 141346-08-9; **4g** (isomer 1), 141346-09-0; **4g** (isomer 2), 141434-13-1; **4h**, 141346-10-3; **5a**, 141346-11-4; **5b**, 141346-12-5; **5c**, 141346-13-6; **5d**, 141346-14-7; **5e**, 141346-15-8; **5f**, 141346-16-9; *trans*-**5g**, 141346-17-0; *cis*-**5g**, 141346-18-1; *trans*-**5h**, 141346-19-2; *cis*-**5h**, 141434-14-2; **7f**, 141346-20-5; **7g**, 141346-21-6; **7h**, 141346-22-7; **8b**, 141346-23-8; **8c**, 141346-24-9; **8e**, 141346-25-0; **8f**, 141346-26-1; **8g**, 141346-27-2; **8h**, 141346-28-3.

Supplementary Material Available: ^{1}H- and ^{13}C-NMR spectra for compounds **5f**, *trans*-**5h**, and *cis*-**5h** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Asymmetric Synthesis. 26.[1] An Expeditious Enantioselective Synthesis of the Defense Alkaloids (−)-Euphococcinine and (−)-Adaline via the *CN*(*R*,*S*) Method

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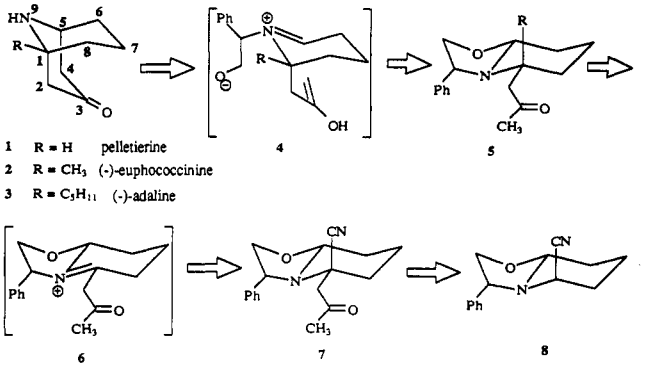
The unnatural enantiomer (−)-euphococcinine (**2**) and the natural enantiomer of (−)-adaline (**3**), two homotropane alkaloids, were each prepared in three steps from chiral (−)-2-cyano-6-oxazolopiperidine synthon **8** by the *CN*(*R*,*S*) method. The key steps of these syntheses are the formation of a chiral quaternary center α to the piperidine nitrogen with complete stereocontrol and a subsequent intramolecular Mannich reaction. The previously unknown absolute configuration of natural (+)-euphococcinine was deduced from the synthesis of its enantiomer (−)-**2**.

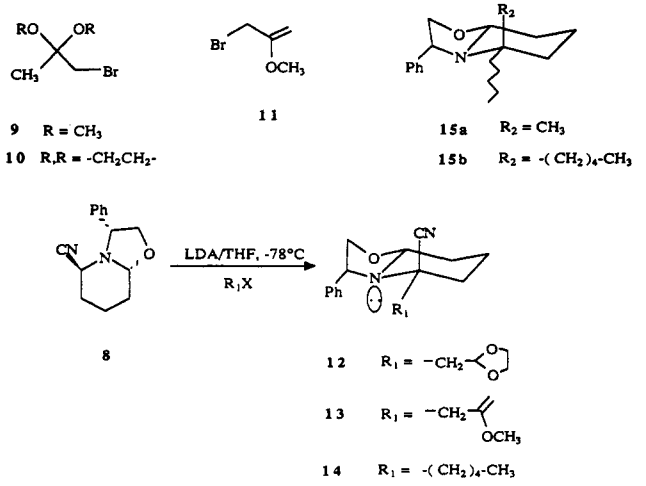
(+)-Euphococcinine (**2**) has been found in both the vegetable and the animal kingdoms. It was first isolated from *Euphorbia atoto*[2] and has also been found in the defense secretion of ladybugs *Cryptolaenus montrouzieri*[3a] and *Epilachna varivestis*.[3b] A pentyl analog, (−)-adaline (**3**), was also isolated from secretion of the ladybugs *Cryptolaenus montrouzieri*[3a] and *Adalia bipunctata*.[4] These alkaloids were found to exhibit repulsive activity against different insects. The absolute configuration of (−)-adaline has been determined to be 1*R*, 5*S*.[5] It is proposed that the absolute configuration of (+)-euphococcinine is 1*S*, 5*R*,[6] but this has yet to be proved.

