Eiseniachlorides A and B (1 and 2) are C18 oxylipin consisting of cyclopentane and a 14-membered lactone, which corresponds to chlorohydrin biosynthesized via the nucleophilic opening of chlorine atoms to the oxirane of ecklonialactones A and B (3 and 4) isolated from the brown algae, Ecklonia stolonifera, by Kurata et al. (Fig. 1). While no report on the synthesis of eiseniachloride B (2) exists, Fürstner and colleagues confirmed that eiseniachloride A (1) is rapidly generated together with other oxirane-opening compounds when ecklonialactone A (3) is kept in CDCl3. Since CHCl3 was used in the extraction operation performed by Kimura et al., 1 and 2 may be an artifact of 3 and 4. Thus far, the synthesis of ecklonialactone B (4) has been reported by Fürstner's39 and Hieresemann's groups,38 both of which conducted excellent protecting group-free synthesis. Meanwhile, our laboratory has also reported the synthesis of marine oxylipins and has achieved the total synthesis of both hybridolactone40 and agarphylactone. Herein, we describe a novel total synthesis of eiseniachloride B (2) and ecklonialactone B (4) starting from optically active lactol 5, which was the intermediate of hybridolactone.40

**Results and Discussion**

Our synthesis began with the treatment of lactol 5 with EtMgBr in tetrahydrofuran (THF) to obtain diol 6 in 68% isolated yield and its C-16 epimer 7 (the numbering is based on the isolation paper of eiseniachloride B36) in isolated yields of 68 and 8%, respectively (Chart 1). The ring-closing metathesis of the diol 6 using a first-generation Grubbs catalyst cleanly generated trans-cyclopentene 8 in an 86% yield, followed by the selective protection of the primary hydroxy group with a tert-butylimethylsilyl (TBS) group that produced alcohol 9 in a 98% yield. The secondary alcohol 9 was then treated with tert-butylhydroperoxide (TBHP) in the presence of catalytic VO(acac), which led exclusively to α-epoxide 10 as a single diastereomer in a 90% yield. The stereochemical outcome can be rationalized in terms of the electrophilic reagents attacking the involved coordination of the hydroxy group at C-16 to the V5+/TBHP complex (Fig. 2).

Following the acylation of the α-epoxide 10 with methoxyacetyl chloride in pyridine to produce ester, desilylation was performed using tetra-n-butylammonium fluoride (TBAF) in THF/AcOH (20:1) for 2.5 h to selectively cleave the TBS group to produce ester 11 in a 91% yield over two steps (Chart 2). With the 11 in hand, the end result of our total synthesis could be investigated. Primary alcohol 11 was oxidized using...
Dess–Martin periodinane (DMP) before the corresponding aldehyde was treated with phosphonium ylide derived from 9-methoxy-9-oxononyltriphenylphosphonium bromide, LiHMDS, HMPA, THF, r.t., 60%.

Chart 2. Synthesis of Ecklonialactone B (4) and Eiseniachloride B (2)

Reagents and conditions: (a) TBSCl, Et3N, DMAP, CH2Cl2, r.t., 98%; (b) TBHP, VO(acac)2, CH2Cl2, r.t., 86%; (c) Grubbs 1st catalyst, CH2Cl2, room temperature (r.t.), 86%; (d) Dess–Martin periodinane (DMP) before the corresponding chlorine source following a number of trials. The treatment of ecklonialactone B (4) using hexachloroacetone and lithium hexamethyldisilazide (LiHMDS) in the presence of triphenylphosphine in CH2Cl2 for 5 min smoothly cleaved the oxirane to produce eiseniachloride B (2) in a 60% yield. We were highly satisfied to find that the spectroscopic data, which included 1H- and 13C-NMR spectra, IR spectrum, and high-resolution (HR) MS results, were identical to those previously reported for natural products. Furthermore, the optical rotations of synthetic 2 and 4, which were [α]D20 = −112.4 (c = 0.023, CHCl3) and [α]D20 = −44.2 (c = 0.24, CHCl3), agreed with those reported for natural eiseniachloride B ([α]D20 = −126 (c = 0.065, CHCl3))36) and ecklonialactone B ([α]D20 = −49.3 (c = 1.08, CHCl3)),37,38 respectively.

