A New Synthesis of (±)-Vincamine via Oppolzer's Aldehyde

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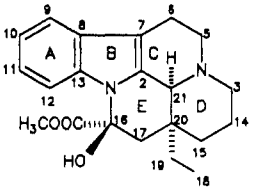
High-yield syntheses of the indole alkaloid vincamine (1) and some of its desethyl analogues based on the use of the known tetracyclic aldehydes **14** and **3** are described. Pentacyclic α-(dimethylamino)-β-hydroxylactam **15**, the key intermediate in this vincamine synthesis, was prepared from aldehyde **14** (Oppolzer's aldehyde) by reaction with LDA enolate of *N,N*-dimethylglycine methyl ester **2**. After dehydration, hydrolysis, and methanolysis, (±)-vincamine (1) was obtained in good yield.

Vincamine (1) is an indole alkaloid present in several *Vinca* species.[1] Because of its potent pharmacological activity, especially its cerebral vasodilatory effects, vincamine has been the subject of intensive pharmacological and synthetic study.[2]



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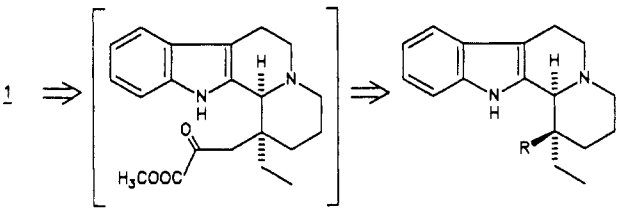
A formal total synthesis of (±)-1 was recently reported from our laboratory.[3] We have also published the synthesis of aldehyde **3**[4a] and its conversion to desethylhomoeburnamonine.[4b] Continuing this work we now describe a new method to create the E ring of vincamine-type alkaloids and show how the strategy can be applied to the synthesis of (±)-vincamine, 1.[5]

The usual approach to the synthesis of vincamine is to create at the final stage an α-oxo ester intermediate, which cyclizes spontaneously, generating the E ring of vincamine (Scheme I). Generally the α-oxo group is protected or a suitable masked precursor is used. In this work we investigated the use of α-(dimethylamino)acrylic esters which, after acid treatment, give the corresponding α-oxo esters. The acrylic esters can be synthesized from aldehydes and an enolate of *N,N*-dimethylglycine ester as described by Horner and Renth.[6] We used *N,N*-dimethylglycine methyl ester, **2**, which was easily prepared from methyl bromoacetate and dimethylamine hydrochloride by the procedure of Gate et al.[7]

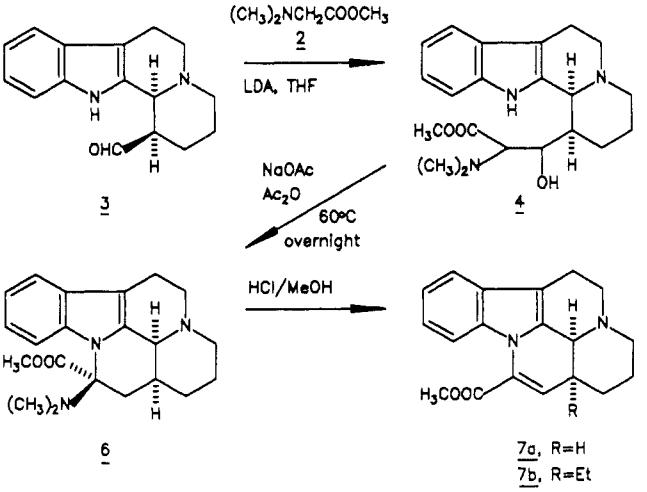
Model Studies. Synthesis of (±)-Desethylapovincamine, 7a. Our attempts to condense aldehyde **3** with glycine ester **2** using sodium hydride as base[6] were unsuccessful. However, aldehyde **3** reacted smoothly with lithium diisopropylamide (LDA) derived enolate of **2** to give α-(dimethylamino)-β-hydroxy ester **4** (*erythro* isomer) as the only isolable product in 54% yield (Scheme II). Dehydration of **4** turned out to be difficult. Several common methods used in the preparation of didehydro amino acid derivatives[8] (e.g. Ac_2O/pyridine, Ac_2O/pyridine/4-(dimethylamino)pyridine (DMAP), etc.) were tried but only heating in Ac_2O with NaOAc[9] was effective. Under these conditions, however, the fifth ring directly cyclized to give the pentacyclic vincamine derivative **6**[10] in 81% yield. The structure of **6** was deduced mainly from its ^{13}C NMR spectrum, which lacked the expected enamine signals of **5** but showed characteristic chemical shifts of a pentacyclic *cis*-indoloquinolizidine skeleton (see Chart I). Furthermore, in the IR spectrum of **6** a single absorption was detected in the carbonyl region, apparently suggesting the presence of an equatorial methoxycarbonyl group.[10a]