In this paper we wish to report a new application of the established *CN*(*R*,*S*) method[7] to the enantioselective synthesis of **2** and **3**[6,8] from synthon **8**.[9] As depicted retrosynthetically in Scheme I, the strategy used involved stepwise introduction of an acetone equivalent and an alkyl chain in regio- and stereocontrolled manner. We show here that the Lewis acid TBDMSOTf is a very efficient agent for the selective formation of the appropriate iminium **6** from **7**, allowing formation of the quaternary center.

Scheme I



Scheme II



Results

Although several electrophilic equivalents of the acetonyl

(1) Part 25: Ratovelomanana, V.; Vidal, L.; Royer, J.; Husson, H.-P. *Heterocycles* **1991**, *32*, 879.

(2) Hart, N. K.; Johns, S. R.; Lamberton, J. A. *Aust. J. Chem.* **1967**, *20*, 561.

(3) (a) Brown, W. V.; Moore, B. P. *Aust. J. Chem.* **1982**, *35*, 1255. (b) Eisner, T.; Goetz, M.; Aneshausley, D.; Ferstandig-Arnold, G.; Meinwald, J. *Experientia* **1986**, *42*, 204.

(4) Tursch, B.; Braekman, J.-C.; Daloze, D.; Hootele, C.; Losman, D.; Karlsson, R.; Pasteels, J.-M. *Tetrahedron Lett.* **1973**, 201.

(5) Tursch, B.; Chome, C.; Braekman, J.-C.; Daloze, D. *Bull. Soc. Chim. Belg.* **1973**, *82*, 699.

(6) Hill, R. K.; Renbaum, L. A. *Tetrahedron* **1982**, *38*, 1959.

(7) Referring to the desire to obtain a *R* or *S* configuration α to the nitrogen by substitution of the CN group.

(8) For previous racemic syntheses of adaline and euphococcinine see: refs 5 and 6 and: (a) Alder, K.; Betzing, H.; Kuth, R.; Dortman, H. H. *Liebigs Ann. Chem.* **1959**, *620*, 73. (b) Gossinger, E.; Witkop, B. *Monatsh. Chem.* **1980**, *111*, 803. (c) Gnecco Medina D. H.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1983**, *24*, 2099.

(9) Bonin, M.; Grierson, D. S.; Royer, J.; Husson, H.-P. *Org. Synth.* **1991**, *70*, 54.

0022-3263/92/1957-4211$03.00/0

moiety have been reported,[10] we have encountered serious difficulties in acetonylation of synthon 8. Despite the fact that 8 condenses easily with bromoacetaldehyde ethylene acetal to give 12 (85% yield),[11] no alkylation product could be detected when α-bromo acetone ketals 9 and 10 were used as electrophiles (Scheme II). The neopentylic character of the electrophilic centers of 9 and 10 is probably the reason for their nonreactivity.[12]

We then turned to other reagents that, after alkylation, could afford a derivative transformable into key intermediate 7 (Scheme I) in a keto-protected form. A series of such reagents[10] (propene oxide, 1,2-dibromopropene, nitropropene, allylbromide) was tested without success. Yields were poor or zero for either the alkylation step or the subsequent reaction required for generation of the acetonyl function.

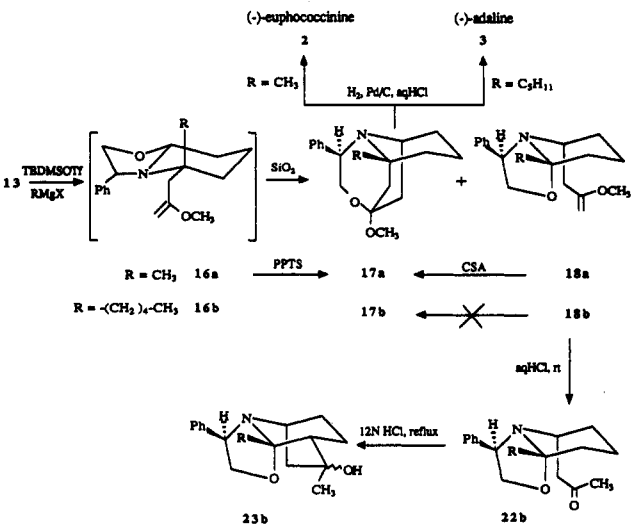
Finally, we found that 3-bromo-2-methoxy-1-propene (11), prepared by elimination of methanol from 9 by the method of Jacobson et al.,[10h] condensed with the anion derived from 8 to give 13[11] in 82% yield (Scheme II). The allylic position of the bromine makes it a better leaving group (S_N2 or S_N2' reaction).