Conclusion

In conclusion, in this paper, a concise asymmetric total synthesis of eiseniachloride B (2) and ecklonialactone B (4) was achieved. Our synthetic strategy involved a face-selective epoxidation and Shina macrolactonization for the construction of 4-membered lactone. The synthesis of 2 was achieved in a 12.1% overall yield through a 11-step process starting from lactol 5.

Experimental

General Experimental Procedures Optical rotations were measured with a JASCO P-1030 polarimeter. IR spectra were recorded with a JASCO FT-IR/620 spectrometer. 1H- and 13C-NMR spectra were recorded on a Bruker Biospin AVANCE III HD 400 (400 MHz for 1H, 100 MHz for 13C) and a Bruker Biospin AVANCE III HD 500 (500 MHz for 1H, 125 MHz for 13C). The reported chemical shifts (δ) in parts per million (ppm) were relative to the internal CHCl3 (7.26 ppm for 1H and 77.0 ppm for 13C), the coupling constant (J) values were measured in hertz. The coupling patterns are denoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). HR-electrospray ionization (HR-ESI)-MS spectra were obtained using a Micromass LCT spectrometer with a time-of-flight (TOF) analyzer. Precoated silica gel plates with a fluorescent indicator (Merck 60 F254) were used for analytical and preparative TLC. Flash column chromatography was performed using Kanto Chemical silica gel 60N (spherical, natural) 40–50 µm. All reagents and solvents were of commercial quality and were used as received.

(2R,3R,4S)-3-Allyl-2-vinylhexane-1,4-diol (6) and (2R,3R,4R)-3-allyl-2-vinylhexane-1,4-diol (7) To a solution of lactol 5 (162 mg, 1.05 mmol) in THF (10.5 mL) was added ethylmagnesium bromide (1.01 M solution in THF, 3.10 mL, 3.13 mmol) at −78 °C. After stirring for 1 h at 0 °C, the reaction mixture was diluted with Et2O, washed with saturated aqueous NH4Cl solution, H2O and brine, and then concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/AcOEt = 3:1 to 1:1) to give diol 6 (131 mg, 68% yield) as a colorless oil and diol 7 (14.5 mg, 8% yield) as a colorless oil.

Diol 6: 1H-NMR (CDCl3, 400 MHz) δ: 5.88 (1H, m), 5.79 (1H, m), 5.22 (1H, s), 5.19 (1H, m), 5.08 (1H, m), 5.03 (1H, m), 3.63...
(2H, d, J = 6.7 Hz), 3.55 (1H, dt, J = 8.5, 4.6 Hz), 2.60 (1H, m), 2.29–2.12 (2H, m), 1.71 (1H, m), 1.69–1.45 (2H, m), 1.63 (1H, brs), 1.60 (1H, brs), 0.97 (3H, t, J = 7.4 Hz); 13C-NMR (CDCl3, 100 MHz) δ: 138.6 (CH), 137.7 (CH), 118.1 (CH), 116.4 (CH), 74.9 (CH), 64.0 (CH2), 46.8 (CH), 44.0 (CH), 32.4 (CH2), 28.1 (CH2), 10.6 (CH3); IR (neat) cm−1: 3304, 2976, 2933, 1639, 1051; low resolution (LRMS (ESI-TOF) m/z: 207 (M + Na)+; HRMS (ESI-TOF) m/z: 207.1356 (Calcd for C11H20O2Na: 207.1361); [α]D 25 +6.1 (c = 0.96, CHCl3).