The formation of **6** was postulated as follows: the enamine ester **5** is formed from **4**, and this is protonated to

Scheme I. Retrosynthetic Analysis of Vincamine



Scheme II. Synthesis of Desethylapovincamine 7a



(1) For isolation, chemistry, and pharmacology of vincamine, see: Taylor, W. I., Farnsworth, N. R., Eds. *The Vinca Alkaloids*; Marcel Dekker: New York, 1973.

(2) For syntheses of vincamine, see, e.g.: Atta-ur-Rahman; Sultana, M. *Heterocycles* **1984**, *22*, 841.

(3) (a) Lounasmaa, M.; Jokela, R. *Heterocycles* **1986**, *24*, 1663. (b) Lounasmaa, M. Synthetic Studies in the Field of Indole Alkaloids. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1988, Vol. 1, Stereoselective Synthesis (Part A), pp 89–122.

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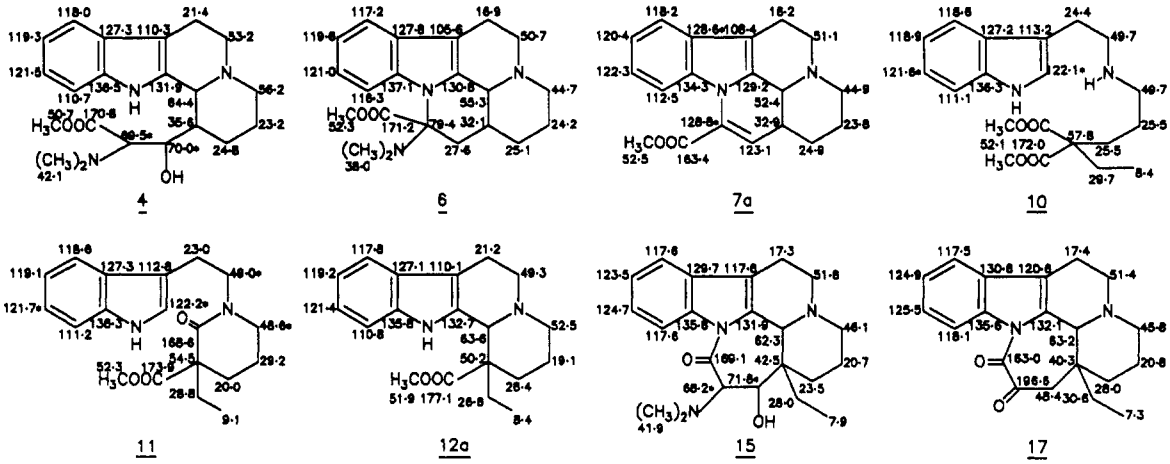
(8) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1988**, 159.

