

Reagents in the Charts 1, 2 & 3

1) DMSO/(COCl)₂/CH₂Cl₂, TEA; 2) HC(OEt)₃/Amberlyst 15; 3) Na/NH₃; 4) *t*-BuLi in pentane, 4 in THF; 5) H₂SO₄(1%) in H₂O-acetone; 6) CrO₃/pyridine/CH₂Cl₂; 7) NH₄OH/MeOH; 8) EtMgBr/Et₂O-THF, CuCl/MeCH=CHCH₂Br(mainly *trans*)/Et₂O-THF; 9) MeOH/Amberlyst 15; 10) LAH/Et₂O; 11) MsCl/TEA/CH₂Cl₂; 12) NaCN/Aliquat 336/CH₂Cl₂-H₂O; 13) HCl(25%)-MeOH, H₂O; 14) NaI/Aliquat 336/CH₂Cl₂-H₂O

head synthonnes were considered according to the oxidation states of C-1 and C-4 of the chiral epoxides, i.e. CH₂OR, CH(OR)₂ or COR for C-1, and CHO or COX for C-4 functionality. In this report, we describe the synthesis using the chiral epoxide **4** as the head part.

The synthesis of **4** started with the Sharpless' epoxide **2**,⁵⁾ [α]_D = -23.9°(c=2.04, CHCl₃). Swern oxidation⁶⁾ of **2** followed by acetalization⁷⁾ gave **3** in 76% yield.⁸⁾ The benzyl group of **3** was difficult to cleave off with H₂/Pd-C even at 50 atm. Deprotection was attained by treatment with Na/NH₃.⁹⁾ Swern oxidation of the resulting alcohol gave the chiral epoxy aldehyde **4** in 65% yield from **3** (Chart 1).

The head epoxide **4** and the lithio derivative of (*E,E*)-3,6-octadienyl iodide^{3c)} (**5**) was connected to give a pair of isomers, **6a** and **6b** from **5** in 63% and 16% yields, respectively. The stereochemistry of these isomers was assigned at the stage of lactones, **9a** and **9b**, by their spectral comparisons with the reported data.^{3b,3e)} The acetal **6a** was hydrolyzed with H₂SO₄ in aqueous acetone at 55°C for 20 h to give a mixture of **7a** and **8a**. The cyclic acetal **7a** was separated and hydrolyzed under the same conditions to obtain **8a** (total 62% yield from **6a**). The cyclic hemiacetal **8b** was obtained from **6b** in 20% yield by a single treatment with H₂SO₄ in aqueous acetone.

Collins oxidation¹⁰⁾ of **8a** gave **9a** in 66% yield, and the oxidation of **8b** under the same conditions gave **9b**¹¹⁾ in 71% yield. Ammonolysis of **9a** followed by Collins oxidation gave **1** as a white powder in 45% yield with 94% ee.¹²⁾ The recrystallization of the product from benzene gave colorless prisms, mp 93°C (lit.⁴⁾ 93°C), which were used for [α]_D measurements.¹²⁾ The ¹H-NMR, EI-MS and IR data of the synthetic **1** were identical with those of natural cerulenin (Chart 2).

In the tail part synthesis, a preliminary experiment for the introduction of C₁ unit at C-5 with NaCN was examined. The (*E,E*)-dienol **11**,¹³⁾ prepared from **10** in 50% yield after purification with AgNO₃-impregnated silica gel column chromatography, was mesylated¹⁴⁾ and treated with NaCN in the presence of phase transfer catalyst, aliquat 336¹⁵⁾ in CH₂Cl₂-H₂O to give **12** in 70% yield. The nitrile **12** was treated successively with HCl(25%)-MeOH and ice-water¹⁶⁾ at 0°C to give the corresponding methyl ester **13** in 77% yield.¹⁷⁾ The methyl ester **13** was reduced with LAH to give the alcohol **14**^{3c)} which was converted into iodide **5** in 74% yield from **14** via the mesylate of **14**. The iodide **5** was obtained in 38% yield from the alcohol **11** (Chart 3).

The synthesis method described is applicable for preparations of optically active analogues with a variety of tail-chains, and labeled **1**. Experimental details and further studies will be described elsewhere.

