

Use of the Oxazole–Olefin Diels–Alder Reaction in the Total Synthesis of the Monoterpene Alkaloids (–)-Plectrodorine and (+)-Oxerine

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A full account of the total synthesis of two monoterpene alkaloids, (–)-plectrodorine [(–)-1] and (+)-oxerine [(+)-3], is presented. The key steps involved are the formation of the oxazole alcohol 10 from the γ -butyrolactone 9 and the intramolecular Diels–Alder reaction of the oxazole–olefins 13a, b. Since the sign of specific rotation for the synthetic (+)-3 was different from that reported for natural oxerine, the absolute configuration of this alkaloid is not yet fully understood.

Key words oxazole–olefin; Diels–Alder reaction; cyclopenta[*c*]pyridine; monoterpene alkaloid; plectrodorine; oxerine

Oxazoles have been shown to behave as dependable azadiene components in Diels–Alder reactions.¹⁾ Since Kondrat'eva reported the first example of a Diels–Alder reaction of an oxazole with an olefin to produce a pyridine in 1957,^{2,3)} this methodology has become a valuable tool for the preparation of highly substituted pyridines, such as pyridoxine and its analogues. Despite an early recognition of the practical value of the oxazole–olefin Diels–Alder reaction, there are few reports applying this cycloaddition intramolecularly to the synthesis of pyridine-containing natural products.^{4–19)} In the present study, we sought to explore the feasibility of intramolecular oxazole–olefin Diels–Alder reaction for an efficient construction of two monoterpene alkaloids possessing the cyclopenta[*c*]pyridine ring system.^{20–23)}

Plectrodorine (**1**), selected as the first target for the monoterpene alkaloids, was isolated as a racemate together with isoplectrodorine (**2**) from the aerial parts of *Plectronia odorata* (Rubiaceae) by Koch and co-workers.²⁴⁾ The structure and relative stereochemistry of **1** were elucidated through a combination of spectral analysis and chemical transformation. The Koch group²⁵⁾ then described the isolation of oxerine from the aerial parts of *Oxera morieri* (Verbenaceae) and proposed its absolute stereochemistry to be (5*R*,7*S*)-**3** by partial synthesis of oxerine from harpagide of known absolute configuration.²⁶⁾ We chose (5*R*,7*S*)-**3** as the second target to demonstrate the versatility of our synthetic strategy, although racemic synthesis of oxerine has been accomplished by several research groups.^{27–30)} A brief account of the results reported here has been published in a preliminary form.³¹⁾

For the construction of the cyclopenta[*c*]pyridine skeleton via the intramolecular Diels–Alder reaction of oxazoles, we planned to employ the oxazole–olefin **4**. The introduction of suitable olefinic dienophiles to the oxazole aldehyde **5** would provide **4**, whereas the oxazole ring of **5** was envisaged to arise from the addition of α -lithiated methyl isocyanide to

the γ -butyrolactone **6** according to the procedure of Jacobi.^{32,33)}

The requisite γ -butyrolactone **6** was readily obtained from Seebach's dioxolanone **7**.^{34,35)} Thus, reduction of **7** with $\text{BH}_3 \cdot \text{Me}_2\text{S}$ followed by alkaline hydrolysis and acid-promoted lactone formation afforded **6** in 73% yield. The absolute configuration of **6** was further substantiated by the identity of specific rotation of the benzoate **8**, derived from **6**, with the data reported in the literature.³⁶⁾ After protection of the tertiary hydroxy group in **6** with *tert*-butyldimethylsilyl triflate (TBDMSOTf) to afford the lactone **9**, the formation of an oxazole ring was carried out by treatment of **9** with 2.5 eq of α -lithiated methyl isocyanide in THF at -78°C for 3 h followed by addition of AcOH, a slight modification of the Jacobi method,^{32,33)} giving the alcohol **10** in 66% yield. With a view to introducing an olefinic dienophile, the alcohol **10** was converted into the aldehyde **11** in 85% yield by means of the Swern oxidation.³⁷⁾

Coupling reaction of the aldehyde **11** and methyl *trans*-3-iodoacrylate³⁸⁾ with CrCl_2 and a catalytic amount of NiCl_2 in DMSO ^{39–41)} was first performed directed toward the synthesis of plectrodorine (**1**), furnishing the allylic alcohol **12a** as a 2:1 diastereoisomeric mixture in 61% yield. The oxazole–olefin **13a** desired for the intramolecular Diels–Alder reaction was then obtained in 89% yield by oxidation of **12a** with the Dess–Martin periodinane.^{42–44)} When a 0.05 M solution of **13a** in *o*-dichlorobenzene (*o*-DCB) was heated at 150°C for 48 h, the bicyclic pyridine **14a** was obtained in 37% yield, together with recovered **13a** (23%). On treatment

