November, 1985] Bull. Chem. Soc. Jpn., 58, 3337—3345 (1985)

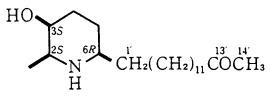
Total Synthesis of (−)-Deoxocassine and Its Diastereomers

Kazuo Kurihara, Takashi Sugimoto, Yutaka Saitoh, Yukinobu Igarashi,
Hiroshi Hirota, Yoshihiko Moriyama,† Takahiko Tsuyuki,* Takeyoshi Takahashi,*
and Qui Khuong-Huu††
Department of Chemistry, Faculty of Science, The University of Tokyo,
Hongo, Bunkyo-ku, Tokyo 113
††*Institut de Chimie des Substances Naturelles, Centre National de la Recherche Scientifique,*
91190-Gif-sur-Yvette, France
(Received July 12, 1985)

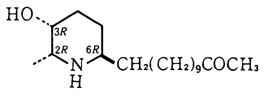
(−)-Deoxocassine [(2*R*,3*R*,6*S*)-6-dodecyl-2-methyl-3-piperidinol] and its diastereomers with 2*R*-configuration were synthesized starting from D-alanine by a route involving the intramolecular aminomercuration of an ε,ζ-unsaturated amine.

A number of piperidine alkaloids were isolated from plants of *Prosopis*,[1a] *Cassia*,[1b,c] *Azima*,[1d] and *Bathiorhamnus*[1e] species and from venoms of fire ants, *Solenopsis* species[1f] and their structures were elucidated. In these alkaloids, three substituents generally exist on the piperidine ring; a methyl or hydroxymethyl group at C-2, a hydroxyl or acyloxyl group at C-3, and a long alkyl side chain at C-6. Frequently there occur congeners from the same plant, and stereochemical investigation on the substituents between the congeners reveals that the same or homologous substituents on the same carbon atoms of the piperidine rings often possess the opposite configurations each other. For example, Christofidis *et al.*[1b] obtained three piperidine alkaloids, (+)-spectaline (**1**), (+)-iso-6-cassine (**2**), and (−)-cassine (**3**) from leaves of *Cassia spectablis* DC (Leguminosae). The absolute configurations of 2-methyl, 3-hydroxyl, and 6-alkyl side chain in these compounds were found to be (2*S*,3*S*,6*R*), (2*R*,3*R*,6*R*), and (2*R*,3*R*,6*S*) for **1**, **2**, and **3**, respectively.

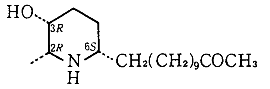
Many synthetic investigations of the piperidine alkaloids have been reported.[2] Recently we reported a total synthesis of (−)-deoxoprosopinine and (−)-deoxoprosophylline[3] using an intramolecular aminomercuration.[4] From an interest in the occurrence of diastereomeric compounds such as **2** and **3** from the same origin, a total synthesis of (−)-deoxocassine (**4**)[5] and its diastereomers was planned. Although (−)-deoxocassine (**4**) is corresponding to a deoxo derivative of (−)-cassine (**3**), the compound (**4**) was also registered as desoxoprosafrinine and desoxoprosafrinone in Ratle's dissertation.[5] The original piperidine alkaloids, (−)-prosafrinine (**5**) and (−)-prosafrine (**6**) were isolated from *Prosopis africana* (Guill and Perr.) Taub.[1a] This paper describes a total synthesis of (−)-deoxocassine (**4**) and two diastereomers (**7** and **8**) with 2*R*-configuration starting from D-alanine by a route utilizing the intramolecular aminomercuration.[4]



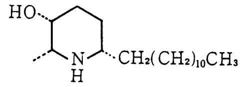
1



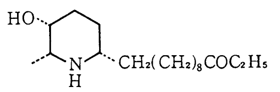
2



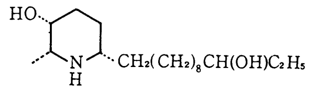
3



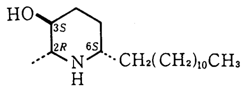
4



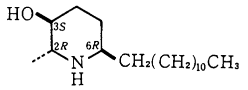
5



6



7



8

N-Phthaloylation[6] and the Rosenmund reduction[7] of D-alanine afforded (2*R*)-2-phthalimidopropanal (**9**), the aldehydic proton of which appeared as a sharp singlet at δ 9.68 in the ^{1}H NMR spectrum. The aldehyde (**9**) was treated with diallylzinc[8] in tetrahydrofuran (THF) at −30 to −10 °C to afford diastereomeric alcohols (**10** and **11**) in 51 and 10% yields, respectively. The major alcohol (**10**) showed double quartet signals due to $C_{(2)}$–H at δ 4.37 ($J_{2,3}$=4 Hz), while the corresponding signal of the minor alcohol (**11**) appeared at δ 4.42 as a quintet (J=7 Hz). The stereostructure of the major alcohol (**10**) was inferred to be an *erythro* isomer [(2*R*,3*S*)-2-phthalimido-5-hexen-3-ol] and the minor one (**11**) (2*R*,3*R*)-*threo* isomer by the Cram's rule, and these assignments were further confirmed by Horeau's method.[9] The *erythro* and *threo* isomers (**10** and **11**) were treated with racemic 2-phenylbutyric anhydride

---

† Present address: Institute of Chemistry, Kyoto Prefectural University of Medicine, Taishogun, Kita-ku, Kyoto 603.

and the reaction mixtures were worked up as usual, respectively. The 2-phenylbutyric acid obtained from the reaction with **10** showed $[\alpha]_D$ −0.015° (*c* 0.2, optical yield 10%) and the 2-phenylbutyric acid from **11** $[\alpha]_D$ +0.031° (*c* 0.2, optical yield 21%) showing that the asymmetric centers (C-3) of the secondary alcohols (**10** and **11**) possess *S* and *R* configurations, respectively.

Since the minor alcohol (**11**) with (3*R*)-configuration should be required for a preparation of (−)-deoxocassine (**4**), a direct conversion of the configuration at C-3 of the major alcohol (**10**) was attempted first using an adoptation of Mitsunobu's method.[10] However, treatment of **10** with an acid such as benzoic acid or formic acid in the presence of triphenylphosphine and diethyl azodicarboxylate did not afford any desired ester. When the reaction was conducted in the presence of *N*,*N*-dimethylformamide dineopentylacetal[10c,11] and bis(diethylamino)chlorophosphine,[10d,12] only a complex mixture was produced, respectively.

On oxidation with pyridinium chlorochromate, the main alcohol (**10**) gave a ketone (**12**) in 88% yield, which was subjected to reduction with zinc borohydride to afford two alcohols (**10** and **11**) in 25 and 53% yields, respectively. The main reduction product was completely identical, including the optical purity, with the alcohol (**11**) obtained as the minor product by the reaction of aldehyde (**9**) with diallylzinc.

The (2*R*,3*R*)-alcohol (**11**) was treated with methoxymethyl chloride in triethylamine and acetonitrile to afford (2*R*,3*R*)-*N*,*N*-phthaloyl-3-methoxymethoxy-5-hexen-2-amine (**13**) quantitatively. The methoxymethyl derivative (**13**) was subjected to hydroboration to give (4*R*,5*R*)-4-methoxymethoxy-5-phthalimido-1-hexanol (**14**) in 83% yield, which was oxidized with pyridinium chlorochromate. (4*R*,5*R*)-4-Methoxymethoxy-5-phthalimidohexanal (**15**), susceptible to air-oxidation, was obtained in 85% yield. The Wittig reagent which was generated from dodecyltriphenylphosphonium bromide (prepared by Chasin's procedure[13]) and butyllithium in hexane, was quickly treated with the aldehyde (**15**) in THF at −78 °C. The usual work-up gave (2*R*,3*R*)-3-methoxymethoxy-2-phthalimido-6-octadecene (**16**) in 60% yield. The olefin (**16**) is inferred to mainly consist of a (*Z*)-isomer, because no band due to *trans*-olefin was observed in the IR spectrum. This conclusion was confirmed by the separate synthetic route (*vide infra*).