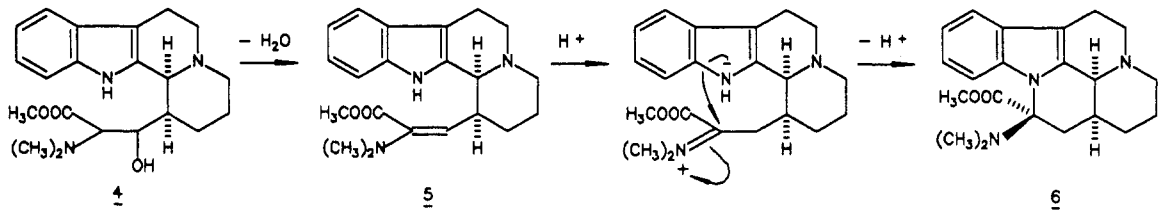
(9) Kato, T.; Higuchi, C.; Mita, R.; Yamaguchi, T. Jpn. Patent 60 190 749, 1985; *Chem. Abstr.* **1986**, *104*, 109267j.

(10) Related vincamine derivatives have previously been prepared: (a) Pfäffli, P.; Hauth, H. *Helv. Chim. Acta* **1978**, *61*, 1682. (b) Rossey, G.; Wick, A.; Wenkert, E. *J. Org. Chem.* **1982**, *47*, 4745.

Chart I. ^{13}C NMR Data of Compounds 4–17



Scheme III. Possible Formation of Pentacycle 6



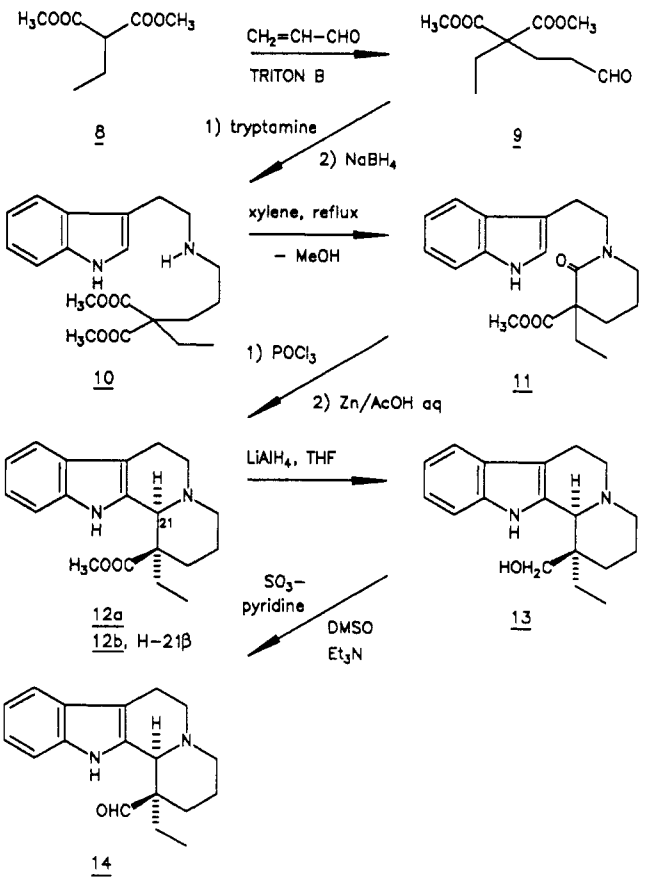
the iminium species which is then attacked by the indole nitrogen lone pair. Subsequent deprotonation affords the pentacycle **6** (Scheme III).

Desethylapovincamine, **7a**, synthesized previously by Potier and co-workers,[11] was obtained in 45% yield by treating **6** with hydrogen chloride in refluxing methanol.

Synthesis of Aldehyde 14 (Oppolzer's Aldehyde). Having a promising method in hand we directed our attention to the vincamine series. Aldehyde **14** has been the key intermediate in many vincamine syntheses. Its synthesis was first introduced by Oppolzer et al.,[12] and since then three other approaches have been presented: Danieli et al.,[13] Govindachari and Rajeswari,[14] and Langlois et al.[15a] Conversion of **14** to vincamine has been accomplished in six steps by Oppolzer's group[12] and in two steps (also in one-pot) by Langlois and co-workers.[15b] In a patent publication, Paracchini and Corvi-Mora[16] report obtaining vincamine and some of its derivatives from **14** via glycidic ester condensation. Danieli and co-workers[13] synthesized apovincamine **7b** from aldehyde **14** and methyl chloroacetate.