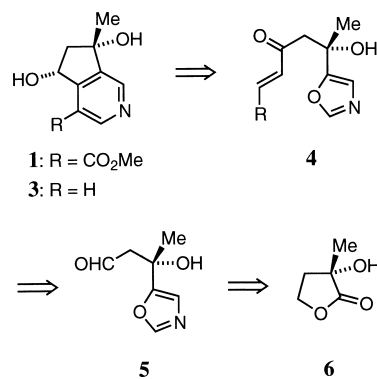
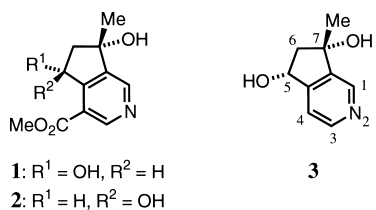
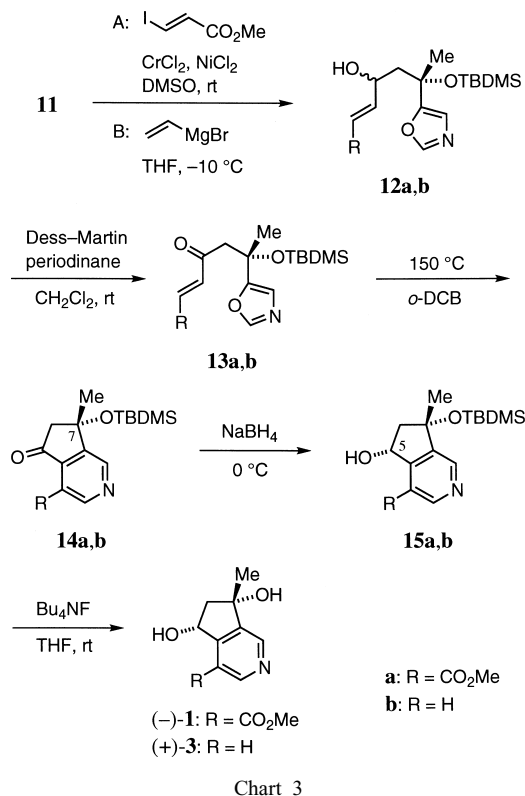
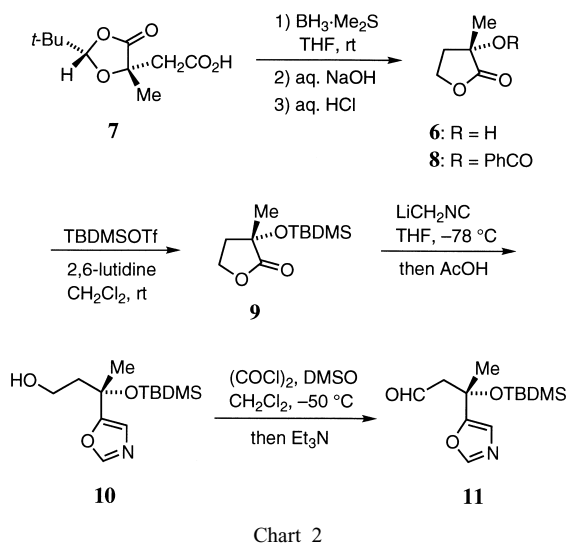


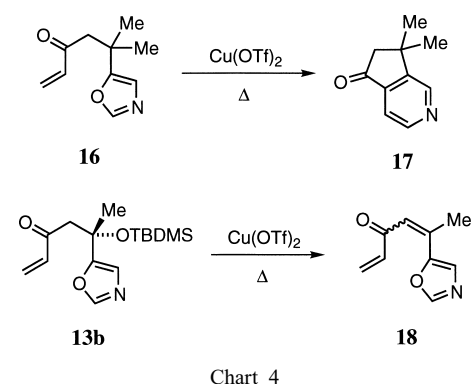
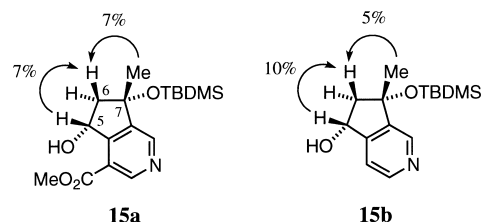
Chart 1

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of the solution at the higher temperature (180 °C) for 24 h, both the yield of **14a** and the recovery of **13a** decreased to 19% and 10%, respectively. The carbonyl group of **14a** was reduced with NaBH₄ in MeOH at 0 °C to generate the alcohol **15a** (75% yield), whose stereochemistry was determined on the basis of 7% NOE enhancements of C(6)-H β signal observed on separate irradiations of C(5)-H and C(7)-Me signals, together with its C(5)-epimer (10% yield). The high stereoselectivity in reduction of **14a** is probably due to access of the hydride from an orientation avoiding the bulky *tert*-butyldimethylsilyloxy group at the 7-position. Finally, deprotection of **15a** with tetrabutylammonium fluoride gave the first target (–)-**1** in 73% yield. The synthetic (–)-**1** proved to be virtually identical with natural plectrodorine²⁴ by a direct comparison of the UV, ¹H-NMR, and mass spectra.