Diol 7: 1H-NMR (CDCl3, 400 MHz) δ: 5.89–5.71 (2H, m), 5.19–5.00 (4H, m), 3.76–3.54 (3H, m), 2.58 (2H, brs), 2.44 (1H, m), 2.25–2.20 (2H, m), 1.71 (1H, m), 1.65–1.43 (2H, m), 0.95 (3H, t, J = 7.4 Hz); 13C-NMR (CDCl3, 100 MHz) δ: 139.0 (CH), 138.2 (CH), 117.1 (CH), 116.1 (CH2), 73.3 (CH), 62.9 (CH3), 46.6 (CH), 44.8 (CH), 31.1 (CH), 27.5 (CH2), 10.9 (CH3); IR (neat) cm−1: 3304, 2926, 2934, 1640, 1047; LRMS (ESI-TOF) m/z: 207 (M + Na)+; HRMS (ESI-TOF) m/z: 207.1355 (Calcd for C11H20O2Na: 207.1361); [α]D 25 +15.7 (c = 0.19, CHCl3).

(S)-1-(((1R,2R)-2-(Hydroxymethyl)cyclopent-3-en-1-yl)propan-1-ol (8) To a stirred solution of diol 6 (171 mg, 0.928 mmol) in CH2Cl2 (186 mL) was added Grubs 1st catalyst (38.2 mg, 0.0464 mmol). After stirring for 1 h, the reaction mixture was concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/AcOEt = 1:1) to give cyclopentane 8 (125 mg, 86% yield) as a colorless oil.

1H-NMR (CDCl3, 400 MHz) δ: 5.73 (1H, m), 5.47 (1H, m), 3.87 (1H, dd, J = 3.6, 10.0 Hz), 3.46 (1H, t, J = 7.8 Hz), 3.35 (1H, t, J = 10.0 Hz), 2.90–2.57 (2H, brs), 2.85 (1H, m), 2.51 (1H, m), 2.13–2.02 (2H, m), 1.66 (1H, m), 1.40 (1H, m), 1.00 (3H, t, J = 7.5 Hz); 13C-NMR (CDCl3, 100 MHz) δ: 130.8 (CH), 130.7 (CH), 76.6 (CH), 66.9 (CH), 53.5 (CH2), 50.6 (CH3), 28.5 (CH2), 9.5 (CH3); IR (neat) cm−1: 3304, 3052, 2961, 1463, 1077; LRMS (ESI-TOF) m/z: 179 (M + Na)+; HRMS (ESI-TOF) m/z: 179.1045 (Calcd for C10H16O3Na: 179.1048); [α]D 25 −80.8 (c = 0.18, CHCl3).

(S)-1-(((1R,2R)-2-(1(S)-(Butyldimethylsilyloxy)methyl)cyclopent-3-en-1-yl)propan-1-ol (9) To a stirred solution of diol 8 (746 mg, 4.78 mmol) in CH2Cl2 (4.80 mL) were added NaHCO3 (287 mg, 4.78 mmol) in CH2Cl2 (4.80 mL) were added NaHCO3 (287 mg, 4.78 mmol) and TBHP (5.29 M solution in CH2Cl2, 2.30 mL, 12.2 mmol) at r.t. After stirring for 2 h, dimethylsulfoxide (2.93 mL, 39.6 mmol) was added to the reaction mixture. After stirring 30 min, the mixture was filtered through silica gel and then concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/AcOEt = 8:1) to give epoxide 10 (1.02 g, 90% yield) as a colorless oil.