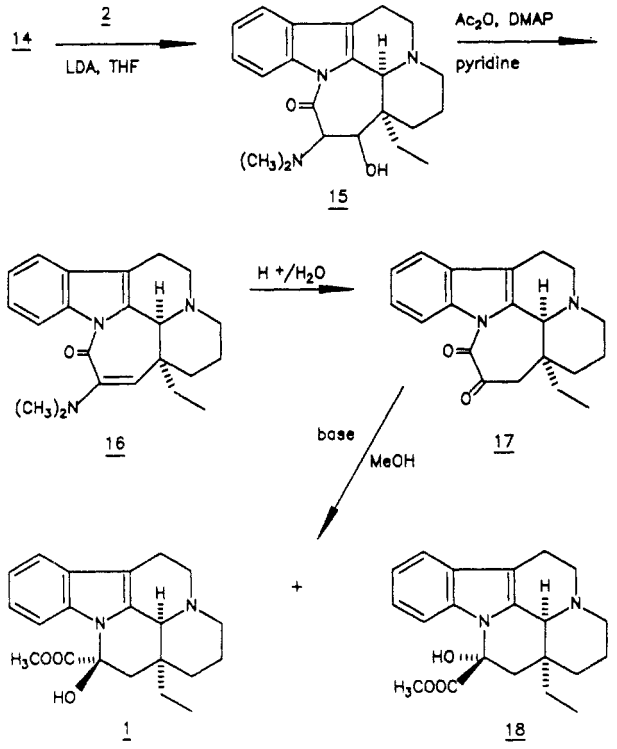
We prepared aldehyde **14** by a combination of the literature methods (Scheme IV).[14,15a,15b] Alcohol **13** was synthesized according to ref 14 and oxidized according to ref 15a or 15b. Michael reaction of dimethyl ethylmalonate (**8**) with acrolein in the presence of Triton-B gave oxo ester **9**. This compound was then condensed with tryptamine to an imine intermediate, which was immediately reduced with $NaBH_4$ to the secondary amino ester **10**. Cyclization to lactam **11** was effected in boiling xylene with a Dean–Stark trap to remove the formed methanol. Bischler–Napieralski cyclization gave, after reduction of the formed iminium species with zinc in aqueous acetic acid, 39% of the desired cis isomer **12a** and 17% of the trans isomer

Scheme IV. Synthesis of Aldehyde 14



(11) Thal, C.; Sévenet, T.; Husson, H.-P.; Potier, P. *C. R. Acad. Sci., Ser. C* **1972**, *275*, 1295.
(12) Oppolzer, W.; Hauth, H.; Pfäffli, P.; Wenger, R. *Helv. Chim. Acta* **1977**, *60*, 1801.
(13) Danieli, B.; Lesma, G.; Palmisano, G. *Gazz. Chim. Ital.* **1981**, *111*, 257.
(14) Govindachari, T. R.; Rajeswari, S. *Indian J. Chem., Sect. B* **1983**, *22*, 531.
(15) (a) Langlois, Y.; Pouilhès, A.; Gênin, D.; Andriamialisoa, R. Z.; Langlois, N. *Tetrahedron* **1983**, *39*, 3755. (b) Gênin, D.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y. *J. Org. Chem.* **1987**, *52*, 353.
(16) Paracchini, S.; Corvi-Mora, P. Eur. Patent 45 918, 1982; *Chem. Abstr.* **1982**, *96*, 218094n.