The *N*-phthaloyl group of **16** was removed by treatment with an excess of hydrazine monohydrate to give (2*R*,3*R*,6*Z*)-3-methoxymethoxy-6-octadecen-2-amine (**17**), which, without purification, was subjected to the aminomercuration with mercury(II) acetate in methanol and successively to the demercuration with sodium borohydride. Since the reaction product was shown to be a complex mixture of several reaction products, the chromatographic separation was attempted, but the desired piperidine derivatives (**18** and/or **19**) could not be isolated. Then separation of the mixture was attempted after *N*-protection. However, neither *N*-*t*-butoxycarbonyl,[14] *N*-trityl, nor *N*-methoxycarbonyl derivative[15] could be prepared, while *N*-tosyl and *N*-acetyl derivatives could not be successfully deprotected. Then the mixture was treated with benzyloxycarbonyl chloride[16] and the reaction mixture was separated by silica-gel column chromatography to afford the sole product. The *N*-protected product was obtained only in a 15% isolation yield from **16** through three steps. The poor yield may be due to the facts that both dephthaloylation and aminomercuration yielded complex reaction mixtures. Any other diasteromeric isomer could not be isolated from the reaction mixture. The reaction product showed the molecular ion peak at *m*/*z* 461 and prominent fragment peaks at *m*/*z* 292 and *m*/*z* 91, indicating that the reaction product is one of the diastereoisomers of *N*-benzyloxycarbonylpiperidines (**20** and **21**).

The *N*-benzyloxycarbonylpiperidine was subjected to hydrogenolysis in the presence of 5% palladium on carbon to give the *N*-deprotected product (**18**) in 36% yield, which was successively treated with 1 M (1 M=1 mol dm^{-3}) hydrochloric acid in methanol at reflux temperature for 2 h. The reaction product, after alkalification, was extracted with ether and purified by column chromatography on alumina to give one diastereomer of (2*R*,3*R*)-6-dodecyl-2-methyl-3-piperidinols as white crystals, mp 47.5—48.5 °C, $[\alpha]_D^{18}$ −12.3°, in 44% yield. The physical and spectral data being identical with those of deoxocassine, and also desoxoprosafrinine and desoxoprosafrinone described in the Ratle's dissertation[5] (Table 1), the compound obtained by this preparation was determined to be (−)-deoxocassine (**4**) with a (2*R*,3*R*,6*S*)-configuration.

Stereochemistries of the synthetic (−)-deoxocassine (**4**) were further confirmed by ^{13}C and ^{1}H NMR and IR spectral measurements. The absolute configurations of (+)-spectaline (**1**) and (+)-iso-6-cassine (**2**) are (2*S*,3*S*,6*R*) and (2*R*,3*R*,6*R*), respectively and ^{13}C NMR shift values of C-2, C-3, C-6, and C-1′ are reported as shown in Table 2. The shift values observed in the synthetic (−)-deoxocassine (**4**) are nearly the same as those of the all-*cis*-substituted piperidine derivative, (+)-spectaline (**1**), indicating that two compounds possess the same relative configurations. Since the synthetic **4** possesses the (2*R*,3*R*) configuration, the stereochemistry of **4** was established to be (2*R*,3*R*,6*S*).

In ^{1}H NMR spectrum of the synthetic **4**, a methine proton at C-3 resonated at δ 3.56 as a multiplet signal, whose half-width was 4.8 Hz and a methine proton at C-2 was observed at δ 2.76 as double quartet

TABLE 1. COMPARISON OF PHYSICAL AND SPECTRAL DATA OF **4** WITH THOSE OF LITERATURE[5)]

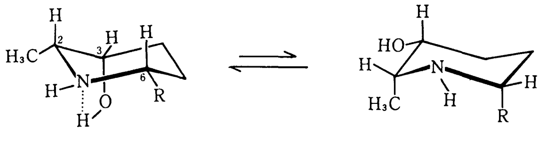
	4	Deoxoprosafrinone	Deoxoprosafrinine	Deoxocassine
mp (θ_m/°C)	47.5—48.5	50.5	50	50.5
$[\alpha]_D$	−12.3°	−8°	−12°	−11°
^{1}H NMR (δ)				
terminal-				
CH_3	0.88	0.88	0.88	0.88
$CH_{(2)}$-CH_3	1.11 (d, J=6.4 Hz)	1.11 (d, J=6.5 Hz)	1.11 (d, J=6.5 Hz)	1.08 (d, J=6.5 Hz)
-$(CH_2)_{11}$-	1.26	1.24	1.24	1.25
$C_{(3)}$-H	3.56	3.55	3.55	3.53
MS m/z (%)	283 (0.4) 114 (100) 96 (5)	283 (1) 114 (47) 96 (2.2)	284 (2) 114 (59) 96 (3)	

TABLE 2. ^{13}C NMR SPECTRA AND $W_{1/2}$ AND $J_{2,3}$ VALUES OF ^{1}H NMR SPECTRA OF **4**, **1**[1b)], AND **2**[1b)]

	Synthetic-**4**	**1**	**2**
^{13}C NMR spectra (δ)			
C-3	68.02	67.6	68.9
C-2	57.27	57.0	50.4
C-6	55.85	55.7	49.5
C-1′	36.97	37.1	34.0
^{1}H NMR spectra (δ)			
$C_{(2)}$-H	2.76 (dq, $J_{2,3}$=1.4 Hz)	2.90 (br m, $J_{2,3}$=1.5 Hz)	3.06 (oct, $J_{2,3}$=3 Hz)
$C_{(3)}$-H	3.56 (m, $W_{1/2}$=4.8 Hz)	3.55 (br s, $W_{1/2}$=6 Hz)	3.66 (quint, J=6.5, 3.2, and 3 Hz)

signals with $J_{2,3}$=1.4 Hz, indicating that the $C_{(3)}$-H and $C_{(2)}$-H are in β-(equatorial) and β-(axial) orientations, respectively. These values are similar to those observed in (+)-spectaline (**1**), but apparently different from those of (+)-iso-6-cassine (**2**)[1b)] (see Table 2).

In 2,6-dialkyl-3-piperidinols with all *cis*-configurations, two possible conformers (**A** and **B**) would exist in equilibrium and **A** is expected to be much more preferable, because of a formation of an intramolecular hydrogen bonding between the axial-OH and a lone pair of the nitrogen atom[17)] and also a conformation with two alkyl side chain at C-2 and C-6 in equatorial orientations (Fig. 1). In a dilute solution of the synthetic **4** in carbon tetrachloride, the hydrogen-bonded OH absorption (E_b) was observed at 3523 cm^{-1} in the IR spectrum, while the free OH absorption (E_f) at 3629 cm^{-1} and their intensity ratio (E_b/E_f) was 14. These findings observed in ^{13}C and ^{1}H NMR and IR spectral measurements lead to the conclusion that the synthetic **4** is formulated as (2*R*,3*R*,6*S*)-6-dodecyl-2-methyl-3-piperidinol, identical with the natural (−)-deoxocassine.

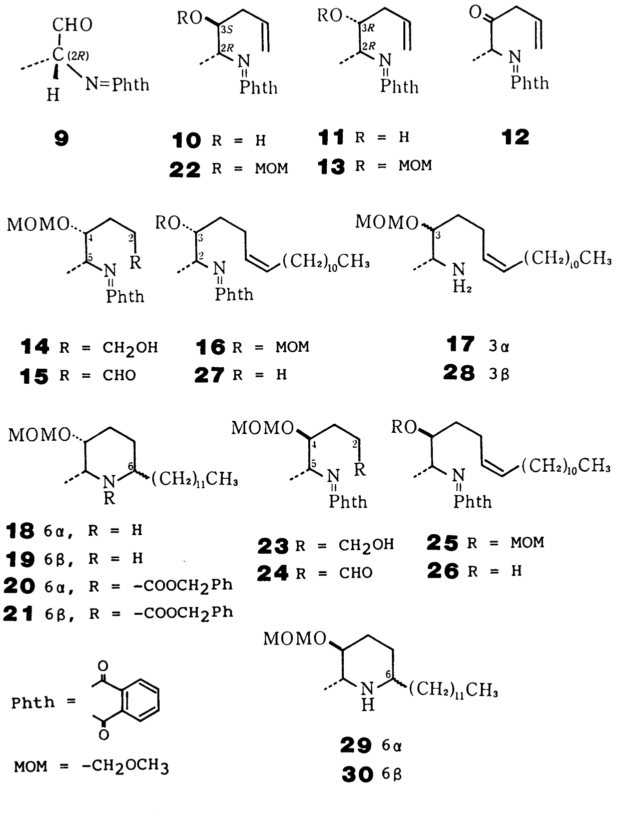


A **B**

R = $-(CH_2)_{11}CH_3$ or $-(CH_2)_{12}COCH_3$

Fig. 1.

