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Collective Total Synthesis of Ecklonialactones, Eiseniachlorides and Analogs

Alexandre Guy,^[a] Shanice Delly,^[a] Jean-Marie Galano,^[a] Thierry Durand,^[a] and Camille Oger^{*[a]}

Ecklonialactones, Eiseniachlorides, and Egregiachlorides are synthesized in living organisms via the lipoxygenase-mediated oxidation of polyunsaturated fatty acids. Originally isolated and identified from brown seaweed (*Ecklonia stolonifera*, *Eisenia bicyclis*, and *Egrecia menziesii*), and later replicated on milligram scale through chemical synthesis, the full biological activities of these compounds remain to be elucidated. To

bridge this gap in knowledge, we propose a unified methodology to synthesize the 14-membered macrocyclic structures of Ecklonialactones, Eiseniachlorides and analogs using a versatile and convergent approach. This study delineates the synthesis of Ecklonialactone A, B, C, D, and Eiseniachlorides A and B, as well as *ent*-Ecklonialactone B, 16-*epi*-Ecklonialactone B and 12,13-*diepi*-Ecklonialactone B.

Introduction

A diverse array of bioactive compounds has been isolated from algae, encompassing both saturated and unsaturated fatty acids. Notably, the metabolism of polyunsaturated fatty acids (PUFAs) yields oxygenated derivatives known as oxylipins, primarily catalyzed by enzymes, such as lipoxygenases.^[1] This process generates a plethora of structures, contingent upon the parent PUFA and the biosynthetic pathways involved. Ecklonialactones and Eiseniachloride were sourced from various red and brown macroalgae and identified by research groups led by Higgs,^[2] Gerwick,^[3–8] Kurata,^[9,10] and Kimura.^[11] The first Ecklonialactone compounds, originating from the laminariaceous brown alga *Ecklonia stolonifera* Okamura, were unearthed in 1989 by Kurata *et al.*, and named Ecklonialactone B (1) and A (2) (Figure 1).^[9] Subsequently, Ecklonialactones C, D, E, and F were also discovered by the same group, still sourced from *Ecklonia stolonifera* (Figure 1, 3–6).^[10] A year following Kurata *et al.*, the Gerwick group reported finding Ecklonialactones A, B, and E in *Egrecia menziesii* algae.^[6] Furthermore, the Kimura group discovered Ecklonialactones A, C, D, and F in the *Eisenia bicyclis* algae. Alongside, they identified five halogenated (chlorine and iodine) compounds closely related to Ecklonialactones in structure, along with four other oxylipins.^[11] These newly discovered halogenated compounds were named Eiseniachlorides (X=Cl) and Eiseniaiodides (X=I), in reference to the parent alga (see 7–9, Figure 1). Other marine oxylipins have also been isolated from algae.^[1] Egregiachlorides, found in *Egrecia*

menziesii, lack a macrocycle but still contain a chlorine atom (see 10, 12 and 13 in Figure 1).^[7] Moreover, Plasmodiophorols (Figure 1, see 11 and 14) gained attention in 2021,^[12] and their formation was attributed to the hydroperoxide bicyclase CYP50918 A1 of *Plasmodiophora brassicae* (Rhizaria, SAR). To date, few total syntheses of the marine oxylipins mentioned above have been documented. Ecklonialactone B (1) has been synthesized by three research groups: Fürstner, Hiersemann, and Ota and Miyaoka, along with their collaborators.^[13–15] Also, Hatakeyama's team synthesized Ecklonialactone B while synthesizing the 9,10-dihydro-Ecklonialactone B, although they obtained a mixture of *Z/E* isomers.^[16] Additionally, Fürstner's group also prepared Ecklonialactone A (2). It's noteworthy that Prof. Fürstner's team observed the spontaneous opening of the oxirane ring in Ecklonialactone A when left in the NMR tube, dissolved in non-distilled and non-anhydrous CDCl₃, resulting in the formation of the Eiseniachloride A structure.^[13] However, to date, only one consciously prepared Eiseniachloride structure has been reported by Ota *et al.*,^[14] namely Eiseniachloride B. Finally, similar to Hatakeyama's method, Hiersemann's group conducted a final catalytic hydrogenation of Ecklonialactone B to obtain its saturated analog, the 9,10-dihydro-Ecklonialactone B.^[15] Despite the discovery and characterization of these compounds over thirty years ago, and the advancements in chemical syntheses, it seems that their biological activities have been relatively underexplored. However, the Kimura group reported an interesting preliminary study indicating that isolated Ecklonialactone A (2), Eiseniachloride A (13Cl-8), Eiseniachloride B (13Cl-7), Eiseniachloride C (15Cl-9), and Egregiachloride A (16Cl-12) may exhibit antibacterial activities against *Staphylococcus aureus* and *Bacillus subtilis*.^[11]

Undoubtedly, these compounds hold great promise, warranting thorough biological activity testing. Consequently, in recent years, our group has dedicated significant efforts to devising convergent and adaptable strategies aimed at accessing marine oxylipins for the purpose of investigating their biological activity.

[a] Dr. A. Guy, S. Delly, Dr. J.-M. Galano, Dr. T. Durand, Dr. C. Oger
Institut des Biomolécules Max Mousseron, IBMM, Université de Montpellier,
CNRS, ENSCM. 1919 route de Mende, 34293 Montpellier, France
E-mail: camille.oger@umontpellier.fr