The next problem to be tackled was the introduction of the alkyl chain (methyl or pentyl) onto 13 via the iminium ion generated by selective elimination of the nitrile group. The formation of such a quaternary center by reaction with a Grignard reagent is documented.[13] However, in our case it is possible to generate two different iminium ions. Thus, in addition to the stereochemical problem, a regioselectivity problem arises.

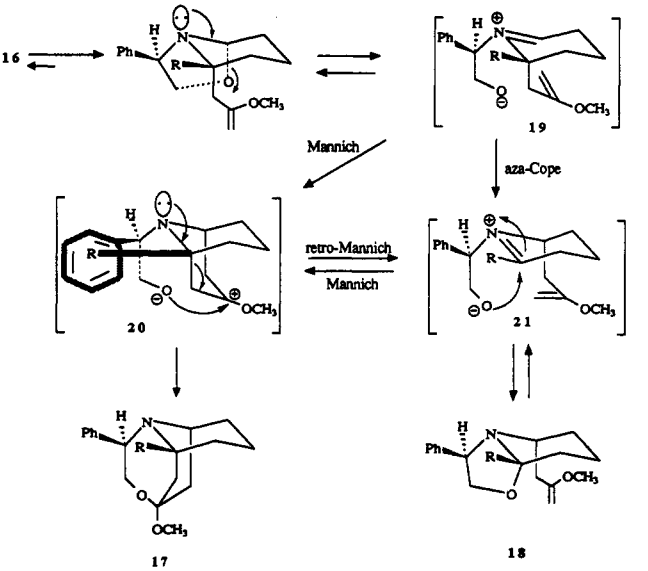
Several attempts to generate the iminium ion from the α-amino nitrile 13 using silver salts[11a,14] led only to complex mixtures. To prevent a possible interaction between the silver salt and the Grignard reagent,[15] we decided to use trimethylsilyl trifluoromethanesulfonate (TMSOTf) to promote elimination of the nitrile. We anticipated that, despite a possible complexation of the oxazolidine oxygen atom with the Lewis acid, elimination would generate the desired iminium preferentially, since only the cyano group of 13 is antiperiplanar to the nitrogen lone pair.

In order to verify this postulate, the 2-cyano-2-pentyl derivative 14, having no sensitive functionality other than the α-aminonitrile/oxazolidine system, was prepared by alkylation of 8 with pentyl bromide in 86% yield.

Scheme III



Scheme IV



Treatment of a CH_2Cl_2 solution of 14 at room temperature with 1 equiv of TMSOTf followed by addition at −78 °C of 1 equiv of methyl or pentyl Grignards in ether led to the formation of dialkylpiperidines 15a (61% yield) and 15b (73% yield),[11] respectively (Scheme II) with complete regio- and stereochemical control at the newly formed quaternary center.

Coming back to the key intermediate 13 of our synthetic scheme, we assessed the feasibility of the TMSOTf-mediated reaction by NMR. Addition of 1 equiv of TMSOTf in a $CDCl_3$ solution of 13 resulted in the disappearance of the CN signal at 118.3 ppm and the appearance of a new resonance signal at 189 ppm due to the iminium carbon. The oxazolidine carbon remained nearly unchanged at 93.5 ppm. This reaction appeared to be reversible because of the formation of TMSCN, which acts as a source of cyanide ion and regenerates the starting material. Nevertheless, no trace of iminium ion formation on the oxazolidine side could be detected.

We were thus confident that 13 could be alkylated in the desired manner. However, treatment of the preformed iminium ion in CH_2Cl_2 solution with methyl- or pentylmagnesium bromide in ether at −78 °C gave only a low yield of alkylated material plus recovered starting material. Higher reaction temperatures and longer reaction times did not increase the yield of alkylated material. This result