The *erythro*-alcohol (**10**) was treated with methoxymethyl chloride to afford a methoxymethyl derivative (**22**) in 98% yield, which was converted into (4*S*,5*R*)-4-methoxymethoxy-5-phthalimidohexanal (**24**) in 71% yield from **22** through **23**. The Wittig reaction gave (2*R*,3*S*)-3-methoxymethoxy-2-phthalimido-6-octadecene (**25**) in 62% yield, which was shown to contain a small amount of (*E*)-isomer; a very weak band at 964 cm^{-1} due to *trans*-olefin was observed together



9

10 R = H
22 R = MOM

11 R = H
13 R = MOM

12

14 R = CH_2OH
15 R = CHO

16 R = MOM
27 R = H

17 3α
28 3β

18 6α, R = H
19 6β, R = H
20 6α, R = $-COOCH_2Ph$
21 6β, R = $-COOCH_2Ph$

23 R = CH_2OH
24 R = CHO

25 R = MOM
26 R = H

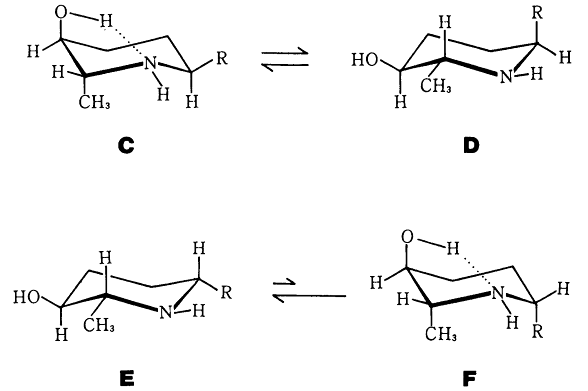
Phth =

MOM = $-CH_2OCH_3$

29 6α
30 6β

with an absorption at 765 cm^{-1} with medium intensity in the IR spectrum.

The olefin (**25**) was also prepared by the Grignard reaction. The *N*-phthaloyl aldehyde (**9**) was treated with a Grignard reagent prepared from (*Z*)-3-pentadecenyl bromide[3] and magnesium to give a diastereomeric mixture (3:1) of (2*R*,6*Z*)-2-phthalimido-6-octadecen-3-ols (**26** and **27**). Since the Grignard reagent reacted with also the phthaloyl group to yield a complex mixture, the isolation yield of the mixture of **26** and **27** was 23%. The configurations at C-3 were determined by the ^{1}H NMR spectral measurement. The major alcohol (**26**) showed double quartet signals ($J_{2,3}$=4 Hz) due to $C_{(2)}$-H at δ 4.35, while the minor alcohol (**27**) afforded a quintet signal (*J*=6.5 Hz) due to $C_{(2)}$-H at δ 4.43. These shift values and coupling constants are almost the same as those of the (3*S*)-alcohol (**10**) and (3*R*)-alcohol (**11**), respectively (*vide supra*). Methoxymethylation of the (2*R*,3*S*,6*Z*)-isomer (**26**) gave a methoxymethyl derivative in 54% yield, which was completely identical with **25**. Although this synthetic route containing the Grignard reaction consisted of only 2 steps, the overall yield was less than 10%. On the contrary, the route through the Wittig reaction comprised 5 steps and gave **25** in 12% overall yield. Both routes gave **25** in nearly the same yields, but the latter was much preferable to the former in respect of separation procedure of the reaction products.



R = $-(CH_2)_{11}CH_3$

Fig. 2.

On hydrazinolysis, the phthaloyl derivative (**25**) yielded (2*R*,3*S*,6*Z*)-3-methoxymethoxy-6-octadecen-2-amine (**28**) in 82% yield. The ε,ζ-unsaturated amine (**28**) was subjected to the aminomercuration and demercuration as before and separation by column chromatography on alumina gave two piperidine derivatives (**29** and **30**) in 17 and 43% yields, respectively. The piperidine derivatives (**29** and **30**) were heated under reflux in 4 M acetic acid overnight to give 6-dodecyl-2-methyl-3-piperidinols (**7**) and (**8**), respectively.

The stereochemistry of C-6 in **7** and **8** was determined by examining intensities of the IR absorption bands due to the intramolecular OH····N bonded (E_b) and free OH forms (E_f) in the dilute solution of **7** and **8** in carbon tetrachloride.[17] The piperidine derivative (**8**) obtained from the major product (**30**) exhibits free OH band at 3631 and 3626 cm^{-1} and hydrogen-bonded OH bands at 3531 cm^{-1} with approximately equal intensities (E_b/E_f=1), while the minor one (**7**) shows only free OH band at 3631 cm^{-1}. In 2α-methyl-3β-piperidinols with 6β-alkyl side chain, the conformation-determining effects of the *trans*-placed methyl and the alkyl side chain likely canceled out and two conformers (**C** and **D**) with the "OH-axial" and "OH-equatorial" conformations could exist in equilibrium. This is the case of **8**. On the other hand, the piperidine derivative (**7**) would exist exclucively in a triequatorial conformation (**E**) and, therefore, the IR spectrum of **7** measured in the dilute solution would exhibit no hydrogen-bonded OH band (Fig. 2). Thus the structures of two diastereomers **7** and **8** were determined to be (2*R*,3*S*,6*S*)- and (2*R*,3*S*,6*R*)-6-dodecyl-2-methyl-3-piperidinols, respectively.

Experimental

General Procedures. Melting points were measured on a Mel-temp capillary melting-point apparatus (Laboratory Devices) and uncorrected. IR spectra were measured with a Hitachi 260-30, a Hitachi EPI-G2, a JEOL JIR-103 (FT), or a JEOL JIR-100 (FT) spectrometer. ^{1}H NMR spectra were taken with a Hitachi R-20B (60 MHz), a Hitachi R-24B (60 MHz), a Varian EM-390 (90 MHz), a JEOL FX-90Q (90 MHz), a JEOL JNM-PS100 (100 MHz), or a JEOL GX-270 (270 MHz) spectrometer and ^{13}C NMR spectra with a JEOL FX-90Q (22.5 MHz) or a JEOL GX-270 (67.8 MHz) spectrometer in $CDCl_3$ solution containing TMS as an internal standard. High and low resolution mass spectra were taken on a JEOL JMS-D300 mass spectrometer at 70 eV. Measurements of optical rotations were carried out with a JASCO DIP-181 polarimeter. Thin-layer chromatography (TLC) was carried out on Kieselgel GF_{254} (E. Merck) and Alumina B-10F (Wako) in 0.25mm-thickness for analytical use and 0.5 mm-thickness for preparative use. Wakogel C-200 (Wako), Aluminium Oxide W-200 neutral (ICN Pharmaceuticals), and Florisil 100-200 mesh (Wako) were used for column chromatography.

(2R)-2-Phthalimidopropanal (9). *N*-Phthaloyl-D-alanine (mp 144.5—145.0 °C, $[\alpha]_D^{22}$ +22.4°; 15 g) was dissolved in benzene (40 ml) and thionyl chloride (15 ml) was added. The mixture was refluxed for 1 h and then an excess of thionyl chloride was removed *in vacuo* completely, and the residue was allowed to stand overnight under reduced pressure.

A mixture of the acid chloride and 10% palladium on carbon (4 g) in benzene (150 ml) was refluxed with stirring, while hydrogen was bubbled continuously. The reaction was monitored by titration of evolved hydrogen chloride with alkali. After the usual work-up, crystallization from benzene gave (2*R*)-2-phthalimidopropanal (**9**; 10.4 g) as white crystals, mp 109.0—110.5 °C; $[\alpha]_D^{22}$ −32.5° (*c* 1.04, EtOH); ^{1}H NMR δ=1.62 (3H, d, *J*=7 Hz, C*H*$_3$-CH-(N=phth)-), 4.75 (1H, q, *J*=7 Hz; CH$_3$-C*H*(N=phth)-), 7.83 (4H, m; aromatic H's), and 9.68 (1H, s; -CHO); IR (KBr) 1768, 1730, 1710, 1385, 1032, 872, and 721 cm^{-1}; MS (EI) *m/z* (%) 174 (100); CI-MS (methane) *m/z* (%) 204 ([M+1]$^+$; 100) and 174 (14); Found: C, 64.90; H, 4.33; N, 6.99%. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89%.

(2R,3S)- and (2R,3R)-2-Phthalimido-5-hexen-3-ols (10 and 11). Allyl bromide (12.1 g) was added dropwise to THF (35 ml) containing zinc turnings (6.54 g) at room temperature under a nitrogen atmosphere, and then the mixture was heated at 50 °C for 1 h. After cooling, a small amount of unchanged zinc (0.84 g) was filtered off to give a yellow solution (50 ml; 1.74 mmol/ml) of diallylzinc, concentration of which was estimated from the amount of consumed zinc.