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REFERENCES AND NOTES

- 1) a) S. Omura, Methods in Enzymology, **72**, 520 (1981); b) S. Omura, Bacteriological Reviews, **40**, 681 (1976).
- 2) H. Funabashi, S. Iwasaki, S. Okuda and S. Omura, Tetrahedron Lett., **24**, 2673 (1983).
- 3) a) R. K. Boeckmann, Jr. and E. W. Thomas, J. Am. Chem. Soc., **99**, 2805 (1977); b) R. K. Boeckmann, Jr. and E. W. Thomas, J. Am. Chem. Soc., **101**, 987 (1979); c) E. J. Corey and D. R. Williams, Tetrahedron Lett., **1977**, 3847; d) A. A. Jakubowski, F. S. Guziec, Jr. and M. Tishler, Tetrahedron Lett., **1977**, 2399; e) A. A. Jakubowski, F. S. Guziec, Jr., M. Sugiura, C. C. Tam, M. Tishler and S. Omura, J. Org. Chem., **47**, 1221 (1982); f) K. Mikami, N. Kishi and T. Nakai, Chem. Lett., **1981**, 1721; g) T. Ohta, H. Tsuchiyama and S. Nozoe, Heterocycles, **24**, 1137 (1986).
- 4) a) N. Sueda, H. Ohru and H. Kuzuhara, Tetrahedron Lett., **1979**, 2039; b) M. Pietraszkiewicz and P. Sina, Tetrahedron Lett., **1979**, 4741.
- 5) T. Katsuki, A. W. M. Lee, P. Ma, V. S. Martin, S. Masamune, K. B. Sharpless, D. Tuddenham and F. J. Walker, J. Org. Chem., **47**, 1373 (1982).
- 6) a) A. J. Mancuso, S.-L. Huang and D. Swern, J. Org. Chem., **43**, 2480 (1978); b) K. Omura and D. Swern, Tetrahedron, **34**, 1651 (1978); c) A. J. Mancuso, D. S. Brownfain and D. Swern, J. Org. Chem., **44**, 4148 (1979).
- 7) S. A. Patwardhan and S. Dev, Synthesis, **1974**, 348.
- 8) Satisfactory IR, NMR and EI-MS data were obtained for all synthetic intermediates.
- 9) E. J. Reist, V. J. Bartuska and L. Goodman, J. Org. Chem., **29**, 3725 (1964).
- 10) R. Ratcliffe and R. Rodehorst, J. Org. Chem., **35**, 4000 (1970).
- 11) Because of a shortage of the sample, **9b** was not converted to **1**.
- 12) Optical purity was calculated from $[\alpha]_D$ values of **9a**, $[\alpha]_D^{+53.1^\circ}$ ($c=0.51$, CHCl_3), and the reported one, $[\alpha]_D^{+56.5^\circ}$ ($c=0.8$, CHCl_3).^{4a} Synthetic **1** showed $[\alpha]_D^{-6.5^\circ}$ ($c=0.09$, CHCl_3). The difference between the value and the reported one, $[\alpha]_D^{-12^\circ}$ ($c=1$, CHCl_3),^{1a} is the result of the facile equilibration between **1** and its diastereomeric hydroxy lactams.^{3e}
- 13) C. B. du Jassonneix and J. Y. Lallemand, Bull. Soc. Chim. Fr., **1977**, 1223.
- 14) R. K. Crossland and K. L. Servis, J. Org. Chem., **35**, 3195 (1970).
- 15) a) M. S. Newman, T. G. Barbee, Jr., C. N. Blakesley, Z. ud Din, S. Gromelski, Jr., V. K. Khanna, L.-F. Lee, J. Radhakrishnan, R. L. Robey, V. Sankaran, S. K. Sankarappa and J. M. Springer, J. Org. Chem., **40**, 2863 (1975); b) C. M. Starks, J. Am. Chem. Soc., **93**, 195 (1971); c) H. Kobler, K.-H. Schuster and G. Simchen, Liebigs Ann. Chem., **1946** (1978).