(10) For some representative examples see: (a) Nienhouse, E. J.; Irwing, R. M.; Finni, G. R. *J. Am. Chem. Soc.* **1967**, *89*, 4557. (b) Negishi, E.; Luo, F.-T. *J. Org. Chem.* **1983**, *48*, 2427. (c) Miller, R. B. *Synth. Commun.* **1972**, *2*, 267. (d) Miyano, M.; Dorn, C. R. *J. Org. Chem.* **1972**, *37*, 268. (e) Stork, G.; Jung, M. E. *J. Am. Chem. Soc.* **1974**, *96*, 3682. (f) Miyashita, M.; Yanami, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1976**, *98*, 4679. (g) Horning, D. E.; Kavadias, G.; Muchowski, J. M. *Can. J. Chem.* **1970**, *48*, 975. (h) Jacobson, R. M.; Raths, R. A.; McDonald, J. H., III. *J. Org. Chem.* **1977**, *42*, 2545. (i) Hosomi, A.; Shirahata, A.; Araki, Y.; Sakurai, H. *J. Org. Chem.* **1981**, *46*, 4631. (j) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1980**, *102*, 5699. (k) Schuda, P. F.; Bernstein, B. *Synth. Commun.* **1984**, *14*, 293. (i) Gu, X.-P.; Nishida, N.; Ikeda, I.; Okahara, M. *J. Org. Chem.* **1987**, *52*, 3192. (m) Vergne, F.; Aitken, D. A.; Husson, H.-P. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1346.

(11) These compounds have the stereochemistry depicted in Scheme II since the reaction proceeds with retention of configuration see: (a) Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754. (b) Yue, C.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1990**, *55*, 1140.

(12) The low electrophilicity of bromoketals 9 and 10 has been already reported: (a) Stork, G.; Gardner, J. O.; Boeckman, R. K.; Parker, K. A. *J. Am. Chem. Soc.* **1973**, *95*, 2014. (b) Larchevêque, M.; Valette, G.; Cuvigny, T. *Tetrahedron* **1979**, *35*, 1745.

(13) (a) Itzhak, Y.; Kalir, A.; Weissman, B. A.; Cohen, S. *J. Med. Chem.* **1981**, *24*, 496. (b) Kudzma, L. V.; Spencer, H. K.; Severnack, S. A. *Tetrahedron Lett.* **1988**, *29*, 6827.

(14) Overman, L. E.; Okazaki, M. E.; Jacobson, E. J. *J. Org. Chem.* **1985**, *50*, 2403.

(15) (a) Tamura, M.; Kochi, J. *J. Am. Chem. Soc.* **1971**, *93*, 1483. (b) Whitesides, G. M.; Gutowski, F. D. *J. Org. Chem.* **1976**, *41*, 2882.

is probably due to competition between the Grignard reagent and TMSCN initially formed. To suppress this side reaction, we replaced TMSOTf with the more hindered TBDMSOTf.

Thus, sequential treatment of **13** with TBDMSOTf and methylmagnesium iodide afforded compounds **17a** and **18a**[16] (Scheme III) in acceptable overall yields (50% and 30%, respectively). It is clear that these two structures cannot be formed directly from **13**. Indeed, examination of the crude reaction mixture by ^{13}C NMR showed the intermediate formation of **16a**, which rapidly rearranged upon contact with silica gel by opening of the oxazolidine ring. Cyclic ketal **17a** could arise from a Mannich reaction of iminium **19** followed by trapping of the intermediate oxonium **20** (Scheme IV). Formation of new oxazolidine **18a** may result from trapping of iminium ion **21**, which arises from **19** either through an aza-Cope rearrangement[17] or through stepwise Mannich–retro-Mannich reactions (Scheme IV). Compound **18a** could be transformed smoothly into **17a** by a Mannich reaction with a catalytic amount of camphorsulfonic acid in CH_2Cl_2 at room temperature. Since both **16a** and **18a** could be converted into **17a**, the crude reaction mixture of **13** with methyl Grignard was treated with PPTS to afford **17a** directly in 70% yield.

The final steps, consisting of hydrolysis of the ketal function and hydrogenolysis of the chiral appendage, were achieved in a one-pot reaction (H_2, Pd/C, dilute HCl in MeOH) to give (−)-euphococcinine ($[\alpha]_D^{20}$ −6.5° (CH_3OH, *c* 1.8) (lit.[2] $[\alpha]_D$ +6° (CH_3OH, *c* 2.0)) in 70% chemical yield.

In the synthesis of (−)-adaline, alkylation of **13** with pentylmagnesium bromide afforded a mixture of **17b** and **18b**[16] in 16% and 58% yields, respectively. However, no trace of **16b** was detected. The most intriguing feature was the failure of the attempted Mannich reaction of enol ether **18b** to give ketal **17b**. The use of PTSA, PPTS, CSA, TMSOTf, or $TiCl_4$ afforded only intractable mixtures or unchanged starting material. Treatment of **18b** with aqueous HCl resulted in hydrolysis of the enol ether to give ketone **22b**[16] in 90% yield. Interestingly, under more drastic conditions (concd HCl in MeOH at reflux for 24 h), isoquinuclidine **23b**[16] was formed from **18b**. This unexpected product shows that it is extremely difficult for **18b** to undergo the desired Mannich reaction.