The solution (47 ml; 81.8 mmol) of diallylzinc was added dropwise to a solution of the aldehyde (**9**; 11 g, 54.5 mmol) in THF (120 ml) at −40 °C under a nitrogen atmosphere. After stirring for 1 h at −30 to −10 °C, THF-water (1:1, 30 ml) and 1 M hydrochloric acid (20 ml) were added, and the reaction product was extracted with ether (400 ml). The extract was washed with a saturated sodium hydrogencarbonate solution (30 ml) and a saturated sodium chloride solution (40 ml), dried over magnesium sulfate, and evaporated under reduced pressure to give a residue. The residue was chromatographed on a column of silica gel (250 g) using hexane–ethyl acetate (7:1) as eluent to give alcohol (**10**; 6.8 g) and alcohol (**11**; 1.34 g). **10**: mp 84.0—84.5 °C (from hexane–ethyl acetate); $[\alpha]_D^{28}$ −7.7° (*c* 0.31, EtOH); ^{1}H NMR δ=1.48 (3H, d, *J*=7 Hz; C*H*$_3$-CH-(N=phth)-), 2.29 (2H, t-like, *J*=6 Hz; -C*H*$_2$-CH=CH$_2$), 3.50 (1H, d, *J*=3 Hz; -OH), 4.07 (1H, m; -C*H*(OH)-), 4.37 (1H, dq, *J*=4 and 7 Hz; CH$_3$-C*H*(N=phth)-), 5.13 (2H, m, -CH=C*H*$_2$), 5.89 (1H, ddt, *J*=18, 9, and 6 Hz; -C*H*=CH$_2$), and 7.78 (4H, m; aromatic H's); IR (KBr) 3450, 1705, 1390, 1020, and 722 cm^{-1}; MS (EI) *m/z* (%) 227 (2), 204 (29), and 174 (56); CI-MS (methane) *m/z* (%) 246 ([M+1]$^+$; 100), 228 (91), 204 (30), and 174 (34); Found: C, 68.70; H, 6.23; N, 5.65%. Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71%. **11**: mp 107.5—108.5 °C (from hexane–ethyl acetate); $[\alpha]_D^{30}$ −35.1° (*c* 0.30, EtOH); ^{1}H NMR δ=1.49 (3H, d, *J*=7 Hz; C*H*$_3$-CH(N=phth)-), 2.23 (2H, t-like, *J*=7 Hz; -C*H*$_2$-CH=CH$_2$), 3.17 (1H, d, *J*=8.5 Hz; -OH), 4.02 (1H, q, *J*=7 Hz; -C*H*(OH)-), 4.42 (1H, quint, *J*=7 Hz; CH$_3$-C*H*(N=phth)-), 5.05 (1H, d, *J*=18 Hz; ${}^{\mathrm{H}}{>}\mathrm{C{=}C}{<}^{\mathrm{H}}_{H}$), 5.07 (1H, d, *J*=9 Hz, ${}^{\mathrm{H}}{>}\mathrm{C{=}C}{<}^{H}_{\mathrm{H}}$), 5.90 (1H, ddt, *J*=18, 9, and 7 Hz; -C*H*=CH$_2$), and 7.80 (4H, m; aromatic H's); IR (KBr) 3510, 3260, 2940, 2920, 1690, 1640, 1560, 1395, 1392, 1168, 1022, and 722 cm^{-1}; MS (EI) *m/z* (%) 227 (9), 204 (82), and 174 (75); CI-MS (methane) *m/z* (%) 246 ([M+1]$^+$; 100), 228 (59), 204 (25), and 174 (16): Found: C, 68.82; H, 6.13; N, 5.97%. Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16 N, 5.71%.

(2R)-2-Phthalimido-5-hexen-3-one (12). A solution of (2*R*,3*S*)-2-phthalimido-5-hexen-3-ol (**10**; 10.1 g) in dichloromethane (60 ml) was added to a suspension of pyridinium chlorochromate (26.3 g) in dichloromethane (120 ml) and the mixture was stirred for 17 h at room temperature. The reaction mixture was decanted to afford a supernatant liquid and a black residue. The supernatant liquid was passed through a column of Florisil (45 g). The black residue was dissolved in a saturated sodium hydrogencarbonate solution and extracted with ether. The ethereal extract was washed with brine, dried over magnesium sulfate, and combined with the eluate from the Florisil column. The combined solution was evaporated and purified by column chromatography on silica gel (180 g). Elution with a mixture of hexane–acetone (4:1) afforded (2*R*)-2-phthalimido-5-hexen-3-one (**12**; 8.8 g) in 88% yield, mp 56.0—57.0 °C; $[\alpha]_D^{18}$ +23.0° (*c* 2.6 EtOH); ^{1}H NMR δ=1.67 (3H, d, *J*=7 Hz; C*H*$_3$-CH(N=phth)-), 3.27 (2H, d, *J*=7 Hz; -C*H*$_2$-CH=CH$_2$), 4.85 (1H, q, *J*=7 Hz; CH$_3$-C*H*(N=phth)-), 5.07 (1H, d, *J*=18 Hz; ${}^{\mathrm{H}}{>}\mathrm{C{=}C}{<}^{\mathrm{H}}_{H}$), 5.11 (1H, d, *J*=9 Hz; ${}^{\mathrm{H}}{>}\mathrm{C{=}C}{<}^{H}_{\mathrm{H}}$), 5.90 (1H, ddt, *J*=18, 9, and 7 Hz: -C*H*=CH$_2$), and 7.80 (4H, m; aromatic H's); IR (KBr) 1780, 1720, 1395, 1020, and 720 cm^{-1}; MS (EI) *m/z* (%) 243 (M$^+$; 3), 202 (42), and 174 (100); Found: C, 69.02; H, 5.12; N, 5.84%; MW 243.0881. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76%; M, 243.0894.

Reduction of Ketone (12) with Zinc Borohydride. Anhydrous zinc chloride (4.0 g) was added in ether (50 ml) and the mixture was refluxed for 1 h in a nitrogen atmosphere to yield an ethereal solution of zinc chloride, which was added dropwise to a suspension of sodium borohydride (2.7 g) in ether (150 ml). The mixture was stirred for 2 d at room temperature and decanted to afford a zinc borohydride solution (200 ml).

To an ice-cooled solution of (2*R*)-2-phthalimido-5-

hexen-3-one (**12**; 9.05 g) in ether (400 ml) the zinc borohydride solution (64 ml) above prepared was added in a nitrogen atmosphere and stirring was continued for 5 h at 0 °C. After addition of a solution (200 ml) of ammonium chloride, the organic layer was separated and evaporated to give a residue, which was chromatographed on silica gel. Elution with a mixture of hexane–ethyl acetate (5:1) afforded alcohol (**10**; 2.26 g) and alcohol (**11**; 4.87 g) in 25 and 53% yields, respectively. **10**: Mp 80.5—81.5 °C; $[\alpha]_D^{21}$ −10.4° (*c* 0.70, EtOH). **11**: Mp 107.5—108.5 °C; $[\alpha]_D^{22}$ −36.0° (*c* 3.0, EtOH).

*(2R,3R)-N,N-Phthaloyl-3-methoxymethoxy-5-hexen-2-amine (**13**).* Methoxymethyl chloride (12.7 g) was added to a mixture of alcohol (**11**; 4.86 g) and triethylamine (16.2 g) in acetonitrile (40 ml). The mixture was refluxed for 2.5 h in a flask equipped with a calcium chloride tube. After cooling to room temperature, water (30 ml) and a saturated solution (50 ml) of sodium hydrogencarbonate were added and the reaction product was extracted with ether. Evaporation and separation by column chromatography on silica gel (150 g) eluted with hexane–ethyl acetate (6:1) afforded (2*R*,3*R*)-*N*,*N*-phthaloyl-3-methoxymethoxy-5-hexen-2-amine (**13**; 5.71 g) quantitatively as a colorless oil, $[\alpha]_D^{23}$ −119° (*c* 0.36, $CHCl_3$); ^1H NMR δ=1.49 (3H, d, *J*=7 Hz; CH_3-CH(N=phth)-), 2.51 (2H, m; -CH_2-CH=CH_2), 3.00 (3H, s; CH_3O-), 4.28 (2H, m; -*CH*(N=phth)-*CH*(OMOM)-), 4.50 (2H, s; -OCH_2O-), *ca.* 5.16 (2H, m, -CH=CH_2), 6.00 (1H, ddt, *J*=17, 9, and 7 Hz; -*CH*=CH_2), and 7.80 (4H, m; aromatic H's); IR (neat) 2940, 1770, 1710, 1385, 1145, 1090, 1038, 920, 881, and 722 cm^{-1}; MS *m/z* (%) 248 (15) and 174 (100); CI-MS (methane) *m/z* (%) 290 ([M+1]$^+$; 13), 259 (18), 258 (100), 228 (13), and 174 (5); Found: C, 66.21; H, 6.81; N, 4.73%. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84%.