1H-NMR (CDCl3, 400 MHz) δ: 3.77 (1H, brs), 3.65 (1H, dd, J = 5.2, 10.0 Hz), 3.55 (1H, dd, J = 6.4, 10.0 Hz), 3.54 (1H, m), 3.47 (1H, d, J = 2.6 Hz), 3.33 (1H, m), 2.54 (1H, dt, J = 1.7, 6.5 Hz), 2.20 (1H, ddd, J = 1.2, 10.9, 14.4 Hz), 2.11 (1H, m), 1.95 (1H, d, J = 14.4 Hz), 1.45 (1H, m), 1.35 (1H, m), 0.92 (3H, t, J = 7.6 Hz), 0.89 (9H, s), 0.06 (6H, s); 13C-NMR (CDCl3, 100 MHz) δ: 75.4 (CH), 64.2 (CH2), 61.8 (CH), 59.3 (CH), 43.7 (CH2), 42.6 (CH), 33.4 (CH2), 29.3 (CH3), 25.8 (CH2)×3, 18.1 (C), 10.5 (CH3), −5.5 (CH3), −5.6 (CH2); IR (neat) cm−1: 3434, 2956, 2929, 1472, 1257, 1105; LRMS (ESI-TOF) m/z: 309 (M + Na)+; HRMS (ESI-TOF) m/z: 309.1855 (Calcd for C15H18O2SiNa: 309.1862); [α]D 25 −25.5 (c = 0.09, CHCl3).

1H-NMR (CDCl3, 400 MHz) δ: 4.85 (1H, d, J = 3.3, 8.2 Hz), 4.06 (1H, d, J = 16.3 Hz), 4.02 (1H, d, J = 16.3 Hz), 3.64–3.56 (2H, m), 3.48 (1H, m), 3.46 (3H, s), 3.42 (1H, m), 2.27–2.16 (2H, m), 1.99 (1H, m), 1.89 (1H, dd, J = 2.9, 15.0 Hz), 1.72 (1H, m), 1.49 (1H, m), 0.85 (3H, t, J = 7.4 Hz); 13C-NMR (CDCl3, 100 MHz) δ: 169.9 (C), 79.4 (CH), 70.0 (CH2), 63.6 (CH3), 60.4 (CH), 59.4 (CH2), 58.4 (CH2), 45.2 (CH3), 43.3 (CH2), 29.8 (CH3), 25.2 (CH2), 9.2 (CH3); IR (neat) cm−1: 3461, 2937, 1747, 1196, 1128; LRMS (ESI-TOF) m/z: 267 (M + Na)+; HRMS (ESI-TOF) m/z: 267.1198 (Calcd for C13H20O2Na: 267.1208); [α]D 25 −71.1 (c = 0.38, CHCl3).

3-Ethyl-1a,2a,3R,5S,5a-6-oxabicyclo[3.1.0]hex-3-ylpropan-1-ol (10) To a stirred solution of silyl ether 9 (1.07 g, 3.96 mmol) in CH2Cl2 (19.8 mL) were added VO(acac)2 (210 mg, 0.792 mmol) and TBHP (5.29 M solution in CH2Cl2, 2.30 mL, 12.2 mmol) at r.t. After stirring for 2 h, dimethylsulfoxide (2.93 mL, 39.6 mmol) was added to the reaction mixture. After stirring 30 min, the mixture was filtered through silica gel and then concentrated in vacuo. To a stirred suspension of 9-methoxy-9-oxononyltriphenylphosphonium bromide (2.11 g, 4.11 mmol) in THF (10.0 mL)
were added LiHMDS (1.00 M solution in THF, 3.80 mL, 3.80 mmol) and HMPA (1.20 mL, 6.90 mmol) dropwise at 0°C and the resulting mixture was stirred for 30 min at same temperature. The mixture was cooled to −78°C. A solution of the above crude product in THF (3.40 mL) was then added to the mixture. After stirring for 14 h at r.t., the reaction mixture was diluted with Et2O, washed with saturated aqueous NH4Cl solution, H2O and brine, dried over anhydrous Na2SO4, and then concentrated in vacuo. The residue was passed through a pad of silica gel (hexane/AcOEt = 4:1) and then concentrated in vacuo to give a crude product.

To a stirred solution of the crude ester in THF (4.00 mL) was added LiOH (2.00 M solution in H2O, 20.0 mL, 40.0 mmol) at r.t. After stirring for 18 h, the mixture was acidified with HCl (2.00 M solution in H2O). Extracted with CHCl3, washed with brine, dried over anhydrous Na2SO4, and then concentrated in vacuo to give a crude product.