We next turned our attention to the synthesis of oxerine (**3**). On treatment with vinylmagnesium bromide in THF at –10 °C, the aldehyde **11** was converted into a 1:1 diastereomeric mixture of the allylic alcohol **12b** (82% yield), which was then oxidized with the Dess–Martin periodinane to provide the oxazole–olefin **13b** in 93% yield. The intramolecular Diels–Alder reaction of **13b** was carried out by heating its 0.05 M *o*-DCB solution at 150 °C, affording the desired pyridine **14b** as a sole isolable product in 23% yield with the complete disappearance of **13b** after 9 h. A parallel result was also obtained by the reaction of **13b** at 180 °C. The observed low yield of **14b** is presumably due to the decomposition of the terminal olefin **13b** at elevated temperature. Although we have recently reported that the conversion of the oxazole–olefin **16** into the bicyclic pyridine **17** was promoted by addition of a catalytic amount of Cu(OTf)₂,⁴⁵ the catalyst was not effective for **13b**. Thus, treatment of **13b** in the presence of Cu(OTf)₂ (2 mol%) in *o*-DCB at 180 °C for 40 min proceeded with accompanying deprotection followed by elimination of H₂O, furnishing the olefin **18**⁴⁶ in 38% yield. Reduction of **14b** with NaBH₄ in EtOH at 0 °C provided the alcohol **15b** as a sole isomer in 84% yield. Again, the stereochemistry of **15b** was ascertained by the NOE experiments. The second target (+)-**3** [[α]_D²³ +10.6° (*c*=0.21, MeOH)] was obtained in 91% yield *via* deprotection of **15b** with tetrabutylammonium fluoride. Although the UV, ¹H-NMR, and mass spectra of the synthetic (+)-**3** were



found to match those of natural oxerine [[α]_D²⁰ –11° (*c*=0.20, MeOH)],²⁵ the signs of specific rotation for the two samples were opposite. Unfortunately, we were unable to draw a chiroptical comparison between (+)-**3** and oxerine on account of paucity of the natural sample. The circular dichroism (CD) spectrum and specific rotation [[α]_D²⁴ +8.0° (*c*=0.15, MeOH)] of a sample newly derived from harpagide by Koch as well as its ¹H-NMR spectrum were identical with those of (+)-**3**. However, because of an incomplete identifi-

cation of oxerine and the sample prepared from harpagide, the absolute configuration of oxerine remains undefined until this alkaloid is further isolated from natural sources.

In conclusion, the total synthesis of (–)-plectrodorine [(–)-**1**] and (+)-oxerine [(+)-**3**] possessing the cyclopenta-[c]pyridine ring system has been accomplished in eight steps, respectively, from the γ -butyrolactone **6**. It also exemplifies the usefulness of the intramolecular oxazole–olefin Diels–Alder reaction for the synthesis of annulated pyridine-containing natural products.

Experimental

General Notes All melting points were determined on a Yamato MP-1 capillary melting point apparatus. Flash chromatography⁴⁷ was carried out using Merck silica gel 60 (No. 9385). The organic solutions obtained after extraction were dried over anhydrous MgSO₄ and concentrated under reduced pressure. The ratios of solvents in mixtures are shown in v/v. Spectra reported herein were recorded on a JEOL JMS-SX102A mass spectrometer, a Hitachi 330 UV spectrophotometer, a Shimadzu IR-460 or a Shimadzu FTIR-8100 IR spectrophotometer, a JASCO J-725 spectropolarimeter, or a JEOL JNM-GSX-500 (¹H 500 MHz) NMR spectrometer. Chemical shifts are reported in ppm downfield from internal Me₄Si. Optical rotations were measured with a Horiba SEPA-300 polarimeter using a 1-dm sample tube. The following abbreviations are used: br=broad, d=doublet, dd=doublet-of-doublets, ddd=doublet-of-dd's, m=multplet, s=singlet, sh=shoulder.

(3S)-Dihydro-3-hydroxy-3-methyl-2(3H)-furanone (6) A stirred solution of **7** (326 mg, 1.5 mmol) in THF (8 ml) was cooled to 0 °C, and a 2.0 M solution (1.8 ml, 3.6 mmol) of BH₃·Me₂S in THF was added dropwise over 15 min. After stirring at room temperature for 28 h, H₂O (3 ml) and K₂CO₃ (360 mg) were added successively under cooling. The mixture was then extracted with ether and the ethereal extracts were washed with saturated aqueous NaCl, dried, and concentrated. The resulting yellow oil was dissolved in EtOH (6 ml) and cooled to 0 °C. After addition of 2 N aqueous NaOH (3 ml), the solution was stirred at room temperature for 30 min, concentrated *in vacuo* by half, acidified with 10% aqueous HCl, and continuously extracted with ether for 10 h. The ethereal extracts were dried and concentrated to leave a pale yellow oil, which was purified by flash chromatography [hexane–AcOEt (1 : 1)] to yield **6** (128 mg, 73%) as a colorless oil, [α]_D²³ –36.3° (*c*=0.51, CHCl₃); IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 3410 (OH), 1768 (lactone CO); ¹H-NMR (CDCl₃) δ : 1.51 (3H, s, Me), 2.26 (1H, ddd, *J*=13, 7, 4.5 Hz) and 2.44 (1H, ddd, *J*=13, 8, 8 Hz) [C(4)H₂], 2.66 (1H, s, OH), 4.23 (1H, ddd, *J*=9.5, 8, 7 Hz) and 4.42 (1H, ddd, *J*=9.5, 8, 4.5 Hz) [C(5)H₂]; HR-EI-MS *m/z* Calcd for C₅H₈O₃: 116.0473, Found: 116.0470.