The differences in yields of **17** and **18** for the methyl and pentyl series may be due to the steric factors that probably govern the evolution of intermediate **20**. Formation of ketal **17** necessitates proximity of the phenyl group to the R group. In the case where R = CH_3, there is not important steric hindrance that allows a preferential formation of ketal **17a**. In contrast, in the case where R = C_5H_{11}, an unfavorable steric interaction between the phenyl group and the pentyl chain prevents ketal formation, and thus opening of the azabicyclic system by a retro-Mannich reaction or a Grob fragmentation,[18] which leads to oxazolidine **18**, becomes the main process. The steric explanation could account for the failure to convert **18b** into **17b**.

(−)-Adaline **3** ($[\alpha]_D^{20}$ −12° ($CHCl_3$, *c* 0.6) (lit.[4] $[\alpha]_D$ −13° ($CHCl_3$)) was finally obtained from **17b** in 76% yield by the same procedure used for (−)-euphococcinine.

According to the *CN*(*R*,*S*) strategy, the absolute configuration of the newly created quaternary center is fixed at the alkylation step (**13** to **17**) and is predicted to be 1*R*,5*S* for our two levorotatory synthetic alkaloids. This prediction is confirmed by the identity of the specific rotations of our synthetic and natural (−)-adaline. Thus, we can deduce that natural (+)-euphococcinine possesses the 1*S*,5*R* configuration.

Experimental Section

General. General experimental conditions and spectroscopic instrumentation used have been described.[19] **3-Bromo-2-methoxy-1-propene (11)** was prepared according to the literature procedure.[12]

Hexahydro-5-(2-methoxyprop-2-enyl)-3-phenyl-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile (13). To a solution of LDA at −78 °C [prepared from 1.6 M *n*-BuLi in hexane (37.5 mL, 60 mmol) and diisopropylamine (8.4 mL, 60 mmol) in THF (20 mL) at −20 °C] was slowly added a solution of **8** (4.56 g, 20 mmol) in THF (80 mL). After the mixture was stirred at −78 °C for 30 min, 2-methoxyallyl bromide (**11**) (5 mL, 28 mmol) was added, and the mixture was stirred at −78 °C for 1 h. A saturated solution of NH_4Cl (20 mL) was added, and the mixture was warmed to room temperature and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried (Na_2SO_4) and concentrated to dryness in vacuo. The residue was purified by flash chromatography (4:1 heptane–Et_2O, saturated with ammonia) to afford **13** as white crystals (4.92 g, 82%): mp 115–117 °C (from heptane–Et_2O); $[\alpha]^{20}_D$ −202° ($CHCl_3$, c 0.44); IR (KBr) 2851, 2213, 1656 cm^{-1}; ^1H NMR (200 MHz) δ 7.20–7.45 (m, 5 H), 4.23 (t, *J* = 8 Hz, 1 H), 4.20 (dd, *J* = 3.0, 10.0 Hz, 1 H), 4.04 (dd, *J* = 4.0, 8.0 Hz, 1 H), 3.89 (d, *J* = 2 Hz, 2 H), 3.71 (dd, *J* = 4.0, 8.0 Hz, 1 H), 3.45 (s, 3 H), 2.35 (dd, *J* = 14.0, 2.0 Hz, 1 H), 1.69 (dd, *J* = 14.0, 2.0 Hz, 1 H), 1.5–2.2 (m, 6 H); ^{13}C NMR (50 MHz) δ 20.1, 29.6, 34.8, 45.6, 54.8, 62.3, 74.8, 85.7, 92.0, 118.3, 127.0, 128.9, 144.1, 157.8; MS (CI) *m*/*z* 299 (MH^+), 272, 227. Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.52; H, 7.52; N, 9.43.