Scheme V. Synthesis of Vincamine 1



12b. The trans isomer can also be utilized in the synthesis of **14**.[14,15a] Lithium aluminum hydride reduction of **12a** in the usual manner yielded alcohol **13**, which was oxidized to aldehyde **14** using the SO_3–pyridine/dimethyl sulfoxide (DMSO) method described by Langlois et al.[15a,b]

(±)-Vincamine (1). The reaction of aldehyde **14** with the LDA enolate of glycine ester **2** furnished directly the cyclized product α-(dimethylamino)-β-hydroxylactam **15** (Scheme V), as esters of this type are easily cyclized under basic conditions.[4b] In our first experiments the yield of the lactam product **15** was unexpectedly poor (<10%), unreacted aldehyde **14** being partly recovered. However, we soon found that the yield could be increased (up to 49%) by adding DMSO (about 3 equiv). DMSO probably acts as a cosolvent.

Dehydration of lactam **15** was accomplished with acetic anhydride/DMAP in pyridine at room temperature. The intermediate enamine **16**[17] readily hydrolyzed to the known oxolactam **17**,[18] and the whole sequence proceeded in excellent yield (96%). Conversion of lactam **17** to vincamine with a base in methanol is well known.[12,18,19] In our hands, methanolysis of **17** with sodium carbonate as base gave, after 1 h of stirring at room temperature, 78% of (±)-vincamine (**1**) and 10% of (±)-16-epivincamine (**18**).

Experimental Section

All reactions were carried out under argon. Solvents were distilled over appropriate drying materials before use. Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. IR spectra (cm^{-1}, $CHCl_3$) were recorded on a Perkin-Elmer 700 spectrophotometer. ^1H NMR (59.8 MHz) and ^{13}C NMR (15.04 MHz) spectra were recorded on a JEOL JNM-FX 60 spectrometer using $CDCl_3$ as solvent. Chemical shifts are given in ppm downfield from TMS ($\delta = 0$). For the ^{13}C NMR data of compounds **4**, **6**, **7a**, **10**, **11**, **12a**, **15**, and **17**, see Chart I. EI and HR mass spectra (70 eV) were measured with a JEOL DX 303/DA 5000 mass spectrometer. Flash chromatography[20] was performed using Merck Kieselgel 60 (230–400 mesh).

α-(Dimethylamino)-β-hydroxy Ester 4. *n*-BuLi (1.1 M, 0.94 mL, 1.03 mmol) was added dropwise to a solution of diisopropylamine (0.14 mL, 1.03 mmol) in dry THF (2 mL) at −80 °C. After 10 min of stirring, methyl *N,N*-dimethylglycinate (120 mg, 1.03 mmol) in THF (1 mL) was added, and the mixture was stirred for 30 min. Aldehyde **3** (87 mg, 0.34 mmol) in THF (2 mL) was added, and stirring was continued for 2 h at −80 °C, after which the mixture was allowed to warm up to room temperature (ca. 1 h). The reaction medium was quenched with dilute aqueous $NaHCO_3$ and extracted with CH_2Cl_2. After drying (Na_2SO_4) and evaporation, the crude mixture was subjected to flash chromatography (CH_2Cl_2–MeOH, 98:2) to afford 68 mg (54%) of ester **4**: mp 84–87 °C (hexane); IR 3350 (OH), 1730 (ester C=O); ^1H NMR δ 7.82 (br s, 1 H), 7.5–7.0 (m, 4 H), 4.04 (d, J = 10 Hz, 1 H), 3.75 (br s, 1 H), 3.63 (s, 3 H), 3.30 (d, J = 10 Hz, 1 H), 2.27 (s, 6 H); MS m/z (relative intensity) 371 (M^+, 8), 312 (5), 256 (18), 255 (100), 224 (33); exact mass 371.2205 (calcd for $C_{21}H_{29}N_3O_3$ 371.2209).

Preparation of Pentacycle 6. Compound **4** (15 mg, 0.04 mmol) was dissolved in freshly distilled acetic anhydride (2 mL), and anhydrous NaOAc (33 mg, 0.4 mmol) was added. The mixture was stirred and heated at 60 °C overnight. The solution was evaporated to dryness on a rotary evaporator, and $NaHCO_3$ (aqueous) was added to the residue, after which it was extracted with CH_2Cl_2. Drying and evaporation gave 11.5 mg (81%) of pentacycle **6** as an amorphous solid: IR 1730 (ester C=O); ^1H NMR δ 8.05–7.8 (m, 1 H), 7.5–7.0 (m, 3 H), 3.63 (s, 3 H), 2.23 (s, 6 H); MS m/z (relative intensity) 353 (M^+, 12), 338 (15), 309 (28), 308 (100), 185 (73); exact mass 353.2088 (calcd for $C_{21}H_{27}N_3O_2$ 353.2103).