(3S)-3-(Benzoyloxy)dihydro-3-methyl-2(3H)-furanone (8) A mixture of **6** (70 mg, 0.6 mmol), Et₃N (121 mg, 1.2 mmol), and 4-(dimethylamino)pyridine (10 mg, 0.08 mmol) in CH₂Cl₂ (3 ml) was stirred at 0 °C, and a solution of benzoyl chloride (127 mg, 0.9 mmol) in CH₂Cl₂ (1 ml) was added. After having been stirred at room temperature for 16 h, the reaction mixture was washed successively with saturated aqueous NaHCO₃ and saturated aqueous NaCl, dried, and concentrated. Purification of the residual solid by flash chromatography [hexane–AcOEt (2 : 1)] provided **8** (127 mg, 96%) as a colorless solid, which was recrystallized from AcOEt–hexane (2 : 1) to afford colorless plates, mp 144–146 °C; [α]_D²³ –16.3° (*c*=0.91, CHCl₃). The melting point, specific rotation, and ¹H-NMR spectral data for this sample were in agreement with those reported in the literature.³⁶

(3S)-3-[(1,1-Dimethylethyl)dimethylsilyloxy]dihydro-3-methyl-2(3H)-furanone (9) A solution of **6** (741 mg, 6.4 mmol) in CH₂Cl₂ (20 ml) was stirred at 0 °C, and TBDMSOTf (3.7 ml, 16.1 mmol) and 2,6-lutidine (2.6 ml, 22.3 mmol) were added in that order. After having been stirred at room temperature for 2 h, the reaction mixture was washed with saturated aqueous NaCl, dried, and concentrated to leave a pale orange oil. Purification by flash chromatography [hexane–AcOEt (10 : 1)] gave **9** (1.46 g, 99%) as a colorless solid, mp 29.5–31 °C; [α]_D²⁴ +12.9° (*c*=0.51, CHCl₃); CI-MS *m/z*: 231 (M+H⁺); IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1771 (lactone CO); ¹H-NMR (CDCl₃) δ : 0.12 and 0.18 (3H each, s, SiMe₂), 0.87 (9H, s, *tert*-Bu), 1.48 (3H, s, CMe), 2.16 (1H, ddd, *J*=13, 7, 7 Hz) and 2.32 (1H, ddd, *J*=13, 7, 5 Hz) [C(4)H₂], 4.21 (1H, ddd, *J*=9, 7, 5 Hz) and 4.35 (1H, ddd, *J*=9, 7, 7 Hz) [C(5)H₂]; HR-FAB-MS *m/z* Calcd for C₁₁H₂₃O₃Si: 231.1416, Found: 231.1418.

(γ S)- γ -[(1,1-Dimethylethyl)dimethylsilyloxy]- γ -methyl-5-oxazolepropanol (10) A solution of methyl isocyanide (246 mg, 6.0 mmol) in THF (12 ml) was stirred at –78 °C in an atmosphere of N₂, and a 1.5 M solu-

tion (4.0 ml, 6.0 mmol) of BuLi in hexane was added dropwise over 15 min. After the mixture had been stirred for 15 min, a solution of **9** (560 mg, 2.4 mmol) in THF (5 ml) was introduced dropwise over 10 min. Stirring was then continued for a further 3 h, and the reaction was quenched by adding AcOH (6.0 ml). The mixture was brought to room temperature and concentrated under reduced pressure. The residue was partitioned between H₂O and ether, and the ethereal extracts were washed with saturated aqueous NaCl, dried, and concentrated. Purification of the residual oil by flash chromatography [AcOEt–hexane (1 : 1)] gave **10** (438 mg, 66%) as a colorless oil, [α]_D²⁴ –27.4° (*c*=0.51, CHCl₃); CI-MS *m/z*: 272 (M+H⁺); IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 3370 (OH); ¹H-NMR (CDCl₃) δ : –0.11 and 0.04 (3H each, s, SiMe₂), 0.89 (9H, s, *tert*-Bu), 1.68 (3H, s, CMe), 1.98 (1H, ddd, *J*=14, 6.5, 5.5 Hz) and 2.20 (1H, ddd, *J*=14, 7, 6 Hz) [C(β)H₂], 2.37 (1H, br, OH), 3.77 [2H, m, C(α)H₂], 6.94 [1H, s, C(4)H], 7.83 [1H, s, C(2)H]; HR-FAB-MS *m/z* Calcd for C₁₃H₂₆NO₃Si: 272.1682, Found: 272.1687.