1-Aza-2-phenyl-4-oxa-5-methoxy-7-methyltricyclo[5.4.1^{5,11}.0]dodecane (17a). To a solution of **13** at room temperature (259 mg, 0.87 mmol) in CH_2Cl_2 (2.5 mL) was added TBDMSOTf (340 μL, 1.48 mmol). The reaction mixture was stirred for 40 min and then was diluted with Et_2O (5 mL). The mixture was cooled to −78 °C while methylmagnesium iodide (1 M solution in ether) was added (2.2 mL, 22 mmol). After 2 h at −78 °C, the reaction was quenched with a saturated solution of NH_4Cl and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to dryness in vacuo. The crude product was redissolved in CH_2Cl_2 (25 mL), PPTS (80 mg) was added, and the mixture was stirred for 10 h at room temperature. The solvent was evaporated, and the residue was purified by flash chromatography (3:1 heptane–Et_2O) to afford **17a** (175 mg, 70%) as a waxy solid: mp 96–98 °C (Et_2O); $[\alpha]^{20}_D$ +68° ($CHCl_3$, *c* 0.87); IR (KBr) 2930, 1610 cm^{-1}; ^1H NMR (200 MHz) δ 7.1–7.5 (m, 5 H), 4.58 (dd, *J* = 12.0, 6.0 Hz, 1 H), 4.28 (t, *J* = 12.0 Hz, 1 H), 4.00 (dd, *J* = 12.0, 6.0 Hz, 1 H), 3.44 (m, 1 H), 3.35 (s, 3 H), 1.25–2.40 (m, 10 H), 0.85 (s, 3 H); ^{13}C NMR (50 MHz) δ 16.0, 31.8, 33.4, 38.9, 40.6, 43.7, 48.4, 53.3, 57.1, 64.9, 67.9, 101.4, 126.2, 126.3, 128.0, 143.8; MS (EI) *m*/*z* 287 (M^+, 34), 286 (72), 256 (28), 242 (100), 226 (36), 168 (41). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.23; H, 8.77; N, 4.87. Found: C, 74.99; H, 8.63; N, 5.10.

Hexahydro-5-(2-methoxyprop-2-enyl)-8a-methyl-3-phenyl-5*H*-oxazolo[3,2-*a*]pyridine (18a). The procedure was the same as that described for **17a** except that the crude alkylation product (before treatment with PPTS) was directly purified by flash chromatography (3:1 heptane–Et_2O) to afford **17a** (50%) and **18a** (32%) as colorless oils. **18a**: IR (neat) 2869, 1656 cm^{-1}; ^1H NMR (200 MHz) δ 7.1–7.4 (m, 5 H), 4.28 (m, 2 H), 3.77 (d, *J* = 1 Hz, 1 H), 3.68 (d, *J* = 1 Hz, 1 H), 3.62 (d, *J* = 4 Hz, 1 H), 3.42 (s, 3 H), 3.25 (m, 1 H), 1.95 (dd, *J* = 14.0, 4.0 Hz, 1 H), 1.6 (s, 3 H), 1.2–1.8 (m, 7 H): ^{13}C NMR (50 MHz) δ 21.7, 22.8, 24.3, 30.1, 42.0, 54.1, 54.6, 59.9, 72.8, 82.0, 96.0, 126.9, 127.1, 128.3, 146.3, 162.0; MS (EI) *m*/*z* 287 ($M^{\cdot+}$, 0.5), 272 (9), 217 (15), 216 (100);

(16) The exact stereochemistry of the quaternary carbon (α to nitrogen) of compounds **18**, **22b**, and **23b** has not been determined. Thus the structures drawn are only visual representations.

(17) (a) Doedens, R. J.; Meier, G. P.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 685. (b) Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Org. Chem.* **1989**, *54*, 1236 and references cited therein.

(18) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535.

(19) Aitken, D. J.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1990**, *55*, 2814.

HRMS calcd for $C_{18}H_{25}NO_2$ 287.1885, found 287.1874.

1-Aza-2-phenyl-4-oxa-5-methoxy-7-pentyltricyclo-[5.4.1^{5,11}.0]dodecane (17b) and Hexahydro-5-(2-methoxyprop-2-enyl)-8a-pentyl-3-phenyl-5*H*-oxazolo[3,2-*a*]pyridine (18b). To a solution of **13** (1.02 g, 3.42 mmol) in CH_2Cl_2 (5 mL) at room temperature was added TBDMSOTf (1.1 mL, 4.79 mmol) was added. After being stirred for 40 min, the reaction mixture was diluted with Et_2O (10 mL) and cooled to −78 °C. Pentylmagnesium bromide (2.6 mL, 5.2 mmol) was then added. After 1.5 h at −78 °C, the reaction was quenched at −78 °C by addition of a saturated solution of NH_4Cl and extracted with CH_2Cl_2 (3 × 40 mL). The extracts were dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by careful flash chromatography (5:1 heptane–Et_2O) to yield **17b** (188 mg, 16%) and **18b** (670 mg, 58%) as white solids and **13** (40 mg, 3.4%).