(±)-Desethylapovincamine (7a). Compound **6** (18 mg, 0.051 mmol) was dissolved in MeOH (3 mL) saturated with anhydrous HCl gas, and the mixture was refluxed for 12 h. Alkaline workup and flash chromatography (CH_2Cl_2–MeOH, 96:4) gave 7 mg (45%) of **7a**: mp 120–125 °C dec (acetone–hexane); IR 1730 (ester C=O), 1640 (C=C); ^1H NMR δ 7.5–7.0 (m, 4 H), 6.39 (d, J = 7 Hz, 1 H), 4.52 (m, 1 H), 3.94 (s, 3 H); MS m/z (relative intensity) 308 (M^+, 68), 307 (27), 265 (47), 264 (100), 238 (60); exact mass 308.1550 (calcd for $C_{19}H_{20}N_2O_2$ 308.1525).

Preparation of Oxo Ester 9. Compound **9** was prepared from dimethyl ethylmalonate (**8**) and acrolein according to ref 14. In the workup the combined CH_2Cl_2 extracts were filtered through a short column of silica to remove the polymers formed during reaction: yield 68%; bp 110–120 °C (1 mmHg); IR 1730 (aldehyde and ester C=O); ^1H NMR δ 9.74 (br s, 1 H), 3.73 (s, 6 H), 2.6–1.5 (m, 6 H), 0.84 (t, J = 7.6 Hz, 3 H); ^{13}C NMR δ 200.5 (d), 171.4 (s, 2 C), 57.0 (s), 52.2 (q, 2 C), 39.0 (t), 26.4 (t), 24.4 (t), 8.4 (q); MS m/z (relative intensity) 216 (M^+, <1), 185 (25), 160 (100), 145 (42), 128 (50).

Preparation of Secondary Amine 10. For experimental details, see ref 14: yield 63%; mp 99–100 °C (CH_2Cl_2–Et_2O); IR 1725 (ester C=O); ^1H NMR δ 8.77 (br s, 1 H), 7.7–6.9 (m, 5 H), 3.66 (s, 6 H), 0.77 (t, J = 7.5 Hz, 3 H); MS m/z (relative intensity) 360 (M^+, 2), 230 (100), 198 (38), 144 (25), 131 (37), 130 (30); exact mass 360.2067 (calcd for $C_{20}H_{28}N_2O_4$ 360.2049).

Cyclization of 10 to Lactam 11. For details, see ref 14. Yield 59%; for IR, UV, MS, and ^1H NMR data of **11**, see ref 15a.

Bischler–Napieralski Cyclization of 11: Esters 12a and 12b. The cyclization was done as described in ref 14 or 15a, except that the iminium intermediate was directly reduced with zinc in aqueous AcOH. Yields 39% (**12a**) and 17% (**12b**). For IR, UV, MS, and ^1H NMR data of **12a**, see ref 15a.

Reduction of Ester 12a to Alcohol 13. For details, see ref 14, 15a, or 15b. Yield 95%; for ^{13}C NMR data of **13**, see ref 13.

Oxidation of Alcohol 13 to Aldehyde 14. For details, see ref 15a or 15b. Yield 86%; for ^{13}C NMR data of **14**, see ref 13.[21]

(17) Enaminolactam **16** could be isolated (MS: 349 (M^+, 100), 334 (42), 306 (25), 305 (30), 263 (35), 251 (54)), but as it was very susceptible to hydrolysis (even on a silica column, if it was eluted without a base) we preferred its direct conversion to **17**.

(18) Warnant, J.; Farcilli, A.; Toromanoff, E. Ger. Patent 2 115 718, 1971; *Chem. Abstr.* **1972**, *76*, 34462m.