(β S)- β -[(1,1-Dimethylethyl)dimethylsilyloxy]- β -methyl-5-oxazolepropanal (11) A solution of oxalyl chloride (0.37 ml, 4.2 mmol) in CH₂Cl₂ (12 ml) was cooled to –60 °C in an atmosphere of N₂, and a solution of DMSO (0.60 ml, 8.5 mmol) in CH₂Cl₂ (2 ml) was added. After the mixture had been stirred for 5 min, a solution of **10** (562 mg, 2.1 mmol) in CH₂Cl₂ (4 ml) was added dropwise over 2 min. Stirring was then continued at –60 °C for a further 30 min. The reaction mixture, after addition of Et₃N (2.4 ml), was brought to room temperature and partitioned between CH₂Cl₂ and H₂O. The CH₂Cl₂ extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a yellow oil. Purification by flash chromatography [hexane–AcOEt (2 : 1)] furnished **11** (474 mg, 85%) as a slightly yellow oil, [α]_D²⁴ –44.1° (*c*=0.51, CHCl₃); FAB-MS *m/z*: 270 (M+H⁺); IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 1725 (CHO); ¹H-NMR (CDCl₃) δ : –0.12 and 0.04 (3H each, s, SiMe₂), 0.87 (9H, s, *tert*-Bu), 1.73 (3H, s, CMe), 2.70 and 2.89 [1H each, dd, *J*=15.5, 3 Hz, C(α)H₂], 6.98 [1H, s, C(4)H], 7.85 [1H, s, C(2)H], 9.86 (1H, dd, *J*=3, 3 Hz, CHO); HR-FAB-MS *m/z* Calcd for C₁₃H₂₄NO₃Si: 270.1526, Found: 270.1525.

(2E,6S)-6-[(1,1-Dimethylethyl)dimethylsilyloxy]-4-hydroxy-6-(5-oxazolyl)-2-heptenoic Acid Methyl Ester (12a) A solution of **11** (472 mg, 1.75 mmol) and methyl *trans*-3-iodoacrylate³⁸ (1.12 g, 5.3 mmol) in DMSO (25 ml) was stirred in an atmosphere of Ar, and CrCl₂ (1.29 g, 10.5 mmol) containing NiCl₂ (2.3 mg, 0.018 mmol) was added in portions. The resulting dark green mixture was then stirred at room temperature for 72 h. The reaction mixture was quenched by addition of saturated aqueous NH₄Cl (10 ml) under cooling and extracted with ether. The combined ethereal extracts were washed with saturated aqueous NaCl, dried, and concentrated. Purification of the residual oil by flash chromatography [hexane–AcOEt (1 : 1)] provided **12a** (381 mg, 61%) as a slightly yellow oil, [α]_D²⁴ –22.6° (*c*=0.57, CHCl₃); FAB-MS *m/z*: 356 (M+H⁺); IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 3410 (OH), 1725 (ester CO); ¹H-NMR (CDCl₃) δ : –0.18 (1H), –0.03 (2H), 0.04 (1H), and 0.12 (2H) (s each, SiMe₂), 0.89 (3H), 0.89 (6H) (s each, *tert*-Bu), 1.72 (2H) and 1.78 (1H) (s each, CMe), 1.80 (1/3H, dd, *J*=14.5, 2 Hz), 1.95 (2/3H, dd, *J*=14.5, 9.5 Hz), 2.01 (2/3H, dd, *J*=14.5, 2.5 Hz), and 2.25 (1/3H, dd, *J*=14.5, 10.5 Hz) [C(5)H₂], 3.72 (2H) and 3.73 (1H) (s each, CO₂Me), 3.85 (2/3H) and 3.88 (1/3H) (br each, OH), 4.48 (2/3H) and 4.71 (1/3H) (m each, CHOH), 6.09 (2/3H) and 6.14 (1/3H) [dd each, *J*=15.5, 2 Hz, C(2)H], 6.81 (2/3H, dd, *J*=15.5, 4.5 Hz) and 6.87 (1/3H, dd, *J*=15.5, 4 Hz) [C(3)H], 6.97 (1/3H) and 6.99 (2/3H) [s each, C(4')H], 7.85 [1H, s, C(2')H]; ⁴⁸HR-FAB-MS *m/z* Calcd for C₁₇H₃₀NO₅Si: 356.1893, Found: 356.1902.

(γ S)- γ -[(1,1-Dimethylethyl)dimethylsilyloxy]- α -ethenyl- γ -methyl-5-oxazolepropanol (12b) A mixture of THF (5 ml) and a 0.95 M solution (1.7 ml, 1.6 mmol) of vinylmagnesium bromide in THF was cooled to –10 °C in an atmosphere of N₂, and a solution of **11** (308 mg, 1.1 mmol) in THF (2 ml) was added dropwise over 5 min. After the mixture had been stirred at –10 °C for 30 min, the reaction was quenched by adding saturated aqueous NH₄Cl (3 ml). The whole was extracted with ether, and the ethereal extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a pale yellow oil. Purification by flash chromatography [hexane–AcOEt (5 : 2)] gave **12b** (280 mg, 82%) as a colorless oil, [α]_D²³ –26.7° (*c*=0.49, CHCl₃); FAB-MS *m/z*: 298 (M+H⁺); IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 3380 (OH); ¹H-NMR (CDCl₃) δ : –0.19, –0.04, 0.03, and 0.11 (3/2H each, s, SiMe₂), 0.88 and 0.93 (9/2H each, s, *tert*-Bu), 1.71 and 1.77 (3/2H each, s, CMe), 1.74 (1/2H, dd, *J*=14.5, 2 Hz), 1.94 (1/2H, dd, *J*=14.5, 3 Hz), 1.99 (1/2H, dd, *J*=14.5, 9 Hz), and 2.27 (1/2H, dd, *J*=14.5, 10.5 Hz) [C(β)H₂], 3.48 and 3.62 (1/2H each, br, s, OH), 4.30 and 4.51 (1/2H each, br, m, CHOH), 5.04 and 5.08 (1/2H each, ddd, *J*=10.5, 1.5, 1.5 Hz, CH=CH₂), 5.20 and 5.28 (1/2H each, ddd, *J*=17.5, 1.5, 1.5 Hz, CH=CH₂), 5.77 and 5.83 (1/2H each, ddd, *J*=17.5, 10.5, 6 Hz, CH=CH₂), 6.96 and 6.97 [1/2H each, s, C(4)H],