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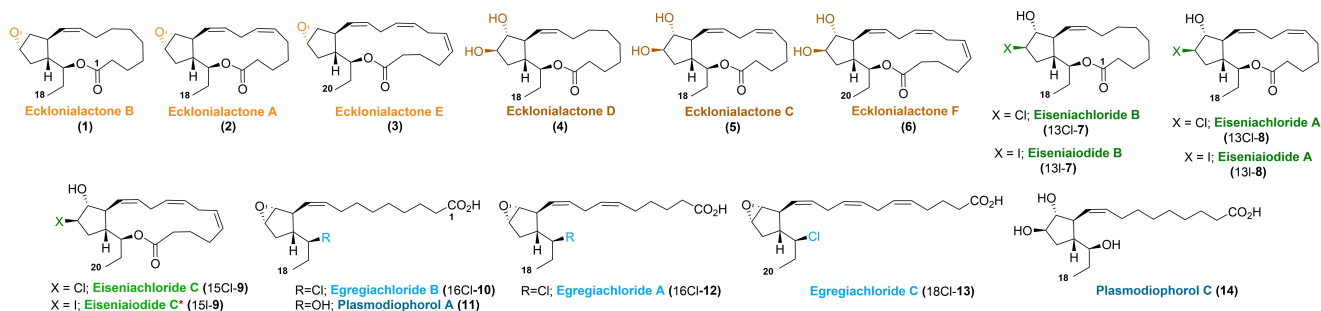


Figure 1. Structures of Ecklonialactones, Eiseniachlorides and iodides, Egregiachlorides and Plasmodiophorols. * Supposed structure.

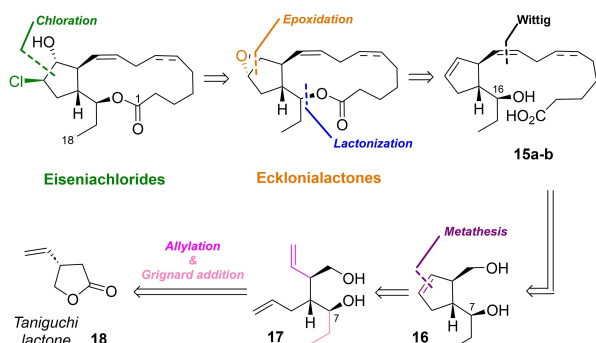
Results and Discussion

Retrosynthetic Approach

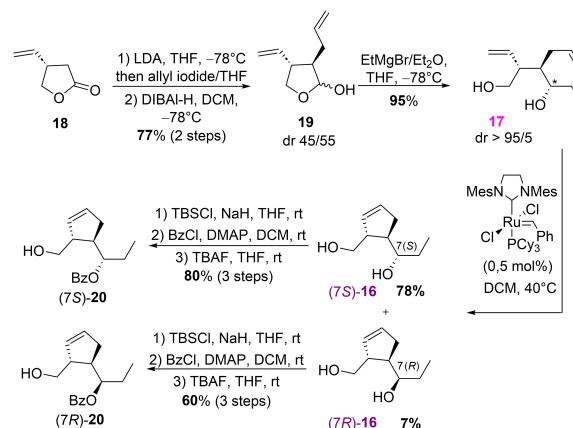
The formation of Eiseniachlorides might come from the derivation from Ecklonialactones via a nucleophilic attack of a chlorinated atom on the epoxide of Ecklonialactones (Scheme 1). Then, a lactonization step might be employed to close the macrocycle prior to epoxidation, enabling access to the initial targets, the Ecklonialactones. The diversity of lateral chain structures (intermediates **15a–b**) as well as the (*Z*)-selectivity of the double bond in the α -position of the five-membered ring will be achieved through Wittig reactions, using appropriate phosphonium salts. The strategy will proceed through a common intermediate (**16**), which possesses the *trans*-configured cyclopentene and two hydroxyl groups. Finally, this main intermediate will be derived from diene **17**, obtained from Taniguchi lactone **18** after allylation and addition of ethyl-Grignard. It is worth noting that the enantiomer of Taniguchi lactone (*ent*-**18**) can also be prepared, thereby facilitating the synthesis of both enantiomers of the Ecklonialactones.

Common intermediates

The synthetic pathway to intermediate **16** starts with Taniguchi lactone **18** (Scheme 2). Both (*R*)- and (*S*)-configured lactones



Scheme 1. Retrosynthetic plan toward Eiseniachlorides and Ecklonialactones.



Scheme 2. Synthesis of common intermediates (7S)-20 and (7R)-20.

were obtained using the well-established two-step procedure outlined by von Kieseritzky *et al.*^[17] Starting from Taniguchi lactone **18** (ee > 99%), the initial step involves a stereocontrolled α -allylation of the lactone utilizing allyl iodide and lithium diisopropylamide (LDA), and yielding the sole *anti*-stereoisomer in 90%. Subsequently, the lactone was reduced efficiently (85% yield) using the DIBAL-H at low temperature, accessing a mixture of anomers in an almost 1:1 ratio. The addition of ethylmagnesium bromide at low temperature gave diol **17** with excellent stereocontrol (dr > 95/5) and yield (95%). At this stage, the first lateral and the diene required for the ring-closing metathesis (RCM) are introduced. Thus, the RCM was performed using Grubbs II catalyst at 40 °C. Thanks to the constraint imposed by the cyclopentene ring, the stereoisomers could be separated by silica gel chromatography, resulting in the major compound (7S)-**16** being obtained in 78% yield and its minor counterpart (7R)-**16** in 7% yield. It is notable that (7R)-**16** was obtained as crystal and its structure was thus confirmed by X-ray analysis^[18] (see Supporting Information).

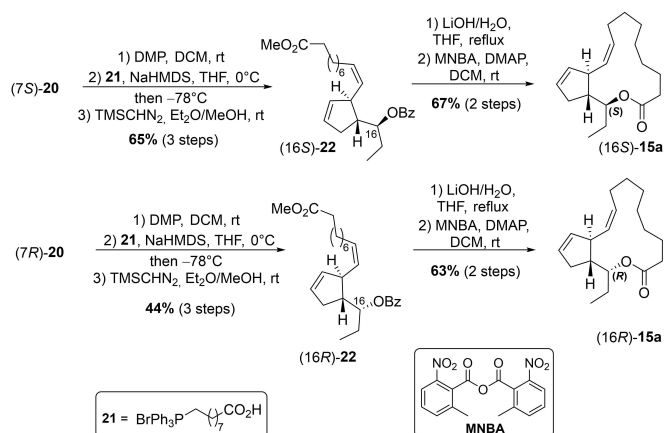
At this juncture, a protection/deprotection sequence was performed to obtain free alcohols (7S)-**20** and (7R)-**20**.