(4R,5R)-4-Methoxymethoxy-5-phthalimido-1-hexanol (14). A diborane solution (6 ml, *ca.* 12 mmol) in THF was added to a solution of the MOM-olefin (**13**; 922 mg) in THF (15 ml) in a nitrogen atmosphere at 0 °C and the reaction mixture was stirred at room temperature for 2 h. After an excess of diborane was destroyed by addition of water (1 ml), 2 M sodium hydroxide solution (4.5 ml) and 30% hydrogen peroxide (7 ml) were added at 0 °C, and the mixture was stirred at 50 °C for 1.5 h followed by extraction with ether (40 ml). The usual work-up afforded an oily residue, which was subjected to separation by column chromatography on silica gel (15 g). Elution with hexane-ethyl acetate (1:1) gave (4*R*,5*R*)-4-methoxymethoxy-5-phthalimido-1-hexanol (**14**; 815 mg) as an oil in 83% yield, $[\alpha]_D^{22}$ −58.9° (*c* 0.48, $CHCl_3$) ^1H NMR δ=1.49 (3H, d, *J*=6.5 Hz; CH_3-CH(N=phth)-), 1.77 (2H, m; -CH_2-CH_2OH), 2.65 (1H, m; -OH), 3.00 (3H, s; CH_3O-), 3.71 (2H, m; -CH_2-OH), 4.32 (2H, m; -*CH*(N=phth)-*CH*(OMOM)-), 4.53 (2H, s; -OCH_2O-), and 7.80 (4H, m; aromatic H's).

(4R,5R)-4-Methoxymethoxy-5-phthalimidohexanal (15). The MOM-alcohol (**14**; 603 mg) in dichloromethane (4 ml) was added to a suspension of pyridinium chlorochromate (1.5 g) in dichloromethane (7 ml) at room temperature. After stirring for 2.5 h, the reaction mixture was decanted to afford a supernatant liquid and a dark-brown residue. The supernatant liquid was diluted with ether, passed through a column of Florisil (6 g), and eluted with ether. The dark-brown residue was dissolved in a sodium hydrogencarbonate solution and extracted with ether. The ethereal extract was combined with the eluate from the Florisil column and chromatographed on a short column of silica gel. Elution with hexane-ethyl acetate gave MOM-aldehyde (**15**; 508 mg) in 85% yield, ^1H NMR δ=1.48 (3H, d, *J*=6.5 Hz CH_3-CH(N=phth)-), 1.90 (2H, m; -CH_2-CH_2-CHO), 2.64 (2H, td, *J*=9 and 1.5 Hz; -CH_2-CHO), 3.00 (3H, s; CH_3O-), 4.26 (2H, m; -*CH*(N=phth)-*CH*(OMOM)-), 4.46 (2H, s; -OCH_2O-), 7.89 (4H, m; aromatic H's), and 9.86 (1H, t, *J*=1.5 Hz; -CHO); IR (neat) 2935, 1770, 1710, 1381, 1140, 1030, 920, 881, and 721 cm^{-1}; MS (EI) *m/z* (%) 244 (5) and 174 (100); CI-MS (methane) *m/z* (%) 306 ([M+1]$^+$; 3), 275 (4), 274 (22), 260 (2), 245 (16), 244 (100), and 174 (4).

*(2R,3R,6Z)-3-Methoxymethoxy-2-phthalimido-6-octadecene (**16**).* Butyllithium (6.5 ml; 11.3 mmol) in hexane was added dropwise to a solution of dodecyltriphenylphosphonium bromide (7.5 g; 14.6 mmol) in dry THF at 0 °C under a nitrogen atmosphere. The red solution was stirred for 20 min at room temperature and 40 min at 40 °C, and then cooled to −78 °C. To the solution was added a solution of the MOM-aldehyde (**15**; 3.45 g) in THF (60 ml), and the mixture was stirred for 20 min at −78 °C and 20 min at 0 °C, and then allowed to stand overnight at room temperature. Ether (200 ml) and water (150 ml) were added and the ethereal layer was separated. The aqueous layer was extracted with ether and the extract was combined with the ethereal layer. The usual work-up gave an oily mixture, which was subjected to separation by column chromatography on silica gel (70 g). Elution was performed with hexane–ethyl acetate (6:1) to afford (2*R*,3*R*,6*Z*)-3-methoxymethoxy-2-phthalimido-6-octadecene (**16**; 3.12 g) as an oil, $[\alpha]_D^{21}$ −49.2° (*c* 0.62, $CHCl_3$); ^1H NMR δ=0.87 (3H, t-like, *J*=6 Hz; terminal CH_3), 1.27 (20H, br s; methylenes), 1.48 (3H, d, *J*=6.5 Hz; CH_3-CH(N=phth)-), 2.05 (4H, m -CH_2-CH=CH-CH_2-), 2.97 (3H, s; CH_3O-), 4.30 (2H, m; -*CH*(N=phth)-*CH*(OMOM)-), 4.51 (2H, s; -OCH_2O-), 5.39 (2H, t, *J*=5 Hz; -CH=CH-), and 7.77 (4H, m; aromatic H's); IR (neat) 2925, 1773, 1712, 1382, 1148, 1038, 922, 884, and 721 cm^{-1}; MS (EI) *m/z* (%) 457 (M$^+$; 0.1), 426 (1), 425 (3), and 174 (100); CI-MS (methane) *m/z* (%) 458 ([M+1]$^+$; 13), 427 (30), 426 (100), 397 (2), 396 (6), and 174 (4); Found: C, 73.53; H, 9.33; N, 3.03%. Calcd for $C_{28}H_{43}NO_4$: C, 73.48; H, 9.47; N, 3.06%.

(2R,3R,6Z)-3-Methoxymethoxy-6-octadecen-2-amine (17). 100% Hydrazine hydrate (0.2 ml) was added to a solution of phthalimido-olefin (**16**; 425 mg) in ethanol (4 ml) at room temperature and the mixture was stirred for 1 h. To the reaction mixture, ether (200 ml) and 2 M sodium hydroxide (10 ml) were added and the ethereal layer was separated. The aqueous layer was extracted with ether repeatedly and the extracts were combined with the ethereal layer. The usual work-up afforded crude ε,ζ-unsaturated amine (**17**; 512 mg) as a pale yellow oil, which was used for next synthetic step without any purification. **17** (crude): ^1H NMR δ=0.87 (3H, t-like, *J*=6 Hz; terminal CH_3); 1.07 (3H, d, *J*=7 Hz $C_{(2)}$-CH_3), 1.31 (22H, br s; methylenes), 1.4—2.2 (4H, m; -CH_2-CH=CH-CH_2-), 2.47 (2H, m; -NH_2), 3.37 (3H, s; CH_3O-), 4.65 (2H, s; -OCH_2O-), and 5.33 (2H, t-like, *J*=6 Hz; -CH=CH-); MS (EI) *m/z* (%) 327 (M$^+$; 3), 296 (4), 282 (6), 266 (3), and 44 (100); Found: *m/z* 327.3119. Calcd for $C_{20}H_{41}NO_2$: M, 327.3139.

Crude (2R,3R,6S)-3-O-Methoxymethyldeoxocassine (18).

Mercury(II) acetate (618 mg) was added to a solution of the ε,ζ-unsaturated amine (**17**; 512 mg) in methanol (4 ml) at room temperature, and the mixture was stirred for 2 d. To the reaction mixture, was added a solution of sodium borohydride (60 mg) in 2 M sodium hydroxide solution (6 ml). The reaction mixture was filtered and the filtrate was extracted with ether. The ethereal layer was worked up as usual to give crude (2*R*,3*R*,6*S*)-3-*O*-methoxymethyldeoxocassine (**18**; 249 mg) as a yellow oil.