7.84 and 7.85 [1/2H each, s, C(2)H]; HR-FAB-MS m/z Calcd for $C_{15}H_{28}NO_3Si$: 298.1838, Found: 298.1842.

(2E,6S)-6-[(1,1-Dimethylethyl)dimethylsilyloxy]-6-(5-oxazolyl)-4-oxo-2-heptenoic Acid Methyl Ester (13a) A solution of **12a** (341 mg, 0.96 mmol) in CH_2Cl_2 (3 ml) was added to a stirred solution of the Dess–Martin periodinane^{42–44} (610 mg, 1.4 mmol) in CH_2Cl_2 (10 ml). After having been stirred at room temperature for 45 min, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (10 ml) containing $Na_2S_2O_3$ (1.8 g). The biphasic mixture was stirred for 5 min and extracted with ether. The organic phases were combined, washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous $NaCl$, dried, and concentrated to leave a yellow oil, which was purified by flash chromatography [hexane–AcOEt (2 : 1)] to afford **13a** (301 mg, 89%) as a pale yellow oil, $[\alpha]_D^{23} -90.7^\circ$ ($c=0.50$, $CHCl_3$); FAB-MS m/z : 354 ($M+H^+$); IR $\nu_{max}^{film} cm^{-1}$: 1731 (ester CO), 1690 (CO); 1H -NMR ($CDCl_3$) δ : -0.16 and -0.03 (3H each, s, $SiMe_2$), 0.84 (9H, s, *tert*-Bu), 1.73 (3H, s, CMe), 2.95 and 3.26 [1H each, d, $J=14$ Hz, C(5) H_2], 3.80 (3H, s, CO_2Me), 6.62 and 7.11 [1H each, d, $J=16$ Hz, C(2)H, C(3)H], 6.94 [1H, s, C(4')H], 7.83 [1H, s, C(2')H];⁴⁸ HR-FAB-MS m/z Calcd for $C_{17}H_{28}NO_3Si$: 354.1737, Found: 354.1743.

(5S)-5-[(1,1-Dimethylethyl)dimethylsilyloxy]-5-(5-oxazolyl)-1-hexen-3-one (13b) A mixture of **12b** (563 mg, 1.9 mmol) and the Dess–Martin periodinane^{42–44} (1.23 g, 2.9 mmol) in CH_2Cl_2 (23 ml) was stirred at room temperature for 80 min. The reaction mixture was worked up as described above for **13a**. Purification of a crude oil by flash chromatography [hexane–AcOEt (5 : 2)] furnished **13b** (521 mg, 93%) as a colorless oil, $[\alpha]_D^{23} -70.8^\circ$ ($c=0.49$, $CHCl_3$); FAB-MS m/z : 296 ($M+H^+$); IR $\nu_{max}^{film} cm^{-1}$: 1694 (CO); 1H -NMR ($CDCl_3$) δ : -0.16 and -0.02 (3H each, s, $SiMe_2$), 0.84 (9H, s, *tert*-Bu), 1.74 (3H, s, CMe), 2.98 and 3.19 [1H each, d, $J=14$ Hz, C(4) H_2], 5.75 (1H, dd, $J=10.5$, 1 Hz) and 6.18 (1H, dd, $J=17.5$, 1 Hz) [C(1) H_2], 6.34 [1H, dd, $J=17.5$, 10.5 Hz, C(2)H], 6.93 [1H, s, C(4')-H], 7.82 [1H, s, C(2')H];⁴⁸ HR-FAB-MS m/z Calcd for $C_{15}H_{26}NO_3Si$: 296.1682, Found: 296.1682.

(7S)-7-[(1,1-Dimethylethyl)dimethylsilyloxy]-6,7-dihydro-7-methyl-5-oxo-5H-cyclopenta[c]pyridine-4-carboxylic Acid Methyl Ester (14a) A solution of **13a** (177 mg, 0.50 mmol) in *o*-DCB (10 ml) was heated at 150 °C in an atmosphere of Ar for 48 h. The reaction mixture was then concentrated *in vacuo* to leave a dark brown oil, which was subjected to flash chromatography [hexane–AcOEt (3 : 1)]. Earlier fractions furnished **14a** (61.8 mg, 37%) as a slightly yellow oil, $[\alpha]_D^{22} +105.7^\circ$ ($c=0.50$, $CHCl_3$); FAB-MS m/z : 336 ($M+H^+$); IR $\nu_{max}^{film} cm^{-1}$: 1730 (CO and CO); 1H -NMR ($CDCl_3$) δ : 0.00 and 0.11 (3H each, s, $SiMe_2$), 0.86 (9H, s, *tert*-Bu), 1.71 (3H, s, CMe), 2.91 and 2.99 [1H each, d, $J=18$ Hz, C(6) H_2], 3.99 (3H, s, CO_2Me), 8.98 [1H, s, C(1)H], 9.17 [1H, s, C(3)H]; HR-FAB-MS m/z Calcd for $C_{17}H_{26}NO_4Si$: 336.1631, Found: 336.1614.