Synthesis of Ecklonialactones A, Ecklonialactone B and its C16-epimer, C12,13-diepimer, ent-Ecklonialactone B, Ecklonialactones C and D

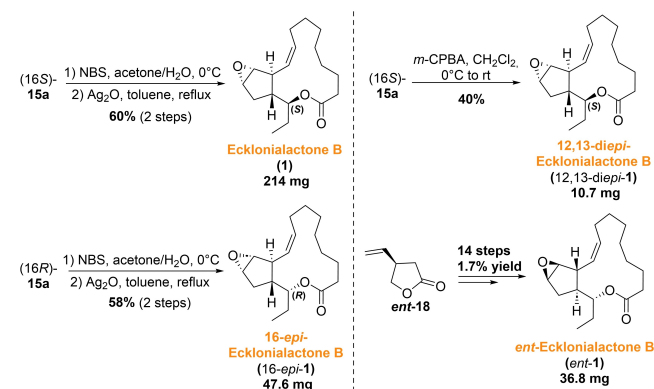
With the crucial chiral intermediates in hands, we proceeded towards the assembly of the targeted Ecklonialactones, with a first focus on Ecklonialactone B and analogs.

Synthesis of the B-series of Ecklonialactones

First, the oxidation of the free hydroxyl group of alcohols (7S)-20 and (7R)-20 were accomplished using Dess-Martin periodinane reagent, and followed by Wittig reactions using prepared (8-carboxyoctyl)triphenyl-phosphonium bromide 21 (see Supporting Information) and NaHMDS as a base (Scheme 3). It should be noted that for purification purposes, the acid functionality was methylated using trimethylsilyl-diazomethane. The coupling compounds (16S)-22 and (16R)-22 were obtained in good yields, ranging from 44 to 65% over three steps, with an excellent stereocontrol of the double bond (only the (Z)-isomer visible by NMR). With the α -chain in place, the protecting groups were removed under basic conditions to



Scheme 3. Preparation of dienes (16S)-15a, (16R)-15a.



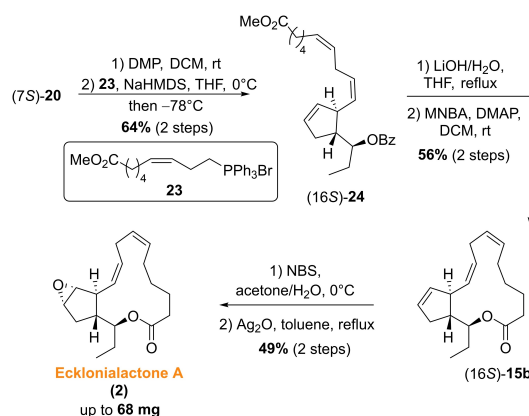
Scheme 4. Synthesis of Ecklonialactone B (1), its C16-epimer (16-epi-1), 12,13-diepi-Ecklonialactone B (12,13-diepi-1) and ent-Ecklonialactone B (ent-1)

expose the functionalities necessary for lactonization.^[19] It is worth noting that for this step, the hydroxy-acids were added to the MNBA/DMAP mixture using a syringe pump over a period of 40 hours, followed by further agitation for two additional hours to ensure completion. Both macrolactones (16S)-15a and (16R)-15a were obtained in yields of 67% and 63%, respectively, over these two steps.

Once these compounds were obtained, the final chemo- and stereoselective epoxidation was conducted. Leveraging previous studies,^{[15][16]} the epoxidation was carried out in two steps (Scheme 4), starting with the formation of bromohydrin intermediates and subsequent nucleophilic substitutions using silver (I) oxide. This resulted in the synthesis of Ecklonialactone B (1), as well as its C16-epimer 16-epi-1, in yields of 60% and 58%, respectively. The use of *m*-CPBA afforded the 12,13-diepi-Ecklonialactone B (12,13-diepi-1) with a moderate yield of 40% (not optimized). As mentioned earlier, thanks to the preparation of (*R*)-Taniguchi lactone (*ent*-18), the *ent*-Ecklonialactone B (*ent*-1) was accessible using the same strategy, maintaining consistent stereocontrol for each stereogenic center. This synthesis was achieved in 14 steps with 1.7% overall yield, corresponding to an average yield of 75% per step.

Synthesis of Ecklonialactone A

Starting from intermediate (7S)-20 the synthesis of Ecklonialactone A was accomplished using the same strategy, albeit employing phosphonium salt 23^[20] (see Supporting Information). Thus, starting from intermediate (7S)-20, the synthesis of Ecklonialactone A was completed in six additional steps (Scheme 5). These steps included Dess-Martin oxidation and Wittig reaction, saponification, and macrolactonization, using the same conditions as for Ecklonialactone B. Finally, the two-step stereo- and chemoselective epoxidation was executed. As a result, Ecklonialactone A (2) was obtained with an overall yield of 17.6% (from intermediate (7S)-20). It is noteworthy that the yield of the final two steps is lower in the last synthesis. Considering that the structure of this oxylipin contains an additional unsaturation on the side chain, the chemoselectivity



Scheme 5. Synthesis of Ecklonialactone A (2)

of the epoxidation is affected, primarily influencing the formation of the bromohydrin, resulting in the formation of diepoxide compounds.

Synthesis of Ecklonialactone C and D

In 1994, the Gerwick group conducted research aimed at determining the absolute configuration of Ecklonialactones.^[6] Perchloric acid (HClO₄) was used to open the epoxide of Ecklonialactone A (2) and to produce the *anti*-diol of Ecklonialactone C (5). Also, the same conditions were applied in this work to Ecklonialactones B (1) and A (2), resulting in the structures of Ecklonialactones D (4) and C (5) being obtained with yields of 23% and 41%, respectively (Scheme 6).

Synthesis of Eiseniachlorides A and B

During our research, Ota and Miyaoka synthesized Eiseniachloride A from Ecklonialactone A, using hexachloroacetone as chlorine source in the presence of triphenylphosphine.^[14] Consequently, we tested the same conditions on Ecklonialactones B and A, and successfully yielded the desired Eiseniachlorides (Scheme 7).