- 16) a) S. Baldwin, J. Org. Chem., **26**, 3280 (1961); b) S. G. Davies and G. H. Whitham, J. Chem. Soc., Perkin I, **1976**, 2279.
- 17) L. M. du Plessis and J. A. D. Erasmus, S. Afr. J. Chem., **31**, 75 (1978).
- 18) [Selected ^1H -NMR data (δ , CDCl_3)] **1**: 1.66 (3H, m, CH_3), 2.31 (2H, 'q', $J=7$ Hz, H-6), 2.63 (1H, dt, $J=17.4, 7.2$ Hz, H-5), 2.65 (2H, m's, H-9), 2.69 (1H, dt, $J=17.4, 7.5$ Hz, H-5), 3.73 (1H, d, $J=5.4$ Hz, H-2), 3.87 (1H, d, $J=5.4$ Hz, H-3), 5.32-5.51 (5H, m's, $\text{CH}=\text{CH} \times 2$ & NH), 6.3 (1H, bs, NH); **4**: 1.20, 1.24 (3H $\times 2$, t $\times 2$, $J=7.0$ Hz, $\text{CH}_3 \times 2$), 3.38 (1H, dd, $J=4.4, 4.5$ Hz, H-2), 3.42 (1H, dd, $J=3.2, 4.5$ Hz, H-3), 3.57, 3.58, 3.70, 3.70 (1H $\times 4$, dq $\times 4$, $J=9.4, 7.0$ Hz, $\text{CH}_2 \times 2$), 4.77 (1H, d, $J=3.2$ Hz, H-4), 9.50 (1H, d, $J=4.4$ Hz, H-1); **5**: 1.66 (3H, d, $J=6.4$ Hz, $\text{CH}_3\text{CH}=\text{CH}$), 2.56 (2H, dt, $J=7.2, 7.2$ Hz, $\text{H}=\text{CHCH}_2\text{CH}_2\text{I}$), 2.68 (2H, 'bt', $J=6$ Hz, $\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}$), 3.15 (2H, t, $J=7.2$ Hz, CH_2I), 5.3-5.6 (4H, m's, $\text{CH}=\text{CH} \times 2$); **6a**: 1.24, 1.27 (3H $\times 2$, t $\times 2$, $J=7.0$ Hz, $\text{OCH}_2\text{CH}_3 \times 2$), 1.65 (3H, m, $\text{CH}_3-\text{CH}=\text{CH}$), 1.74 (2H, m's, H-5), 2.10-2.28 (2H, m's, H-6), 2.67 (2H, m's, H-9), 2.7 (1H, bd, $J=2$ Hz, OH), 2.91 (1H, dd, $J=4.1, 8.1$ Hz, H-3), 3.14 (1H, dd, $J=4.1, 5.9$ Hz, H-2), 3.49 (1H, 'q', $J=8$ Hz, H-4), 3.55-3.83 (4H, dq $\times 4$, $\text{OCH}_2\text{CH}_3 \times 2$), 4.52 (1H, d, $J=5.9$ Hz, H-1), 5.36-5.52 (4H, m's, $\text{CH}=\text{CH} \times 2$); **6b**: 1.22, 1.26 (3H $\times 2$, t $\times 2$, $J=7$ Hz, $\text{OCH}_2\text{CH}_3 \times 2$), 1.65 (5H, m's, H-5 and $\text{CH}_3-\text{CH}=\text{CH}$), 2.0 (1H, bd, $J=4$ Hz, OH), 2.08-2.28 (2H, m's, H-6), 2.67 (2H, m's, H-9), 2.99 (1H, dd, $J=4.3, 7.4$ Hz, H-3), 3.19 (1H, dd, $J=4.3, 6.4$ Hz, H-2), 3.53 (1H, dq, $J=9.3, 7.0$ Hz, OCH_2CH_3), 3.6-3.8 (3H, dq $\times 3$, OCH_2CH_3), 3.62 (1H, m, H-4), 4.41 (1H, d, $J=6.4$ Hz, H-1), 5.36-5.52 (4H, m's, $\text{CH}=\text{CH} \times 2$); **9a**: 1.66 (3H, m, CH_3), 1.76 (2H, m's, H-5), 2.20 (2H, m's, H-6), 2.68 (2H, m's, H-9), 3.77 (1H, d, $J=2.2$ Hz, H-2), 3.96 (1H, d, $J=2.2$ Hz, H-3), 4.59 (1H, dd, $J=6.3, 6.8$ Hz, H-4), 5.34-5.55 (4H, m's, $\text{CH}=\text{CH} \times 2$); **9b**: 1.66 (3H, m, CH_3), 1.84, 1.93 (1H $\times 2$, m $\times 2$, H-5), 2.21 (2H, m's, H-6), 2.68 (2H, m's, H-9), 3.77 (1H, d, $J=2.5$ Hz, H-2), 4.06 (1H, d, $J=1.3, 2.5$ Hz, H-3), 4.47 (1H, ddd, $J=1.3, 6.3, 7.4$ Hz, H-4), 5.36-5.56 (4H, m's, $\text{CH}=\text{CH} \times 2$).

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