Later fractions in the above chromatography gave the starting oxazole-olefin **13a** (41.4 mg, 23% recovery).

(7S)-7-[(1,1-Dimethylethyl)dimethylsilyloxy]-6,7-dihydro-7-methyl-5H-cyclopenta[c]pyridin-5-one (14b) A solution of **13b** (292 mg, 0.99 mmol) in *o*-DCB (20 ml) was heated at 150 °C in an atmosphere of Ar for 9 h. The reaction mixture was then concentrated *in vacuo* to leave a dark brown oil, which was purified by flash chromatography [hexane–AcOEt (4 : 1)] to afford **14b** (62.8 mg, 23%) as a slightly yellow solid, mp 58–59 °C; $[\alpha]_D^{28} +84.8^\circ$ ($c=0.50$, $CHCl_3$); FAB-MS m/z : 278 ($M+H^+$); IR $\nu_{max}^{Nujol} cm^{-1}$: 1728 (CO); 1H -NMR ($CDCl_3$) δ : -0.05 and 0.04 (3H each, s, $SiMe_2$), 0.86 (9H, s, *tert*-Bu), 1.73 (3H, s, CMe), 2.86 and 2.94 [1H each, d, $J=18.5$ Hz, C(6) H_2], 7.52 [1H, dd, $J=5$, 1.5 Hz, C(4)H], 8.78 [1H, d, $J=5$ Hz, C(3)H], 9.08 [1H, d, $J=1.5$ Hz, C(1)H]; HR-FAB-MS m/z Calcd for $C_{15}H_{24}NO_2Si$: 278.1576, Found: 278.1573.

5-(5-Oxazolyl)-1,4-hexadien-3-one (18) A stirred mixture of **13b** (70.4 mg, 0.24 mmol) and $Cu(OTf)_2$ (1.7 mg, 2 mol%) in *o*-DCB (4.8 ml) was heated at 180 °C in an atmosphere of Ar for 40 min. The reaction mixture was concentrated *in vacuo*, and the residual brown oil was purified by flash chromatography [hexane–AcOEt (5 : 2)] to give **18** (14.8 mg, 38%) as a pale yellow solid, mp 35–36 °C; EI-MS m/z : 163 (M^+); IR $\nu_{max}^{Nujol} cm^{-1}$: 1665 (CO); 1H -NMR ($CDCl_3$) δ : 2.47 (3H, s, Me), 5.85 (1H, d, $J=10.5$ Hz) and 6.31 (1H, d, $J=17$ Hz) [C(1) H_2], 6.52 [1H, dd, $J=17$, 10.5 Hz, C(2)H], 6.96 [1H, s, C(4)H], 7.37 [1H, s, C(4')H], 7.93 [1H, s, C(2')-H];⁴⁸ HR-EI-MS m/z Calcd for $C_9H_9NO_2$: 163.0633, Found: 163.0633.

(5R,7S)-7-[(1,1-Dimethylethyl)dimethylsilyloxy]-6,7-dihydro-5-hydroxy-7-methyl-5H-cyclopenta[c]pyridine-4-carboxylic Acid Methyl Ester (15a) A stirred solution of **14a** (50.3 mg, 0.15 mmol) in MeOH (1.5 ml) was cooled to 0 °C, and $NaBH_4$ (5.7 mg, 0.15 mmol) was added. After the mixture had been stirred at 0 °C for 30 min, acetone (0.1 ml) was added. The resulting mixture was concentrated *in vacuo*, and the residual oil

was partitioned between $CHCl_3$ and H_2O . The $CHCl_3$ extracts were washed with saturated aqueous $NaCl$, dried, and concentrated to leave a colorless oil, which was then subjected to flash chromatography [hexane–AcOEt (3 : 1)]. Earlier fractions provided **15a** (38.0 mg, 75%) as a colorless oil, $[\alpha]_D^{24} -4.0^\circ$ ($c=0.94$, $CHCl_3$); FAB-MS m/z : 338 ($M+H^+$); IR $\nu_{max}^{film} cm^{-1}$: 3480 (OH), 1708 (ester CO); 1H -NMR ($CDCl_3$) δ : 0.04 and 0.14 (3H each, s, $SiMe_2$), 0.89 (9H, s, *tert*-Bu), 1.48 (3H, s, CMe), 2.33 (1H, dd, $J=12.5$, 8 Hz) and 2.76 (1H, dd, $J=12.5$, 7.5 Hz) [C(6) H_2], 4.01 (3H, s, CO_2Me), 5.0 (1H, br, OH), 5.39 [1H, dd, $J=8$, 7.5 Hz, C(5)H], 8.79 [1H, s, C(1)H], 9.15 [1H, s, C(3)H]; HR-FAB-MS m/z Calcd for $C_{17}H_{28}NO_4Si$: 338.1788, Found: 338.1791.