The regioselectivity of the opening of oxirane (1) was high (9/1 ratio) and both regioisomers were separable by chromatography. Eiseniachloride B (13Cl-7) and the 12-chloro-Eiseniachloride B (12Cl-25) were therefore obtained in 83% and 10% yield respectively. In the case of Eiseniachloride A, the chlorination

exhibited even better regioselectivity, primarily yielding Eiseniachloride A (13Cl-8) in 87% yield. Only a small amount of its C12-chlorinated isomer (12Cl-26) was obtained after purification.

Conclusions

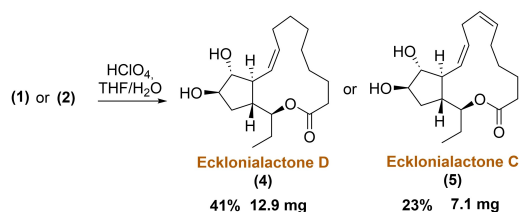
The total synthesis of ten macrocyclic oxylipins was achieved using a unique strategy. Natural Ecklonialactones A, B, C, and D, along with Eiseniachlorides A and B, were successfully synthesized. Additionally, analogs, such as the 16-*epi*-Ecklonialactone B, the C12,13-di-*epimer* of Ecklonialactone B and *ent*-Ecklonialactone B, as well as regioisomers like 12-chloro-Eiseniachloride B were obtained. The strategy permits to access macrocyclic oxylipins from the family of Ecklonialactones and Eiseniachlorides, as well as analogs, in 13 to maximum 15 steps depending on the structure. The natural oxylipins, namely Ecklonialactones A, B, C, D and Eiseniachlorides A and B were obtained with very good yields, ranging from 70% to 86% per steps of synthesis, as well as the analogs such as the 16-*epi*-Ecklonialactone B, the *diepi*-Ecklonialactone B, the *ent*-Ecklonialactone B, and the 12-chloro-Eiseniachloride B (e.g., 67%, 84%, 75%, and 75% respectively). Importantly, thanks to the efficiency of the strategy, significant amounts of these oxylipins were obtained, ranging from 5.6 mg up to 210 mg, which would facilitate their use in biological assays.

Supporting Information

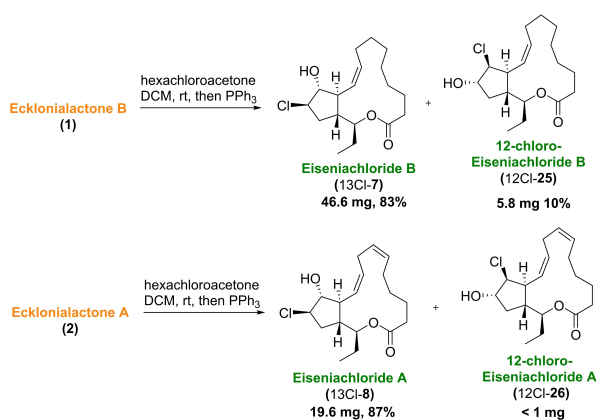
The authors have cited additional references within the Supporting Information.^[21–26] The final step of synthesis for the Ecklonialactones A, B, C, D and Eiseniachlorides A and B, including the full characterizations are described here. Additional syntheses are shown in the Supporting Information.

General Details

All reactions requiring anhydrous conditions were conducted in dry glassware (oven 120 °C) with magnetic stirring under an atmosphere of nitrogen unless otherwise mentioned. Unless otherwise mentioned, all solvents used for reactions were anhydrous. All anhydrous solvents and reagents were dried following standard methods under a nitrogen or argon atmosphere or used as obtained from suppliers (Aldrich, Thermo Fischer). Reactions were monitored by TLC using plates precoated with silica gel 60 with fluorescent indicator 254 nm (Merck). Reaction components were visualized using a 254 nm UV lamp or treatment with acidic *p*-anisaldehyde stain followed by gentle heating. Column chromatography was performed using silica gel 40–63 μm Macherey-Nagel or spherical silica gel Puriflash Si60, 30 μm, Interchim or Advision. Some compounds were purified on Buchi Reveleris apparatus using prepacked columns. Pentane (P), Et₂O, EtOAc, MeOH, CH₂Cl₂, were used for chromatographic separations. Optical rotations were recorded on JASCO P2000-series apparatus are given in 10⁻¹ deg.cm².g⁻¹. The concentrations *c* for the optical rotation data are given in g.cm⁻³. Infrared spectra were taken on a Spectrum one or three (Perkin Elmer) as neat samples using an ATR device and



Scheme 6. Synthesis of Ecklonialactones C (4) and D (5)



Scheme 7. Synthesis of Eiseniachloride B (13Cl-7), 12-chloro-Eiseniachloride B (12Cl-25), and Eiseniachloride A (13Cl-8)

absorptions are given in wave numbers (cm^{-1}). MS (ESI) and high-resolution MS (HRMS) spectra were measured on a Q-ToF micro spectrometer (resolution 100000, Waters) or on mass spectrometers Synapt G2-S (Waters) or Orbitrap ID-X (Waters). Data were obtained by positive or negative electrospray ionization methods between 100 and 1500 Da by direct introduction. NMR spectra were recorded on Bruker AMX400 or Bruker Avance III 500 MHz or 600 MHz (cryoprobe) spectrometers in CDCl_3 or CD_3OD . ^1H NMR chemical shifts were provided in ppm using internal reference at $\delta = 7.26$ ppm for CDCl_3 and $\delta = 3.31$ ppm for CD_3OD and are reported as follow: chemical shift in ppm [multiplicity, coupling constant(s) J in Hz, relative integral, attribution]. The multiplicities are defined as follow: br=broad, m=multiplet, s=singlet, d=doublet, t=triplet, q=quadruplet, quint=quintuplet or combinations thereof. ^{13}C NMR chemical shifts were referenced against the residual solvent central peak ($\delta = 77.16$ ppm for CDCl_3 and $\delta = 49.0$ ppm for CD_3OD). The connectivity was determined by ^1H - ^1H COSY experiments; carbons were assigned according to HSQC and HMBC NMR experiments. The carbon and hydrogen numbering refers to the molecule drawn on the NMR spectra and not on the IUPAC numbering (see inside the Supporting Information). Enantiomeric Excess were determined using chiral HPLC Shimadzu Prominence UFLC and appropriate chiral column and solvents spectra (see inside the Supporting Information). Crystal evaluation and data collection were performed on a Bruker Venture diffractometer with a Cu-K α microsource and equipped with a Photon-II detector.