(2R,3R,6S)-N-Benzyloxycarbonyl-3-O-methoxymethyldeoxocassine (20). Benzyloxycarbonyl chloride (180 mg) was added to an ice-cooled solution of the crude MOM-deoxocassine (**18**; 106 mg) and potassium carbonate (113 mg) in acetone (4 ml). The reaction mixture was stirred at 0 °C for 1.5 h and then for 1 d at room temperature, and filtered. The precipitates were washed with ether and the washings and the filtrate were combined. The usual work-up yielded an oily residue, which was subjected to separation by column chromatography on silica gel (7 g) eluted with hexane–ether (4:1) to afford a benzyloxycarbonyl derivative (**20**; 27.5 mg) as an oil, $[\alpha]_{\mathrm{D}}^{17}$ −2.0° (*c* 1.8, EtOH); ^{1}H NMR δ=0.87 (3H, t-like, *J*=6 Hz; terminal CH$_3$), 1.28 (25H, br s; C$_{(2)}$-CH$_3$ and methylenes), 1.4—2.3 (4H, m; -CH$_2$-CH$_2$-), 3.38 (3H, s; CH$_3$O-), 3.4—5.3 (3H, m; C$_{(2)}$-H, C$_{(3)}$-H, and C$_{(6)}$-H), 4.63 (2H, s; -OCH$_2$O-), 5.12 (2H, s; -C*H*$_2$-C$_6$H$_5$), and 7.33 (5H, m; aromatic H's); IR (neat) 2925, 2850, 1700, 1300, and 1150 cm^{-1}; MS (EI) *m/z* 461 (M$^+$; 1), 429 (1), 292 (42), and 91 (100); Found: *m/z* 461.3544. Calcd for C$_{28}$H$_{47}$NO$_4$: M, 461.3504.

Pure (2R,3R,6S)-3-O-Methoxymethyldeoxocassine (18). The benzyloxycarbonyl derivative (**20**; 59 mg) in ethanol (5 ml) was subjected to hydrogenolysis in the presence of 5% palladium on carbon (146 mg) for 1 d. The usual work-up and separation by column chromatography on alumina (2 g) eluted with hexane–ether (1:1) affoded pure (2*R*,3*R*,6*S*)-3-*O*-methoxymethyldeoxocassine (**18**; 15 mg) as an oil, $[\alpha]_{\mathrm{D}}^{16}$ −20° (*c* 0.57, CHCl$_3$); ^{1}H NMR δ=0.87 (3H, t-like, *J*=6 Hz; terminal CH$_3$), 1.14 (3H, d, *J*=7 Hz; C$_{(2)}$-CH$_3$), 1.27 (22H, br s; methylenes), 1.4—1.8 (4H, m; -CH$_2$-CH$_2$-), 1.8—3.7 (3H, m; C$_{(2)}$-H, C$_{(3)}$-H, and C$_{(6)}$-H), 3.37 (3H, s; CH$_3$O-), and 4.65 (2H, *AB*q, *J*=7 Hz; -OCH$_2$O-); MS (EI) *m/z* (%) 327 (M$^+$; 3), 312 (2), 296 (4), 282 (10), 266 (6), and 158 (100); Found: *m/z* 327.3098. Calcd for C$_{20}$H$_{41}$NO$_2$: M, 327.3145.

(−)-Deoxocassine (4). A solution of the methoxymethyl derivative (**20**; 13 mg) in 1 M hydrochloric acid–methanol was heated under reflux for 2 h. After cooling, 2 M sodium hydroxide solution (1.5 ml) was added and the reaction product was extracted with ether and worked up as usual to give a residue, which was subjected to column chromatographic separation on alumina (1 g). Elution with ether–methanol (9:1) gave (−)-deoxocassine (**4**; 5 mg) as white crystals, mp 47.5—48.5 °C (from methanol); $[\alpha]_{\mathrm{D}}^{18}$ −12.3° (*c* 0.19; CHCl$_3$); ^{1}H NMR δ=0.88 (3H, t-like, *J*=6.0 Hz; terminal CH$_3$), 1.11 (3H, d, *J*=6.4 Hz C$_{(2)}$-CH$_3$), 1.26 (22H, br s; methylenes), 1.3—1.4 (2H, m; C$_{(5)}$-H$_2$), 1.4—1.5 (2H, m; C$_{(4)}$-H$_2$), 1.8—2.0 (1H, m; -$\overset{|}{\mathrm{N}}$H), 2.4—2.7 (2H, m; C$_{(6)}$-H and -OH), 2.76 (1H, qd, *J*=6.5 and 1.4 Hz; C$_{(2)}$-H), and 3.56 (1H, m, *W*$_{1/2}$ 4.8 Hz; C$_{(3)}$-H); ^{13}C NMR δ=14.12, 18.66, 22.69, 25.83, 26.10, 29.35, 29.61, 29.66, 29.80, 31.92, 32.05, 36.97, 55.85, 57.27, and 68.02; MS (EI) *m/z* (%) 283 (M$^+$; 0.4), 282 (0.2), 268 (0.3), 114 (100), and 96 (5); Found: *m/z* 283.2875. Calcd for C$_{18}$H$_{37}$NO: M, 283.2875.

(2R,3S,6S)- and (2R,3S,6R)-Deoxocassines (7 and 8). (3*S*)-Diastereomers (**7** and **8**) of (−)-deoxocassine (**4**) were prepared from (2*R*,3*S*)-2-phthalimido-5-hexen-3-ol (**10**) according to the same procedures as described for preparation of **4**. (2*R*,3*S*)-*N*,*N*-phthaloyl-3-methoxymethoxy-5-hexen-2-amine (**22**): An oil, $[\alpha]_{\mathrm{D}}^{19}$ +30.2° (*c* 0.26, CHCl$_3$); ^{1}H NMR δ=1.54 (3H, d, *J*=6.5 Hz; C*H*$_3$-CH(N=phth)-), 2.33 (2H, m; -C*H*$_2$-CH=CH$_2$), 3.40 (3H, s; CH$_3$O-), 4.40 (2H, m; -C*H*(N=phth)-C*H*(OMOM)-), 4.73 (2H, s; -OCH$_2$O-), 5.04 (2H, m; C*H*$_2$=CH-), 5.86 (1H, ddt, *J*=17, 9, and 7 Hz; -C*H*=CH$_2$), and 7.79 (4H, m; aromatic H's); IR (neat) 2925, 1772, 1710, 1385, 1142, 1095, 1035, 915, 876, and 715 cm^{-1}: MS (EI) *m/z* (%) 248 (52), 228 (20), and 174 (100); CI-MS (methane) *m/z* (%) 290 ([M+1]$^+$; 6), 259 (16), 258 (100), 228 (18), and 174 (13); Found: C, 66.49; H, 6.76; N, 5.06%. Calcd for C$_{16}$H$_{19}$NO$_4$: C, 66.42; H, 6.62; N, 4.84%. (4*S*,5*R*)-4-Methoxymethoxy-5-phthalimido-1-hexanol (**23**): An oil $[\alpha]_{\mathrm{D}}^{19}$ −15.3° (*c* 0.30, CHCl$_3$); ^{1}H NMR δ=1.51 (3H, d, *J*=6.5 Hz; C*H*$_3$-CH(N=phth)-), 1.65 (2H, m; -C*H*$_2$-CH$_2$OH), 1.83 (1H, m; -OH), 3.41 (3H, s; CH$_3$O-), 3.58 (2H, m; -C*H*$_2$-OH), 4.40 (2H, m; -C*H*(N=phth)-C*H*(OMOM)-), 4.72 (2H, s; -OCH$_2$O-), and 7.76 (4H, m; aromatic H's); IR (neat) 3400, 2945, 1772, 1710, 1390, 1142, 1038, and 725 cm^{-1}; MS (EI) *m/z* (%) 174 (100); CI-MS (methane) *m/z* (%) 308 ([M+1]$^+$; 1), 277 (12), 276 (72), 247 (16), 246 (100), and 174 (11); Found: C, 62.28; H, 7.18; N, 4.64%. Calcd for C$_{16}$H$_{21}$NO$_5$: C, 62.52; H, 6.88; N, 4.56%. (4*S*,5*R*)-4-Methoxymethoxy-5-phthalimidohexanal (**24**): An oil; ^{1}H NMR δ=1.56 (3H, d, *J*=6.5 Hz; C*H*$_3$-CH(N=phth)-), 1.90 (2H, m; -C*H*$_2$-CH$_2$-CHO), 2.60 (2H, td, *J*=8.5 and 1.5 Hz; -C*H*$_2$-CHO), 3.43 (3H, s; CH$_3$O-), 4.35 (2H, m; -C*H*(N=phth)-C*H*(OMOM)-), 4.74 (2H, s; -OCH$_2$O-), 7.82 (4H, m; aromatic H's), and 9.78 (1H, t, *J*=1.5 Hz; -CHO); IR (neat) 2950, 1775, 1710, 1385, 1140, 1035, 920, 881, and 723 cm^{-1}; MS (EI) *m/z* (%) 274 (20), 244 (2), and 174 (100); CI-MS (methane) *m/z* (%) 306 ([M+1]$^+$; 6), 275 (9), 274 (57), 260 (5), 245 (17), 244 (100), and 174 (6). (2*R*,3*S*,6*Z*)-3-Methoxymethoxy-2-phthalimido-6-octadecene (**25**): An oil; $[\alpha]_{\mathrm{D}}^{24}$ −14.9° (*c* 0.54, CHCl$_3$); ^{1}H NMR δ=0.88 (3H, t-like, *J*=6 Hz; terminal CH$_3$), 1.25 (20H, br s; methylenes), 1.54 (3H, d, *J*=6.5 Hz; C*H*$_3$-CH(N=phth)-), 1.96 (4H, m; -C*H*$_2$-CH=CH-C*H*$_2$), 3.42 (3H, s; CH$_3$O-), 4.32 (2H, m; -C*H*(N=phth)-C*H*(OMOM)-), 4.75 (2H, s; -OCH$_2$O-), 5.29 (2H, t, *J*=5 Hz; -CH=CH-), and 7.78 (4H, m; aromatic H's); IR (neat) 2925, 1775, 1710, 1382, 1142, 1040, 922, 882, and 723 cm^{-1}; MS (EI) *m/z* (%) 426 (3), 248 (9), and 174 (100); CI-MS (methane) *m/z* (%) 458 ([M+1]$^+$; 2), 427 (31), 426 (100), 397 (4), 396 (14), 276 (15), 248 (3), and 174 (21); Found: C, 73.39; H, 9.28; N, 3.00%. Calcd for C$_{28}$H$_{43}$NO$_4$: C, 73.48; H, 9.47; N, 3.06%. (2*R*,3*S*,6*Z*)-3-Methoxymethoxy-6-octadecen-2-amine (**28**): A pale yellow oil; MS (EI) *m/z* (%) 327 (M$^+$; 13), 312 (1), 296 (9), 282 (14), 266 (5), and 44 (100); Found: *m/z* 327.3145. Calcd for C$_{20}$H$_{41}$NO$_2$: M, 327.3139. (2*R*,3*S*,6*S*)- and (2*R*,3*S*,6*R*)-3-Methoxymethyldeoxocassines (**29** and **30**): To a solution of the ε,ζ-unsaturated amine (**28**; 558 mg) in methanol (20 ml) was added mercury(II) acetate (816 mg) at room temperature, and the mixture was stirred for 2 d. To the reaction mixture was added dropwise a solution of sodium borohydride (145 mg) in 2 M sodium hydroxide solution (15 ml). The usual work-up afforded a crude product, which was subjected to separation by preparative TLC (Wako Alumina B-10F, 20×20 cm, 20 plates, developed