(19) (a) Szántay, Cs.; Szabó, L.; Kalaus, Gy. *Tetrahedron* **1977**, *33*, 1803. (b) Szabó, L.; Kalaus, Gy.; Szántay, Cs. *Arch. Pharm. (Weinheim, Ger.)* **1983**, *316*, 629.

(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Preparation of Lactam 15 from Aldehyde 14. The LDA enolate of **2** was generated as described above from *n*-BuLi (1.6 M, 2.95 mL, 4.74 mmol), diisopropylamine (0.67 mL, 4.74 mmol), and methyl *N,N*-dimethylglycinate (556 mg, 4.74 mmol) in dry THF (6 mL) at −80 °C. Aldehyde **14** (446 mg, 1.58 mmol) in THF (3 mL) and DMSO (0.35 mL, 4.93 mmol) was added, and the mixture was stirred at −80 °C for 2 h. After being warmed up to room temperature (ca. 1 h), the mixture was worked up as above. Flash chromatography (CH_2Cl_2–MeOH, 98:2) gave first 130 mg of a mixture containing mainly the starting aldehyde. Further elution (CH_2Cl_2–MeOH, 90:10) yielded 285 mg (49%) of pure lactam **15**: mp 194–195 °C (CH_2Cl_2–Et_2O); IR 3630 (OH), 2810, 2760 (Bohlmann bands), 1700 (ester C=O); ^1H NMR δ 8.56 (m, 1 H), 7.4–7.1 (m, 3 H), 4.07 (m, 1 H), 3.75 (br s, 1 H), 2.66 (s, 6 H), 0.94 (t, J = 7 Hz, 3 H); MS m/z (relative intensity) 367 (M^+, 100), 283 (38), 281 (25), 267 (13), 253 (14), 237 (12), 197 (17), 170 (15); exact mass 367.2272 (calcd for $C_{22}H_{29}N_3O_2$ 367.2260).

Preparation of Oxolactam 17. Lactam **15** (50 mg, 0.136 mmol) was dissolved in dry pyridine (3 mL). Freshly distilled acetic anhydride (0.5 mL, ca. 40 equiv) and DMAP (5 mg, 0.041 mmol) were added, and the mixture was stirred at room temperature for 30 h. Water (2 mL) was added, and stirring was continued for 10 min. The mixture was basified with aqueous $NaHCO_3$, after which it was extracted with CH_2Cl_2. Usual workup and flash chromatography (EtOAc–hexane, 50:50) gave 42 mg (96%) of oxolactam **17**: mp 152–153 °C (Et_2O) (lit.[19a] mp 156 °C); IR 1730 (ketone C=O), 1695 (lactam C=O); ^1H NMR δ 8.42 (m, 1 H), 7.45–7.25 (m, 3 H), 4.05 (br s, 1 H), 0.92 (t, J = 7.3 Hz, 3 H); MS m/z (relative intensity) 322 (M^+, 100), 321 (44), 294 (67), 293 (58), 266 (66), 265 (62), 237 (26), 197 (28), 170 (21), 169 (25); exact mass 322.1675 (calcd for $C_{20}H_{22}N_2O_2$ 322.1681).

Conversion of Oxolactam 17 to (±)-Vincamine (1) and (±)-16-Epivincamine (18). Oxolactam **17** (41 mg, 0.127 mmol) was dissolved in absolute MeOH (5 mL), and anhydrous Na_2CO_3 (135 mg, 1.27 mmol) was added. After 1 h of stirring at room temperature the solvent was evaporated, water was added, and the mixture was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and evaporated to yield 43 mg of a mixture which, after flash chromatography (CH_2Cl_2–MeOH, 98:2), afforded 36 mg (78%) of (±)-vincamine (**1**), mp 224–225 °C (CH_2Cl_2–Et_2O) (lit.[13] mp 226–229 °C, lit.[19a] mp 234–236 °C). and 4.5 mg (10%) of (±)-16-epivincamine (**18**), mp 201–202 °C (MeOH) (lit.[13] mp 201 °C, lit.[19a] mp 210 °C). The IR, MS, ^1H NMR, and ^{13}C NMR data of (±)-**1** were consistent with those reported in literature.[15b,22]