Preparation of (1aS,2aR,3S,14aS,14bR,Z)-3-ethyl-1 a,2 a,3,6,7,8,9,10,11,12,14 a,14 b-dodecahydrooxireno[2',3':3,4]cyclopenta[1,2-c][1]oxacyclotetradecin-5(2H)-one - Ecklonialactone B (1)

The mixture of bromhydrines (316 mg, 0.846 mmol, 1 equiv.) was dissolved in anhydrous toluene (40 mL) at room temperature. Silver (I) oxide (590 mg, 2.54 mmol, 3 equiv.) was added in one portion. The solution was strictly purged with nitrogen (3 cycles vacuum/ N_2) and refluxed 4 hours with a vigorous stirring. After cooling to room temperature, the solvent was removed under reduced pressure. The crude was adsorbed on silica and purified through silica gel column chromatography using 50 mL of silica gel and a gradient of pentane/ Et_2O , from 95/5 to 80/20, to give the Ecklonialactone B (1) (214 mg, 0.732 mmol, 86%) as a white solid. Rf=0.43 (cyclohexane/ethyl acetate : 3/1); mp = 70–72 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 1721 (C=O); HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{29}\text{O}_3$ 293.21112 $[\text{M} + \text{H}]^+$; found 293.21115; $[\alpha]_{\text{D}}^{20} = -39.7$ (c 0.01 in CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 5.54–5.42 (m, 1H, H_9), 5.16–5.06 (m, 1H, H_{10}), 5.03–4.90 (m, 1H, H_{16}), 3.49 (d, $^3J_{\text{H,H}} = 2.8$ Hz, 1H, H_{13}), 3.24 (d, $^3J_{\text{H,H}} = 2.7$ Hz, 1H, H_{12}), 3.02 (d, $^3J_{\text{H,H}} = 9.7$ Hz, 1H, H_{11}), 2.46–2.31 (m, 2H, H_2), 2.12–2.01 (m, 2H, H_8), 1.96–1.79 (m, 4H, H_3 , H_{14} , H_{15}), 1.71 (dtd, $^2J_{\text{H,H}} = 14.8$, $^3J_{\text{H,H}} = 7.4$, 3.1 Hz, 1H, H_{17}), 1.62–1.52 (m, 1H, H_3), 1.52–1.26 (m, 9H, H_4 , H_5 , H_6 , H_7 , H_{17}), 0.81 (t, $^3J_{\text{H,H}} = 7.4$ Hz, 3H, H_{18}); ^{13}C NMR (101 MHz, CDCl_3) δ 174.1 (C_1), 132.1 (C_{10}), 128.5 (C_9), 78.8 (C_{16}), 61.2 (C_{12}), 57.3 (C_{13}), 46.6 (C_{15}), 40.2 (C_{11}), 33.7 (C_2), 29.0 (C_{14}), 27.0 (2 C, C_4 or C_5 or C_6), 26.5 (C_7), 25.5 (2 C, C_{17} and C_4 or C_5 or C_6), 25.4 (C_8), 24.4 (C_3), 8.9 (C_{18}).

Preparation of (1aS,2aR,3S,10Z,13Z,14aR,14bR)-3-ethyl-1a,2a,3,6,7,8,9,12,14a,14b-decahydrooxireno[2',3':3,4]cyclopenta[1,2-c][1]oxacyclotetradecin-5(2H)-one - Ecklonialactone A (2)

The mixture of bromhydrines (99 mg, 0.266 mmol, 1 equiv.) was dissolved in anhydrous toluene (25 mL) at room temperature. Silver (I) oxide (185 mg, 0.799 mmol, 3 equiv.) was added in one portion. The solution was strictly purged with nitrogen (3 cycles vacuum/ N_2)

prior to refluxed for 2 hours with vigorous stirring. After cooling to room temperature, the solvent was removed under reduced pressure. The crude was adsorbed on silica and purified through silica gel column chromatography using 10 mL of silica gel and a gradient of pentane/ Et_2O , from 95/5 to 80/20, to give the Ecklonialactone A (2) (68.0 mg, 0.234 mmol, 88%) as a white solid. Rf=0.39 (cyclohexane/ethyl acetate : 3/1); mp = 90–93 °C; IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 1714 (C=O); HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{27}\text{O}_3$ 291.1961 $[\text{M} + \text{H}]^+$; found 291.1955; $[\alpha]_{\text{D}}^{20} = -94.7$ (c 0.01 in CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 5.55–5.37 (m, 3H, H_6 , H_7 , H_9), 5.13–5.04 (m, 1H, H_{10}), 4.95–4.85 (m, 1H, H_{16}), 3.49 (d, $^3J_{\text{H,H}} = 2.5$ Hz, 1H, H_{13}), 3.22 (d, $^3J_{\text{H,H}} = 2.5$ Hz, 1H, H_{12}), 3.16–3.04 (m, 2H, H_8 , H_{11}), 2.72–2.60 (m, 1H, H_8), 2.48–2.29 (m, 2H, H_2), 2.12–1.83 (m, 5H, H_3 , H_{14} , H_{15}), 1.83–1.65 (m, 3H, H_3 , H_{17}), 1.51–1.34 (m, 3H, H_4 , H_{17}), 0.80 (t, $^3J_{\text{H,H}} = 7.4$ Hz, 3H, H_{18}); ^{13}C NMR (101 MHz, CDCl_3) δ 173.7 (C_1), 129.9 (C_6 or C_7), 129.6 (C_6 or C_7), 128.1 (C_9), 127.6 (C_{10}), 78.7 (C_{16}), 61.2 (C_{12}), 57.3 (C_{13}), 46.1 (C_{15}), 40.2 (C_{11}), 33.7 (C_2), 28.9 (C_{14}), 28.3 (C_4), 26.4 (C_{17}), 26.1 (C_5), 25.4 (C_8), 24.4 (C_3), 8.8 (C_{18}).