with hexane–ether (1:1)). A band (R_f 0.80) was separated and eluted with ethyl acetate to afford **29** (95 mg) as an oil, and a band (R_f 0.63) afforded **30** (240 mg) as an oil. **29**: $[\alpha]_D^{24}$ +26.4° (c 0.33, $CHCl_3$); ^1H NMR δ=0.87 (3H, t-like, J=6 Hz; terminal CH_3), 1.15 (3H, d, J=6.5 Hz; $C_{(2)}$-CH_3), 1.27 (22H, br s; methylenes), 1.66 (3H, m), 2.15 (1H, m), 2.52 (2H, m), 3.03 (1H, m), 3.34 (3H, s; CH_3O-), and 4.63 (2H, *AB*q, J=6.5 Hz; -OCH_2O-), MS (EI) m/z (%) 327 (M^+; 1), 326 (2), 312 (3), 282 (23), 266 (16), and 158 (100); Found: m/z 327.3115. Calcd for $C_{20}H_{41}NO_2$: M, 327.3139. **30**: $[\alpha]_D^{24}$ +13.6° (c 0.12, $CHCl_3$); ^1H NMR δ=0.92 (3H, t-like, J=6 Hz; terminal CH_3), 1.19 (3H, d, J=7 Hz; $C_{(2)}$-CH_3), 1.30 (22H, br s; methylenes), 1.70 (4H, m), 2.72—3.55 (3H, m), 3.44 (3H, s; CH_3O-), and 4.77 (2H, *AB*q, J=10 Hz; -OCH_2O-); MS (EI) m/z (%) 327 (M^+; 1), 326 (1), 312 (20), 296 (3), 282 (20), 266 (10), and 158 (100); Found: m/z 327.3124. Calcd for $C_{20}H_{41}NO_2$: M, 327.3139. (2*R*,3*S*,6*S*)-Deoxocassine (**7**): A mixture of (2*R*,3*S*,6*S*)-3-methoxymethyldeoxocassine (**29**; 33.5 mg) and 4 M acetic acid (3 ml) was heated under reflux overnight. After neutralization with alkali, extraction with ether and the usual work-up afforded a crude product, which was purified by preparative TLC (Wako Alumina B-10F, 20×20 cm, developed with ether–methanol (20:1)). A band (R_f 0.30) was eluted with ethyl acetate–methanol (1:1) to afford (2*R*,3*S*,6*S*)-deoxocassine (**7**; 21 mg) as a pale yellow solid, $[\alpha]_D^{24}$ +13.1° (c 0.16, $CHCl_3$); ^1H NMR δ=0.87 (3H, t-like, J=6 Hz; terminal CH_3), 1.18 (3H, d, J=7 Hz; $C_{(2)}$-CH_3), 1.27 (22H, br s; methylenes), 1.43—2.25 (6H, m; -CH_2-CH_2-, -$\overset{|}{\mathrm{N}}$H, and -OH), 2.49 (2H, m), and 3.12 (1H, m); MS (EI) m/z 283 (M^+; 12), 282 (7), 268 (7), 265 (2), 250 (2), 114 (100), and 96 (29); Found: m/z 283.2875. Calcd for $C_{18}H_{37}NO$: M, 283.2877. (2*R*,3*S*,6*R*)-Deoxocassine (**8**): (2*R*,3*S*,6*R*)-3-*O*-Methoxymethyldeoxocassine (**30**; 34.7 mg) was deprotected as before to afford **8** (16.6 mg) as an amorphous solid, $[\alpha]_D^{24}$ −3.1° (c 0.15, $CHCl_3$); ^1H NMR δ=0.85 (3H, t-like, J=6 Hz; terminal CH_3), 1.13 (3H, d, J=7 Hz; $C_{(2)}$-CH_3), 1.25 (22H, br s; methylenes), 1.40—2.20 (6H, m; -CH_2-CH_2-, -$\overset{|}{\mathrm{N}}$H, and -OH), 2.87 (2H, m), and 3.35 (1H, m); MS (EI) m/z (%) 283 (M^+; 1), 282 (2), 268 (4), 265 (4), 250 (10), 114 (100), and 96 (39); Found: m/z 283.2873. Calcd for $C_{18}H_{37}NO$: M, 283.2877.