Registry No. (±)-**1**, 2122-39-6; **2**, 7148-06-3; (±)-**3**, 127183-09-9; **4**, 127207-03-8; (±)-**6**, 127183-10-2; (±)-**7a**, 40179-82-6; **8**, 20717-67-9; **9**, 127183-11-3; **10**, 127183-12-4; (±)-**11**, 89240-98-2; (±)-**12a**, 89240-45-9; (±)-**12b**, 89300-54-9; (±)-**13**, 58451-76-6; (±)-**14**, 51049-28-6; (±)-**15**, 127183-13-5; (±)-**17**, 35226-35-8; (±)-**18**, 18210-81-6; CH_2=CHCHO, 107-02-8; tryptamine, 61-54-1.

Supplementary Material Available: NMR spectra for **4**, **6**, **7a**, **9**–**11**, **12a**, **14**, **15**, and **17** (11 pages). Ordering information is given on any current masthead page.

(21) We found the ^{13}C NMR signal of the carbonyl group of **14** at δ 204.8.

(22) Moldvai, I.; Szántay, Cs., Jr.; Tóth, G.; Vedres, A.; Kálmán, A.; Szántay, Cs. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 335.

Defense Mechanisms of Arthropods. 83. α- and β-Necrodol, Novel Terpenes from a Carrion Beetle (*Necrodes surinamensis*, Silphidae, Coleoptera)[1]

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The defensive secretion obtained from the rectal gland of the carrion beetle *Necrodes surinamensis* has been found to consist of a mixture of aliphatic acids and terpene alcohols. Octanoic acid, decanoic acid, (*Z*)-3-decenoic acid, (*Z*)-4-decenoic acid, hexadecanoic acid, and octadecanoic acid are the chief acidic components. The three major terpenes are lavandulol and α- and β-necrodol. The necrodols were shown to have a 1,2,2,3,4-pentamethylcyclopentane framework not previously found among natural monoterpenes. Formulas **9** and **10** are derived for α- and β-necrodol, respectively, chiefly on the basis of mass spectrometric and NMR spectroscopic analysis.

While the chemical weaponry of insects has been studied extensively, there are groups of these animals whose defenses have been largely ignored. One such neglected taxon is the beetle family Silphidae, comprising species of considerable ecological significance that are mostly carrion feeders. Silphid beetles have a single defensive gland that opens into the rectum and voids its products through the anus. Most species discharge their secretion as a liquid ooze.[2] *Necrodes surinamensis*, the so-called red-lined carrion beetle, is unusual in that it ejects its secretion as a spray, which it aims accurately in all directions by rotation of the abdominal tip.[3] In experiments with captive thrushes and ants, *Necrodes* proved highly unacceptable to such predators.[4] Initial indication that the secretion of *Necrodes* might be chemically interesting came from the odor of the spray, which combined the stench characteristic of carrion beetles with an unfamiliar fragrance.

Defensive fluid was collected for chemical analysis by causing beetles to discharge into chilled vials, or from whole glands isolated by dissection. Exploratory experiments revealed that the discharge contained a mixture of fatty acids and neutral monoterpene components. Further analysis was greatly simplified by separation of the fatty acids from the neutral components by extraction with aqueous base. The identification of the fatty acids proved

(1) For Paper 82, see: Peschke, K.; Eisner, T. *J. Comp. Physiol.* **1987**, *161*, 377.
(2) Meinwald, J.; Roach, B.; Hicks, K.; Alsop, D.; Eisner, T. *Experientia* **1985**, *41*, 516.
(3) Eisner, T.; Meinwald, J. *Psyche* **1982**, *89*, 357.
(4) Eisner, T.; Meinwald, J.; Monro, A.; Ghent, R. *J. Ins. Physiol.* **1961**, *6*, 272.