17b: mp 57–59 °C (from Et_2O); $[\alpha]^{20}_D$ +69.4° ($CHCl_3$, *c* 0.52); IR (KBr) 2864 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.1–7.4 (m, 5 H), 4.55 (dd, *J* = 11.0, 5.0 Hz, 1 H), 4.35 (t, *J* = 12 Hz, 1 H), 4.0 (dd, *J* = 11.0, 5.0 Hz, 1 H), 3.45 (m, 1 H), 3.35 (s, 3 H), 0.85–2.30 (m, 18 H), 0.7 (t, *J* = 7 Hz, 3 H); ^{13}C NMR (50 MHz) δ 14.0, 15.7, 22.5, 23.4, 32.4, 33.5, 39.1, 39.2, 39.3, 42.7, 48.3, 56.5, 57.6, 64.5, 68.0, 101.1, 126.2, 127.8, 143.6; MS (EI) *m/z* 344 (55), 312 (48), 298 (100), 282 (68), 242 (35), 224 (42); HRMS calcd for $C_{22}H_{33}NO_2$ 343.2512, found 343.2521.

18b: mp 35 °C (ether); $[\alpha]^{20}_D$ −76° ($CHCl_3$, *c* 0.5); IR (neat) 2864, 1649 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.2–7.5 (m, 5 H), 4.3 (m, 2 H), 3.73 (d, *J* = 2 Hz, 1 H), 3.62 (m, 2 H), 3.4 (s, 3 H), 3.18 (m, 1 H), 1.9 (dd, *J* = 13.0, 4.0 Hz, 1 H), 1.4–2.0 (m, 15 H), 0.95 (t, *J* = 6 Hz, 3 H); ^{13}C NMR (50 MHz) δ 14.2, 21.3, 22.6, 22.9, 23.1, 29.0, 32.5, 36.1, 42.1, 53.9, 54.6, 60.0, 73.3, 82.0, 97.7, 127.2, 128.4, 146.3, 162.1; MS (EI) *m/z* 344 (MH^+, 69), 328 (19), 273 (28), 272 (100), 258 (9), 224 (12). Anal. Calcd for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68; N, 4.08. Found: C, 76.65; H, 9.88; N, 4.02.

(−)-Euphococcinine (2). To a solution of **17a** (280 mg, 0.98 mmol) in methanol (40 mL) containing 1 mL of concd HCl was added Pd/C (10%, 100 mg), and the mixture was stirred at room temperature under a H_2 atmosphere (at ambient pressure). After hydrogen uptake ceased (about 1 h), the reaction mixture was filtered through a celite bed, and the filtrate was concentrated in vacuo. The residue was treated with $NaHCO_3$ (saturated solution) and then extracted with CH_2Cl_2 (4 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness. The crude reaction mixture was purified by flash chromatography (9:1 CH_2Cl_2–MeOH) to give (−)-euphococcinine (105 mg, 70%) as a white powder: mp 32 °C (CH_2Cl_2); $[\alpha]^{20}_D$ −6.5° (CH_3OH, *c* 1.80); IR (KBr) 1702 cm^{-1}; ^{1}H NMR (200 MHz) δ 3.68 (m, 1 H), 2.58 (dd, *J* = 16.0, 7.0 Hz, 1 H), 2.38 (m, 1 H), 2.4 (dd, *J* = 16.0, 1.2 Hz, 1 H), 2.24 (d, *J* = 16 Hz, 1 H), 2.14 (bs, 1 H, NH), 1.4–1.85 (m, 6 H), 1.2 (s, 3 H); ^{13}C NMR (50 MHz) δ 18.1 (CH_3), 31.2, 31.6, 38.6 (C_6), 46.2 (C_4), 49.9 (C_5), 52.3 (C_1), 53.3 (C_2), 210 (C=O); MS (EI) *m/z* 153 (M$^{\bullet+}$, 50), 110 (100), 96 (86); HRMS calcd for $C_9H_{15}NO$ 153.1154, found 153.1152.