To a stirred solution of MNBA (136 mg, 0.395 mmol) and DMAP (96.8 mg, 0.792 mmol) in CH2Cl2 (49.0 mL) was added tritiated (CH2), 26.8 (CH2), 26.3 (CH2), 25.40 (CH2), 25.39 (CH2), 25.3 (CH3), 24.2 (CH3), 8.8 (CH3); IR (KBr) cm−1: 3442, 2926, 2857, 1731, 1460, 1335; LRMS (ESI-TOF) m/z: 351 (M + Na+)2; HRMS (ESI-TOF) m/z: 351.1696 (Calcd for C18H25ClO3Na: 351.1703); [α]D20 = −112.4 (c = 0.23, CHCl3).

**Conflict of Interest** The authors declare no conflict of interest.

**Supplementary Materials** The online version of this article contains supplementary materials.

**References and Notes**

1) Gerwick W. H., Singh I. P., “Lipid Biotechnology,” ed. by Gardner H. W., Kao T. M., Marcel and Dekker, New York, 2002, pp. 249–275.
2) Andreou A., Brodhun F., Feussner L., Prog. Lipid Res., 48, 148–170 (2009).
3) Cutignano A., Lamari N., d’ipollo G., Manzo E., Cimino G., Fontana A., J. Phycol., 47, 233–243 (2011).
4) Ibáñez E., Herrero M., Mendiola J. A., Castro-Puyama M., “Marine Bioactive Compounds: Sources, Characterization and Applications,” ed. by Hayes M., Springer U.S., New York, 2012, pp. 55–98.
5) Higgs M. D., Mulleirn L. J., Tetrahedron, 37, 4295–4262 (1981).
6) Corey E. J., De B., Ponder J. W., Berg J. M., Tetrahedron Lett., 25, 1015–1018 (1984).
7) Nagle D. G., Gerwick W. H., Tetrahedron Lett., 31, 2995–2998 (1990).
8) Proteau P. J., Gerwick W. H., Tetrahedron Lett., 33, 4393–4396 (1992).
9) Todd J. S., Proteau P. J., Gerwick W. H., Tetrahedron Lett., 34, 7689–7692 (1993).
10) Nagle D. G., Gerwick W. H., J. Org. Chem., 59, 7227–7237 (1994).
11) Proteau P. J., Rossi J. V., Gerwick W. H., J. Nat. Prod., 57, 1717–1719 (1994).
12) See Y., Cho K. W., Rho J.-R., Shin J., Kwon B.-M., Bok S.-H., Song J.-Y., Tetrahedron, 52, 10583–10596 (1996).
13) Graber M. A., Gerwick W. H., Cheney D. P., Tetrahedron Lett., 37, 4635–4638 (1996).
14) Choi H., Proteau P. J., Byrum T., Gerwick W. H., Phytochemistry, 73, 134–141 (2012).
15) Bouarab K., Adas F., Gaquerel E., Klaareg B., Salain J.-P., Potin P., Plant Physiol., 135, 1838–1848 (2004).
16) Lion U., Wiesemeier T., Weinberger F., Beltrán J., Flores V., Faugeron S., Correa J., Pohnert G., ChemBioChem, 7, 457–462 (2006).
17) Gaquerel E., Hervé C., Labrière C., Boyen C., Potin P., Salain J.-P., Biochem. Biophys. Acta, 1771, 565–575 (2007).
18) Contreras L., Mella D., Moenne A., Correa J. A., Aquat. Toxicol., 94, 94–102 (2009).
19) Kumar M., Gupta V., Trivedi N., Kumari P., Bijo A. J., Reddy C. R., J. Nat. Prod., 7689–7692 (1993).
20) Critcher D. J., Connolly S., Wills M., Tetrahedron Lett., 36, 3763–3766 (1995).
21) Miyaoka H., Shigemoto T., Yamada Y., J. Nat. Prod., 57, 1717–1719 (1994).
22) Miyaoka H., Tamura M., Yamada Y., Tetrahedron, 56, 8083–8094 (1999).