(1S,12aS,13S,14S,15aR,Z)-13,14-dihydroxy-1-ethyl-4,5,6,7,8,9,10,12 a,13,14,15,15 a-dodecahydrocyclopenta[c][1]oxacyclotetradecin-3(1H)-one - Ecklonialactone D (4)

The Ecklonialactone B (1) (29 mg, 0.1 mmol, 1 equiv.) was diluted in THF (0.4 mL) and molar HClO_4 solution (0.2 mL, 0.2 mmol, 2 equiv.) was added. The solution was stirred overnight at room temperature. saturated solution of NaHCO_3 (2 mL) and EtOAc (5 mL) were added and stirred 5 minutes. The phases were separated. The aqueous phase was extracted with EtOAc (3 \times 3 mL). The combined organic phases were washed with brine (2 \times 3 mL), then dried over MgSO_4 and the solvent was removed under reduced pressure. The crude was adsorbed on silica and purified through silica gel column chromatography using 4 mL of 30 μm spherical of silica gel and a gradient of pentane/ EtOAc , from 80/20 to 40/60. The major fraction was re-purified by HPLC (Nucleodur HTec 250/10, $\text{H}_2\text{O}/\text{ACN}$: 45/55, 6.25 ml/min, $l = 195$ nm, $tr = 5.3$ min) to give the Ecklonialactone D (4) (12.9 mg, 0.041 mmol, 41%) as a colorless oil. Rf=0.21 (cyclohexane/ethyl acetate : 1/3); IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3398 (OH), 1730 (C=O); HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{31}\text{O}_4$ 311.2217 $[\text{M} + \text{H}]^+$; found 311.2223; $[\alpha]_{\text{D}}^{20} = -100.4$ (c 0.005 in CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 5.56 (tdd, $^3J_{\text{H,H}} = 10.7$, 4.4, 1.0 Hz, 1H, H_9), 5.37 (t, $^3J_{\text{H,H}} = 10.2$ Hz, 1H, H_{10}), 4.69 (td, $^3J_{\text{H,H}} = 6.8$, 3.2 Hz, 1H, H_{16}), 4.06 (dt, $^3J_{\text{H,H}} = 9.1$, 5.8 Hz, 1H, H_{13}), 3.58 (dd, $^3J_{\text{H,H}} = 9.2$, 6.2 Hz, 1H, H_{12}), 2.91 (q, $^3J_{\text{H,H}} = 9.7$ Hz, 1H, H_{11}), 2.59–2.41 (m, 2H, H_2), 2.37 (s, 1H, OH), 2.33–2.20 (m, 3H, H_2 , H_{15} , OH), 1.90–1.80 (m, 2H, H_8 , H_{14}), 1.81–1.65 (m, 5H, H_3 , H_{14} , H_{17}), 1.63–1.53 (m, 1H, H_5 or H_6), 1.50–1.40 (m, 2H, H_2), 1.41–1.28 (m, 4H, H_4 , H_5 or H_6), 1.23–1.13 (m, 1H, H_5 or H_6), 0.86 (t, $^3J_{\text{H,H}} = 7.5$ Hz, 3H, H_{18}); ^{13}C NMR (151 MHz, CDCl_3) δ 174.0 (C_1), 132.8 (C_9), 131.6 (C_{10}), 84.9 (C_{12}), 78.1 (C_{16}), 76.7 (C_{13}), 44.6 (C_{11}), 40.8 (C_{15}), 34.7 (C_{14}), 33.5 (C_2), 27.0 (C_7), 26.7 (C_8), 26.3 (C_4 or C_5 or C_6), 26.2 (C_4 or C_5 or C_6), 25.6 (C_3), 25.1 (C_5 or C_6), 24.4 (C_{17}), 10.2 (C_{18}).

Preparation of (1S,8Z,11Z,12aR,13R,14R,15aR)-13,14-dihydroxy-1-ethyl-4,5,6,7,10,12a,13,14,15,15a-decahydrocyclopenta[c][1]oxacyclotetradecin-3(1H)-one - Ecklonialactone C (5)

The Ecklonialactone A (2) (30 mg, 0.1 mmol, 1 equiv.) was diluted in THF (0.4 mL) and molar HClO_4 solution (0.2 mL, 0.2 mmol, 2 equiv.) was added. The solution was stirred 24 hours at room temperature. Saturated solution of NaHCO_3 (3 mL) and EtOAc (5 mL) were added and stirred 5 minutes. The phases were separated. The aqueous phase was extracted with EtOAc (3 \times 3 mL). The combined organic phases were washed with brine (2 \times 3 mL), then dried over MgSO_4