Later fractions in the above chromatography afforded C(5)-epimer (5.2 mg, 10%) of **15a** as a colorless solid, mp 69–72 °C; $[\alpha]_D^{24} +8.8^\circ$ ($c=0.26$, $CHCl_3$); FAB-MS m/z : 338 ($M+H^+$); IR $\nu_{max}^{Nujol} cm^{-1}$: 3140 (OH), 1722 (ester CO); 1H -NMR ($CDCl_3$) δ : -0.03 and 0.01 (3H each, s, $SiMe_2$), 0.81 (9H, s, *tert*-Bu), 1.73 (3H, s, CMe), 2.22 (1H, dd, $J=13.5$, 4.5 Hz) and 2.64 (1H, dd, $J=13.5$, 7.5 Hz) [C(6) H_2], 4.01 (3H, s, CO_2Me), 4.37 (1H, br, OH), 5.61 [1H, m, C(5)H], 8.76 [1H, s, C(1)H], 9.13 [1H, s, C(3)H]; HR-FAB-MS m/z Calcd for $C_{17}H_{28}NO_4Si$: 338.1788, Found: 338.1789.

(5R,7S)-7-[(1,1-Dimethylethyl)dimethylsilyloxy]-6,7-dihydro-7-methyl-5H-cyclopenta[c]pyridin-5-ol (15b) A solution of **14b** (62.1 mg, 0.22 mmol) in EtOH (1.5 ml) was treated with $NaBH_4$ (12.5 mg, 0.33 mmol) at 0 °C for 30 min. The reaction mixture was worked up as described above for **15a**, and purification of a crude oil by flash chromatography [AcOEt–hexane (2 : 1)] provided **15b** (52.8 mg, 84%) as a pale yellow solid, mp 104–107 °C; $[\alpha]_D^{24} +31.0^\circ$ ($c=1.03$, $CHCl_3$); FAB-MS m/z : 280 ($M+H^+$); IR $\nu_{max}^{Nujol} cm^{-1}$: 3140 (OH); 1H -NMR ($CDCl_3$) δ : 0.05 and 0.08 (3H each, s, $SiMe_2$), 0.86 (9H, s, *tert*-Bu), 1.54 (3H, s, CMe), 2.20 and 2.62 [1H each, dd, $J=12.5$, 6.5 Hz, C(6) H_2], 2.6 (1H, br, OH), 5.05 [1H, dd, $J=6.5$, 6.5 Hz, C(5)H], 7.37 [1H, d, $J=5$ Hz, C(4)H], 8.55 [1H, d, $J=5$ Hz, C(3)H], 8.61 [1H, s, C(1)H]; HR-FAB-MS m/z Calcd for $C_{15}H_{26}NO_2Si$: 280.1733, Found: 280.1732.

(5R,7S)-6,7-Dihydro-5,7-dihydroxy-7-methyl-5H-cyclopenta[c]pyridine-4-carboxylic Acid Methyl Ester (–)-Plectrodorine [(–)-1] A 1.0 M solution (0.26 ml, 0.26 mmol) of tetrabutylammonium fluoride in THF was added to a stirred solution of **15a** (29.4 mg, 0.087 mmol) in THF (1.0 ml). After having been stirred at room temperature for 2 h, the reaction mixture was concentrated *in vacuo* to leave a yellow oil. Purification by flash chromatography [$CHCl_3$ –MeOH (15 : 1)] furnished (–)-**1** (14.2 mg, 73%) as a colorless oil, $[\alpha]_D^{24} -78.4^\circ$ ($c=0.40$, MeOH); HR-EI-MS m/z Calcd for $C_{11}H_{13}NO_4$: 223.0844, Found: 223.0847. The UV (MeOH), 1H -NMR ($CDCl_3$), and mass spectral data of this sample were in agreement with those reported for natural plectrodorine.²⁴

(5R,7S)-6,7-Dihydro-7-methyl-5H-cyclopenta[c]pyridine-5,7-diol [(+)-Oxerine] [(+)-3] Deprotection of **15b** (52.8 mg, 0.19 mmol) with tetrabutylammonium fluoride and work-up of the reaction mixture were carried out as described above for (–)-**1**. Purification of a crude oil by flash chromatography [$CHCl_3$ –MeOH (10 : 1)] gave (+)-**3** (28.4 mg, 91%) as a colorless solid, mp 120–122 °C; $[\alpha]_D^{23} +10.6^\circ$ ($c=0.21$, MeOH); CD $\lambda_{ext}^{MeOH} nm$ ($\Delta\epsilon$): 267 (+2.54), 264 (+2.00), 261 (+2.15), 244 (–1.04), 231 (–0.39), 214 (–2.17); HR-EI-MS m/z Calcd for $C_9H_{11}NO_2$: 165.0790, Found: 165.0788. The UV (MeOH), 1H -NMR (CD_3OD), and mass spectral data of this sample were virtually identical with those of natural oxerine.²⁵

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References and Notes

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