Hexahydro-5-acetonyl-8a-pentyl-3-phenyl-5*H*-oxazolo-[3,2-*a*]pyridine (22b). To a solution of **18b** (170 mg, 0.5 mmol) in methanol (4 mL) was added a few drops of concd HCl. After being stirred at room temperature for 40 min, the mixture was evaporated to dryness in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and washed with aqueous $NaHCO_3$ solution. The organic phase was dried (Na_2SO_4) and evaporated. After flash chromatography (3:1 heptane–ethyl acetate) **22b** (147 mg, 90%) was obtained as a colorless oil: ^{1}H NMR (400 MHz) δ 7.2–7.4 (m, 5 H), 4.3 (m, 2 H), 3.6 (dd, *J* = 12.8, 11.0 Hz, 1 H), 3.53 (m, 1 H), 2.34 (dd, *J* = 17.0, 7.0 Hz, 1 H), 1.94 (m, 1 H), 1.94 (dd, *J* = 7.0, 6.5 Hz, 1 H), 1.5 (s, 3 H), 1.2–1.8 (m, 13 H), 0.95 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (50 MHz) δ 14.2, 21.2, 22.8, 23.7, 28.7, 29.7, 32.5, 35.9, 48.8, 50.3, 59.9, 73.0, 97.5, 127.2, 128.7, 146.0, 206.1; MS (EI) *m/z* 329 (M$^{\bullet+}$, 12), 286 (20), 250 (20), 258 (100), 200 (16), 104 (22); HRMS calcd for $C_{12}H_{31}NO_2$ 329.2365, found 329.2370.

Hexahydro-3-phenyl-8a-pentyl-7-hydroxy-7-methyl-5,8-ethano-5*H*-oxazolo[2,3-*a*]pyridine (23b). A solution of **18b** (278 mg, 0.81 mmol) in methanol (8 mL) and concd HCl (0.2 mL) was heated at reflux for 24 h. Methanol was evaporated, and the residue was dissolved in CH_2Cl_2 (10 mL). This solution was washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and then evaporated. The crude product mixture was applied to a column of flash silica. A first elution (3:1 heptane–ethyl acetate) afforded **22b** (80 mg, 30%). A second elution (10:1 CH_2Cl_2–CH_3OH) afforded **23b** (85 mg, 32%) as a colorless oil: ^{1}H NMR (250 MHz) δ 7.2–7.4 (m, 5 H), 5.42 (s, 1 H), 4.34 (m, 2 H), 3.48 (t, *J* = 12.0 Hz, 1 H), 2.82 (bs, 1 H), 2.18 (bd, *J* = 15.0 Hz, 1 H), 2.07 (t, *J* = 3.0 Hz, 1 H), 1.2–1.8 (m, 13 H), 1.3 (s, 3 H), 0.9 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (50 MHz) δ 14.0, 16.7, 22.7, 23.9, 24.9, 30.1, 32.1, 38.9, 39.9, 40.0, 52.4, 65.0, 68.8, 70.5, 102.6, 126.6, 127.1, 128.5, 142.4; MS (EI) *m/z* 330 (23), 329 (M$^{\bullet+}$, 17), 312 (11), 286 (36), 259 (56), 258 (100); HRMS calcd for $C_{21}H_{31}NO_2$ 329.2355, found 329.2359.

(−)-Adaline (3). The procedure described for (−)-euphococcinine was used to convert **17b** (540 mg, 1.57 mmol) into (−)-adaline (250 mg, 76%), which was obtained as a colorless oil: $[\alpha]^{20}_D$ −12° ($CHCl_3$, *c* 0.64); IR (neat) 1700 cm^{-1}; ^{1}H NMR (200 MHz) δ 3.65 (m, 1 H), 2.52 (dd, *J* = 16.0, 6.0 Hz, 1 H), 2.38 (m, 2 H), 2.16 (d, *J* = 16.0 Hz, 1 H), 2.05 (bs, 1 H), 1.27–1.75 (m, 14 H), 0.88 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (50 MHz) δ 14.0 (CH_3), 18.0, 22.4, 22.7, 31.8, 32.5, 36.7, 44.0 (C_6), 46.8 (C_4), 49.9 (C_5), 51.8 (C_2), 54.8 (C_1), 211.3 (C=O); MS (EI) *m/s* 209 (M$^+$, 32), 180 (17), 166 (100), 152 (88), 110 (42), 96 (58). Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.63; H, 11.30; N, 6.66.

Registry No. (−)-**2**, 84026-78-8; (+)-**2**, 15486-23-4; **3**, 41267-60-1; **8**, 88056-92-2; **11**, 26562-24-3; **13**, 141848-08-0; **17a**, 141848-09-1; **17b**, 141848-10-4; **18a**, 141848-11-5; **18b**, 141848-12-6; **22b**, 141879-11-0; **23b**, 141848-13-7.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of compounds **18a**, **17b**, **22b**, and **23b** (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and may be ordered from the ACS; see any current masthead page for ordering information.