and the solvent was removed under reduced pressure. The crude was adsorbed on silica and purified through silica gel column chromatography using 5 mL of 30 μm spherical silica gel and a gradient of pentane/EtOAc, from 80/20 to 40/60. The major fraction was repurified by HPLC (Nucleodur HTec 250/10, H₂O/ACN : 45/55, 6.25 ml/min, $l = 195$ nm, $t_r = 4.4$ min) to give the **Ecklonialactone C (5)** (7.1 mg, 0.023 mmol, 23%) as a colorless oil. Rf = 0.19 (cyclohexane/ethyl acetate: 1/3); IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3393 (OH), 1732 (C=O); HRMS (ESI) m/z calcd for C₁₈H₂₉O₄ 309.2060 [M+H]⁺; found 309.2009; $[\alpha]_{\text{D}}^{20} = -71.4$ (c 0.005 in CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 5.56 (tdd, ³J_{H,H} = 10.9, 3.8, 1.0 Hz, 1H, H₉), 5.49–5.37 (m, 2H, H₆, H₇), 5.37–5.32 (m, 1H, H₁₀), 4.72 (td, ³J_{H,H} = 6.8, 3.9 Hz, 1H, H₁₆), 4.09 (dt, ³J_{H,H} = 8.9, 5.9 Hz, 1H, H₁₃), 3.60 (dd, ³J_{H,H} = 9.0, 6.1 Hz, 1H, H₁₂), 3.41 (ddd, ³J_{H,H} = 15.3, 10.6, 8.7 Hz, 1H, H₈), 2.93 (q, ³J_{H,H} = 9.6 Hz, 1H, H₁₁), 2.54–2.45 (m, 2H, H₂, H₈), 2.45–2.37 (m, 1H, H₅), 2.33 (ddd, ³J_{H,H} = 14.2, 7.4, 4.4 Hz, 1H, H₂), 2.24 (tdd, ³J_{H,H} = 9.7, 8.1, 4.0 Hz, 1H, H₁₅), 2.06 (s, 2H, OH), 1.88 (dt, ³J_{H,H} = 13.9, 8.6 Hz, 1H, H₁₄), 1.84–1.68 (m, 4H, H₃, H₅, H₁₄), 1.65–1.54 (m, 5H, H₄, H₁₇), 1.33–1.22 (m, 1H, H₄), 0.83 (t, ³J_{H,H} = 7.5 Hz, 3H, H₁₈). ¹³C NMR (151 MHz, CDCl₃) δ 174.1 (C₁), 130.8 (C₉), 130.6 (C₁₀), 130.2 (C₆ or C₇), 127.0 (C₆ or C₇), 84.8 (C₁₂), 78.0 (C₁₆), 76.9 (C₁₃), 45.1 (C₁₁), 41.2 (C₁₅), 34.6 (C₁₄), 33.0 (C₂), 27.9 (C₄), 26.9 (C₈), 25.8 (C₅ or C₁₇), 25.79 (C₅ or C₁₇), 24.75 (C₃), 10.1 (C₁₈).

Preparation of (1S,12aS,13R,14R,15aR,Z)-14-chloro-1-ethyl-13-hydroxy-4,5,6,7,8,9,10,12a,13,14,15,15a-dodecahydrocyclopenta[c][1]oxacyclotetradecin-3(1H)-one Eiseniachloride B (13Cl-7) and (1S,12aS,13S,14S,15aR,Z)-13-chloro-1-ethyl-14-hydroxy-4,5,6,7,8,9,10,12a,13,14,15,15a-dodecahydrocyclopenta[c][1]oxacyclotetradecin-3(1H)-one – 12-chloro-Eiseniachloride B (12Cl-25)

The Ecklonialactone B (1) (50 mg, 0.171 mmol, 1 equiv.) was diluted in anhydrous CH₂Cl₂ (15 mL). Hexachloroacetone (104 μL , 0.68 mmol, 4 equiv.) was added. The solution was stirred 1 hour and triphenylphosphine (197 mg, 0.75 mmol, 4.4 equiv.) was added. The mixture was stirred 3 hours more and Et₂O (60 mL) was added. The organic phase was washed with saturated solution of NaHCO₃ (2 \times 30 mL), water (30 mL) and brine (30 mL), then dried over MgSO₄ and the solvent was removed under reduced pressure. The crude was adsorbed on silica and purified through silica gel column chromatography using 10 mL of 30 μm spherical silica gel and a gradient of pentane/Et₂O, from 95/5 to 70/30, to give **Eisenialactone B (13Cl-7)** (46.6 mg, 0.142 mmol, 83%) and its **regioisomer (12Cl-25)** (5.8 mg, 0.017 mmol, 10%).

Eisenialactone B (13Cl-7): Rf = 0.34 (cyclohexane/ethyl acetate: 3/1); IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3429 (OH), 1721 (C=O); HRMS (ESI) m/z calcd for C₁₈H₃₀O₃³⁵Cl 329.18780 [M+H]⁺; found 329.18777; $[\alpha]_{\text{D}}^{20} = -144.5$ (c 0.01 in CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 5.59 (tdd, ³J_{H,H} = 10.7, 4.5, 1.0 Hz, 1H, H₉), 5.38 (t, ³J_{H,H} = 10.1 Hz, 1H, H₁₀), 4.70 (td, ³J_{H,H} = 6.8, 3.2 Hz, 1H, H₁₆), 4.03 (dt, ³J_{H,H} = 9.1, 6.2 Hz, 1H, H₁₃), 3.81 (dd, ³J_{H,H} = 8.8, 6.6 Hz, 1H, H₁₂), 2.96 (q, ³J_{H,H} = 10.0 Hz, 1H, H₁₁), 2.54–2.43 (m, 2H, H₂, H₈), 2.38–2.28 (m, 2H, H₂, H₁₅), 2.24 (s, 1H, OH), 2.12 (dt, ²J_{H,H} = 14.3, ³J_{H,H} = 8.9 Hz, 1H, H₁₄), 2.07–2.00 (m, 1H, H₁₄), 1.87 (dddd, ²J_{H,H} = 15.8, ³J_{H,H} = 7.6, 4.4, 1.7 Hz, 1H, H₈), 1.73–1.66 (m, 4H, H₃, H₁₇), 1.60–1.52 (m, 1H, H₅ or H₆), 1.46–1.29 (m, 6H, H₄, H₇, (H₅ or H₆)), 1.22–1.16 (m, 1H, H₅ or H₆), 0.87 (t, ³J_{H,H} = 7.5 Hz, 3H, H₁₈); ¹³C NMR (151 MHz, CDCl₃) δ 173.9 (C₁), 133.4 (C₉), 131.1 (C₁₀), 85.7 (C₁₂), 77.6 (C₁₆), 62.7 (C₁₃), 45.2 (C₁₁), 41.5 (C₁₅), 36.8 (C₁₄), 33.5 (C₂), 27.0 (C₄ or C₅ or C₆), 26.6 (C₄ or C₅ or C₆), 26.3 (C₈), 26.2 (C₇), 25.6 (C₁₇), 25.1 (C₄ or C₅ or C₆), 24.3 (C₃), 10.2 (C₁₈).