(2R,3S,6Z)-3-Methoxymethoxy-2-phthalimido-6-octadecene (25) (by Grignard reaction). A Grignard reagent[3] (0.68 mmol), prepared from (*Z*)-3-pentadecenyl bromide and magnesium, was added to a solution of *N*-phthaloyl aldehyde (**9**; 100 mg) in THF (1.5 ml) at −45 °C under a nitrogen atmosphere, and the reaction mixture was stirred at −30 °C for 6 h. The usual treatment gave a crude oil (320 mg), which was chromatographed on silica gel (6 g). Fractions containing diastereomeric alcohols (**26** and **27**), eluted with benzene–ether (19:1), were combined and further purified by preparative TLC (silica gel in 1 mm thickness, developed with benzene–ether (7:2) twice) to give a mixture (48 mg) of **26** and **27**. The separation of **26** and **27** was achieved by preparative TLC (silica gel in 0.3 mm thickness, developed with hexane–ethyl acetate (3:1) three times) to afford (2*R*,3*S*,6*Z*)- and (2*R*,3*R*,6*Z*)-2-phthalimido-6-octadecen-3-ols (**26** and **27**; in a ratio of *ca.* 3:1). **26**: mp 34.0—34.5 °C; $[\alpha]_D^{30}$ +9° (c 0.23, $CHCl_3$); ^1H NMR δ=0.87 (3H, t-like; terminal CH_3), 1.27 (18H, br s; methylenes), 1.43 (3H, d, J=7 Hz; CH_3-CH(N=phth)-), 1.50 (2H, m; -O-$\overset{|}{\mathrm{C}}$H-CH_2-), 2.10 (4H, m; -CH_2-CH=CH-CH_2-), 3.70 (1H, d, J=3 Hz; -OH), 4.00 (1H, m; -$\overset{|}{\mathrm{C}}$*H*-OH), 4.35 (1H, qd, J=7 and 4 Hz CH_3-C*H*(N=phth)-), 5.37 (2H, m; -CH=CH-), and 7.80 (4H, m; aromatic H's); IR (neat) 3400, 3300, 2920, 1775, 1710, 1390, 1020, 880, and 720 cm^{-1}; Found: C, 75.40; H, 9.80; N, 3.21%. Calcd for $C_{26}H_{39}NO_3$: C, 75.50; H, 9.51; N, 3.39%. **27**: mp 34.5—35.0 °C; $[\alpha]_D^{19}$ −9° (c 0.23, $CHCl_3$); ^1H NMR δ=0.89 (3H, t-like; terminal CH_3), 1.27 (18H, br s; methylenes), 1.40 (2H, m; -O-$\overset{|}{\mathrm{C}}$H-CH_2-), 1.46 (3H, d, J=6.5 Hz; CH_3-C*H*(N=phth)-), 2.10 (4H, m; -CH_2-CH=CH-CH_2-), 3.24 (1H, d, J=9 Hz; -OH), 3.92 (1H, m; -$\overset{|}{\mathrm{C}}$*H*-OH), 4.43 (1H, quint, J=6.5 Hz; CH_3-C*H*(N=phth)-), 6.37 (2H, m; -CH=CH-), and 7.80 (4H, m; aromatic H's); IR (neat) 3450, 2920, 1775, 1710, 1040, 880, and 720 cm^{-1}. Found: C, 76.64; H, 10.08; N, 3.19%. Calcd for $C_{26}H_{39}NO_3$: C, 75.50; H, 9.51; N, 3.39%.

The (2*R*,3*S*)-alcohol (**26**; 10 mg) was methoxymethylated with methoxymethyl chloride (82 mg) in acetonitrile (1 ml) containing triethylamine (91 mg) by the same procedure as before. A methoxymethyl derivative (**25**; 6 mg) was obtained as an oil, whose spectral data were completely identical with those of the specimen (**25**) obtained by the Wittig reaction.

The authors wish to express their thanks to Professor Takaharu Ohnishi, Tokyo Institute of Technology, for FT-IR measurement, Dr. Hajime Nagano, Ochanomizu University, for NMR measurement at 270 MHz, and Miss Toshiko Seki and Mrs. Kimiyo Saeki, The University of Tokyo, for micro analyses.

References

1) a) Q. Khuong-Huu, G. Rattle, X. Monseur, and R. Goutarel, *Bull. Soc. Chim. Berg.*, **81**, 425, 443 (1972); b) I. Christofidis, A. Welter, and J. Jadot, *Tetrahedron*, **33**, 977 (1977); c) D. Lythgoe and M. J. Vernengo, *Tetrahedron Lett.*, **1967**, 1133; d) G. J. H. Rall, T. M. Smalberger, and H. L. de Waal, *Tetrahedron Lett.*, **1967**, 3465; e) J. Bruneton and A. Cavé, *Tetrahedron Lett.*, **1975**, 739; f) J. G. MacConnell and M. S. Blum, *Tetrahedron*, **26**, 1129 (1971).

2) E. Brown and A. Bourgouin, *Chem. Lett.*, **1974**, 109; *Tetrahedron*, **31**, 1047 (1975); E. Brown and R. Dhal, *J. Chem. Soc., Perkin Trans. 1*, **1976**, 2190; E. Brown and R. Bonté, *Tetrahedron Lett.*, **1975**, 2881; *Bull. Soc. Chim. Fr.*, **1981**, II, 281; E. Brown, R. Dhal, and J. Lavoue, *Tetrahedron Lett.*, **1971**, 1055; E. Brown and R. Dhal, *Bull. Soc. Chim. Fr.*, **1972**, 4292; E. Brown, R. Dhal, and J. Lavoue, *C. R. Acad. Sci., Ser. C*, **272**, 958 (1971); E. Brown, R. Dhal, and P. F. Casals, *Tetrahedron*, **28**, 5607 (1972); S. Hanessian and R. Frenette, *Tetrahedron Lett.*, **1979**, 3391; M. Natsume and M. Ogawa, *Heterocycles*, **14**, 169, 615 (1980); G. Fodor, J.-P. Fumeaux, and V. Sankaran, *Synthesis*, **1972**, 464; A. J. G. Baxter and A. B. Holmes, *J. Chem. Soc., Perkin Trans., 1*, **1977**, 2343; A. B. Holmes, J. Thompson, A. Baxter, and J. Dixon, *J. Chem. Soc., Chem. Commun.*, **1985**, 37; M. Natsume and M. Ogawa, *Heterocycles*, **16**, 973 (1981); R. K. Hill and T. Yuri, *Tetrahedron*, **33**, 1569 (1977); A. Astier and M. M. Plat, *Tetrahedron Lett.*, **1978**, 2051; Y. Matsumura, K. Maruoka, and H. Yamamoto, *Tetrahedron Lett.*, **23**, 1929 (1982); K.

Maruoka, T. Miyazaki, M. Ando, Y. Matsumura, S. Sakane, K. Hattori, and H. Yamamoto, *J. Am. Chem. Soc.*, **105**, 2831 (1983); M. Bonin, J. R. Romero, D. S. Grierson, and H.-P. Husson, *Tetrahedron Lett.*, **23**, 3369 (1982); W. Carruthers, M. J. Williams, and M. T. Cox, *J. Chem. Soc., Chem. Commun.*, **1984**, 1235; T. Wakabayashi, K. Watanabe, Y. Kato, and M. Saito, *Chem. Lett.*, **1977**, 223.

3) Y. Saitoh, Y. Moriyama, T. Takahashi, and Q. Khuong-Huu, *Tetrahedron Lett.*, **21**, 75 (1980); Y. Saitoh, Y. Moriyama, H. Hirota, T. Takahashi, and Q. Khuong-Huu, *Bull. Chem. Soc. Jpn.*, **54**, 488 (1981).

4) J. J. Périé, J. P. Laval, J. Roussel, and A. Lattes, *Tetrahedron*, **28**, 675 (1972); Y. Moriyama, D. Doan-Hoynh, C. Monneret, and Q. Khuong-Huu, *Tetrahedron Lett.*, **1977**, 825.

5) G. Rattle, Thesis of Doctor of Science, The University of Paris, Orsay (1970).

6) G. H. L. Nefkens, G. I. Tesser, and R. J. F. Nivard, *Recl. Trav. Chim. Pays-Bas*, **79**, 688 (1960).

7) W. O. Foyé and W. E. Lange, *J. Am. Pharm. Assoc. Sci. Ed.*, **45**, 742 (1956).

8) M. Gaudemar, *Bull. Soc. Chim. Fr.*, **1962**, 974.

9) A. Horeau, *Tetrahedron Lett.*, **1961**, 506.

10) O. Mitsunobu and M. Yamada, *Bull. Chem. Soc. Jpn.*, **40**, 2380 (1967); A. K. Bose, B. Lal, W. A. Hoffman III, M. S. Manhas, *Tetrahedron Lett.*, **1973**, 1619; M. Asaoka, N. Yanagida, and H. Takei, *ibid.*, **21**, 4611 (1980); O. Mitsunobu and M. Eguchi, *Bull. Chem. Soc. Jpn.*, **44**, 3427 (1971).

11) H. Vorbrüggen and K. Krolikiewicz, *Angew. Chem., Int. Ed. Engl.*, **16**, 876 (1977).

12) P. G. Chantrell, C. A. Pearce, C. R. Toyer, and R. Twaits, *J. Appl. Chem.*, **14**, 563 (1964).

13) E. G. Perkins and D. G. Chasin, *Chem. Phys. Lipids*, **6**, 8 (1971).

14) M. Itoh, D. Hagiwara, and T. Kamiya, *Tetrahedron Lett.*, **1975**, 4393.

15) E. J. Corey, M. G. Bock, A. P. Kozikowski, A. V. Rama Rao, D. Floyd, and B. Lipshutz, *Tetrahedron Lett.*, **1978**, 1051.

16) *cf.* D. Ben-Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952); M. Bergmann and L. Zervas, *Chem. Ber.*, **65**, 1192 (1932).

17) *e.g.*, H. S. Aaron and C. P. Ferguson, *Tetrahedron*, **30**, 803 (1974); M. Tichý and J. Sicher, *Tetrahedron Lett.*, **1962**, 511.