23) Miyaoka H., Shigemoto T., Yamada Y., Heterocycles, 47, 415–428 (1998).
24) Varadarajan S., Mohapatra D. K., Datta A., Tetrahedron Lett., 39, 1075–1078 (1998).
25) Miyaoka H., Shigemoto T., Yamada Y., Tetrahedron, 56, 8083–8094 (1999).
26) Pietruszka J., Wilhelm T., *Synlett*, **2003**, 1698–1700 (2003).
27) Miyaoka H., Hara Y., Shinohara I., Kurokawa T., Yamada Y., *Tetrahedron Lett.*, **46**, 7945–7949 (2005).
28) Pietruszka J., Rieche A. C. M., Schöne N., *Synlett*, **2007**, 2525–2528 (2007).
29) Wang Q., Millet A., Hiersemann M., *Synlett*, **2007**, 1683–1686 (2007).
30) White J. D., Lincoln C. M., Yang J., Martin W. H. C., Chan D. B., *J. Org. Chem.*, **73**, 4139–4150 (2008).
31) Miyaoka H., Hara Y., Shinohara I., Kurokawa T., Kawashima E., Yamada Y., *Heterocycles*, **77**, 1185–1208 (2009).
32) Bishop M., Doum V., Nordschild A. C. M., Pietruszka J., Sandkuhl D., *Synthesis*, **2010**, 527–537 (2010).
33) Becker J., Butt L., von Kiedrowski V., Mischler E., Quentin F., Hiersemann M., *Org. Lett.*, **15**, 5982–5985 (2013).
34) Yassen A. S. A., Ishihara J., Hatakeyama S., *Heterocycles*, **94**, 59–63 (2017).
35) Yalla R., Raghavan S., *Org. Biomol. Chem.*, **17**, 4572–4592 (2019).
36) Kousaka K., Ogi N., Akazawa Y., Fujieda M., Yamamoto Y., Takada Y., Kimura J., *J. Nat. Prod.*, **66**, 1318–1323 (2003).
37) Kurata K., Taniguchi K., Shiraishi K., Hayama N., Tanaka I., Suzuki M., *Chem. Lett.*, **18**, 267–270 (1989).
38) Todd J. S., Proteau P. J., Gerwick W. H., *J. Nat. Prod.*, **57**, 171–174 (1994).
39) Hickmann V., Kondoh A., Gabor B., Alcarazo M., Fürstner A., *J. Am. Chem. Soc.*, **133**, 13471–13480 (2011).
40) Ota K., Sugata N., Ohshiro Y., Kawashima E., Miyaoka H., *Chem. Eur. J.*, **18**, 13531–13537 (2012).
41) The enantiomeric purity was determined to be 90%ee by 'H-NMR analysis, see ref. 40.
42) Diol 6 was correlated to the known TBS ether by a three-step conversion (i. Ac₂O, pyridine; ii. TBSCl, Et₃N, DMAP, CH₂Cl₂; iii. K₂CO₃, MeOH), confirming its stereostructures, see ref. 33.
43) Schwab P., France M. B., Ziller J. W., Grubbs R. H., *Angew. Chem. Int. Ed. Engl.*, **34**, 2039–2041 (1995).
44) Epoxide 10 was correlated to the known benzyl ether by a four-step conversion (i. Ac₂O, pyridine; ii. TBAF, THF; iii. BnBr, NaH, THF; iv. K₂CO₃, MeOH), confirming its stereostructures, see ref. 29.
45) Matikainen J., Kaltia S., Ala-Peijari M., Petit-Gras N., Harju K., Heikkila J., Yksijarvi R., Hase T., *Tetrahedron*, **59**, 567–573 (2003).
46) Wang Y., Soper D. L., Dirr M. J., DeLong M. A., De B., Wos J. A., *Chem. Pharm. Bull.*, **48**, 1332–1337 (2000).
47) Shiina I., Ibuka R., Kubota M., *Chem. Lett.*, **31**, 286–287 (2002).