Regioisomer Eisenialactone B (12Cl-25): Rf = 0.24 (cyclohexane/ethyl acetate: 3/1); IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3423 (OH), 1727 (C=O); HRMS (ESI) m/z calcd for C₁₈H₃₀OClO₃ 329.1878 [M+H]⁺; found 329.1877; $[\alpha]_{\text{D}}^{20} = -108.2$ (c 0.005 in CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 5.57

(tdd, ³J_{H,H} = 10.5, 4.6, 0.8 Hz, 1H, H₉), 5.54–5.47 (m, 1H, H₁₀), 4.82 (td, ³J_{H,H} = 6.8, 3.6 Hz, 1H, H₁₆), 4.29 (d, ³J_{H,H} = 5.0 Hz, 1H, H₁₃), 4.07 (dt, ³J_{H,H} = 4.8, 1.7 Hz, 1H, H₁₂), 3.56 (td, ³J_{H,H} = 9.0, 4.8 Hz, 1H, H₁₁), 2.61–2.42 (m, 3H, H₂, H₁₄, H₁₅), 2.38–2.29 (m, 2H, H₂, H₈), 1.97–1.87 (m, 2H, OH, H₈), 1.73–1.66 (m, 4H, H₃, H₁₇), 1.63–1.51 (m, 1H, H₅ or H₆), 1.49–1.42 (m, 2H, H₇), 1.41–1.31 (m, 5H, H₁₄, H₄, (H₅ or H₆)), 1.29–1.19 (m, 1H, H₅ or H₆), 0.88 (t, ³J_{H,H} = 7.5 Hz, 3H, H₁₈); ¹³C NMR (151 MHz, CDCl₃) δ 173.9 (C₁), 132.4 (C₉), 129.6, (C₁₀) 78.2 (C₁₃), 77.9 (C₁₆), 72.1 (C₁₂), 42.4 (C₁₅), 40.5 (C₁₁), 36.8 (C₁₄), 33.5 (C₂), 27.0 (C₄ or C₅ or C₆), 26.6 (C₄ or C₅ or C₆), 26.3 (C₈), 26.1 (C₇), 25.7 (C₁₇), 25.2 (C₅ or C₆), 24.3 (C₃), 10.3 (C₁₈).

Preparation of (1S,8Z,11Z,12aR,13R,14R,15aR)-14-chloro-1-ethyl-13-hydroxy-4,5,6,7,10,12a,13,14,15,15a-decahydrocyclopenta[c][1]oxacyclotetradecin-3(1H)-one – Eiseniachloride A (13Cl-8)

The Ecklonialactone A (2) (20 mg, 0.0688 mmol, 1 equiv.) was diluted in anhydrous CH₂Cl₂ (6 mL). Hexachloroacetone (41 μL , 0.275 mmol, 4 equiv.) was added. The solution was stirred 1 hour and triphenylphosphine (80 mg, 0.303 mmol, 4.4 equiv.) was added. The mixture was stirred 3 additional hours and Et₂O (20 mL) was added. The organic phase was washed with a saturated solution of NaHCO₃ (2 \times 10 mL), then water (10 mL) and brine (10 mL), dried over MgSO₄ and the solvent was removed under reduced pressure. The crude was adsorbed on silica and purified through silica gel column chromatography using 6 mL of 30 μm spherical silica gel and a gradient of pentane/Et₂O, from 95/5 to 70/30, to give **Eiseniachloride A (13Cl-8)** (19.6 mg, 0.060 mmol, 87%).

Eiseniachloride A (13Cl-8): Rf = 0.34 (cyclohexane/ethyl acetate : 3/1); IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3424 (OH), 1728 (C=O); HRMS (ESI) m/z calcd for C₁₈H₂₈O₃³⁵Cl 327.17215 [M+H]⁺; found 327.17227; $[\alpha]_{\text{D}}^{20} = -178.9$ (c 0.01 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.58 (tdd, ³J_{H,H} = 10.8, 3.7, 1.0 Hz, 1H, H₉), 5.50–5.30 (m, 3H, H₆, H₇, H₁₀), 4.73 (td, ³J_{H,H} = 6.8, 3.9 Hz, 1H, H₁₆), 4.04 (dt, ³J_{H,H} = 8.7, 6.3 Hz, 1H, H₁₃), 3.89–3.80 (m, 1H, H₁₂), 3.41 (ddd, ²J_{H,H} = 15.7, ³J_{H,H} = 10.8, 8.2 Hz, 1H, H₈), 2.96 (q, ³J_{H,H} = 9.3 Hz, 1H, H₁₁), 2.58–2.43 (m, 2H, H₂, H₈), 2.43–2.27 (m, 2H, H₂, H₁₅), 2.27–2.22 (m, 1H, OH), 2.18–1.98 (m, 2H, H₁₄), 1.91–1.67 (m, 3H, H₃, H₅), 1.65–1.52 (m, 3H, H₄, H₁₇), 1.37–1.16 (m, 1H, H₄), 0.83 (t, ³J_{H,H} = 7.5 Hz, 3H, H₁₈); ¹³C NMR (101 MHz, CDCl₃) δ 173.9 (C₁), 131.0 (C₉), 130.3 (C₆ or C₇ or C₁₀), 130.2 (C₆ or C₇ or C₁₀), 126.9 (C₆ or C₇), 85.6 (C₁₂), 77.6 (C₁₆), 62.9 (C₁₃), 45.5 (C₁₁), 42.0 (C₁₅), 36.7 (C₁₄), 33.0 (C₂), 27.9 (C₄), 26.9 (C₈), 25.8 (C₅ or C₁₇), 25.7 (C₅ or C₁₇), 24.7 (C₃), 10.1 (C₁₈).

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Total Synthesis · Natural Product · Oxyipins · Ecklonialactones · Eiseniachlorides

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