

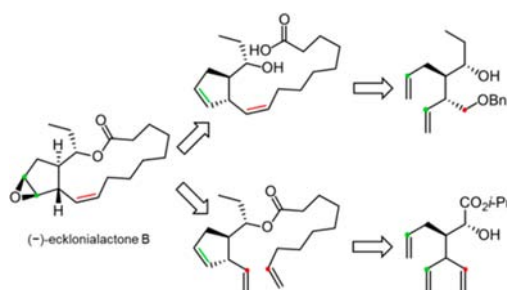
Total Synthesis of (–)-Ecklonialactone B

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ABSTRACT



The total synthesis of (–)-ecklonialactone B as well as the 9,10-dihydro derivative by two different strategies is reported. The catalytic asymmetric Claisen rearrangement of Gosteli-type allyl vinyl ethers delivered elaborated α -keto ester building blocks. Ring-closing metatheses, including a notable diastereotopos-differentiating variant, a *B*-alkyl Suzuki–Miyaura cross-coupling reaction and a regio- and diastereoselective last-step epoxidation are key contributors.

The oxylipins (–)-ecklonialactone A (**1**) and B (**3**) have been isolated from the brown algae *Ecklonia stolonifera* by Kurata *et al.* and *Egregia menziessi* by Gerwick *et al.* (Figure 1).^{1,2} The constitution and configuration of (–)-**1** was deduced from NMR experiments, X-ray crystallography, and analysis of the chiroptical properties of a derivative. The structural assignment of (–)-**3** was deduced from the close similarity of the NMR data of (–)-**1** and (–)-**3** and further evidenced by the experimental observation that hydrogenation of (–)-**1** as well as (–)-**3** afforded (+)-**2**.¹ An initial report on the enantioselective synthesis of the cyclopentanoid segment of (–)-**3** by our group was subsequently followed by the disclosure of the total syntheses of (–)-**1** and (–)-**3** by Hickmann, Alcarazo, and Fürstner.^{3,4} Fürstner's synthesis required a longest linear sequence of 13 steps, avoided any protecting group transformation, and relied on a ring-closing alkyne metathesis for the formation of the 14-membered lactone.

Our retrosynthetic reasoning is summarized in Figure 1. A last-step regio- and diastereoface-differentiating epoxidation of the diene **4** was envisioned in order to circumvent the presence of the labile oxirane already at an early stage of the synthetic sequence toward (–)-**3**.⁴ Subsequent retrosynthetic dismantling of the 14-membered lactone of **4** leads to the chiral cyclopentenoid building block **5** which, in turn, was envisioned to be accessible from the achiral Gosteli-type allyl vinyl ether (*E,Z*)-**6**.⁵

The experimental realization of the planning is illustrated in Scheme 1. Catalytic asymmetric Gosteli–Claisen rearrangement (CAGC)^{6–8} of (*E,Z*)-**6**⁹ on gram scale delivered the α -keto ester **8** which was subjected to highly diastereoselective K–Selectride reduction to afford the

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(9) Prepared in 7 steps (19%) from *cis*-2-butene-1,4-diol including the separation of vinyl ether double bond isomers by preparative HPLC; see ref 3.

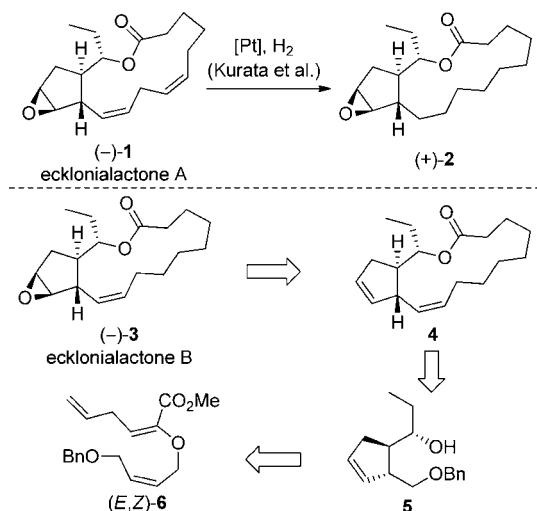


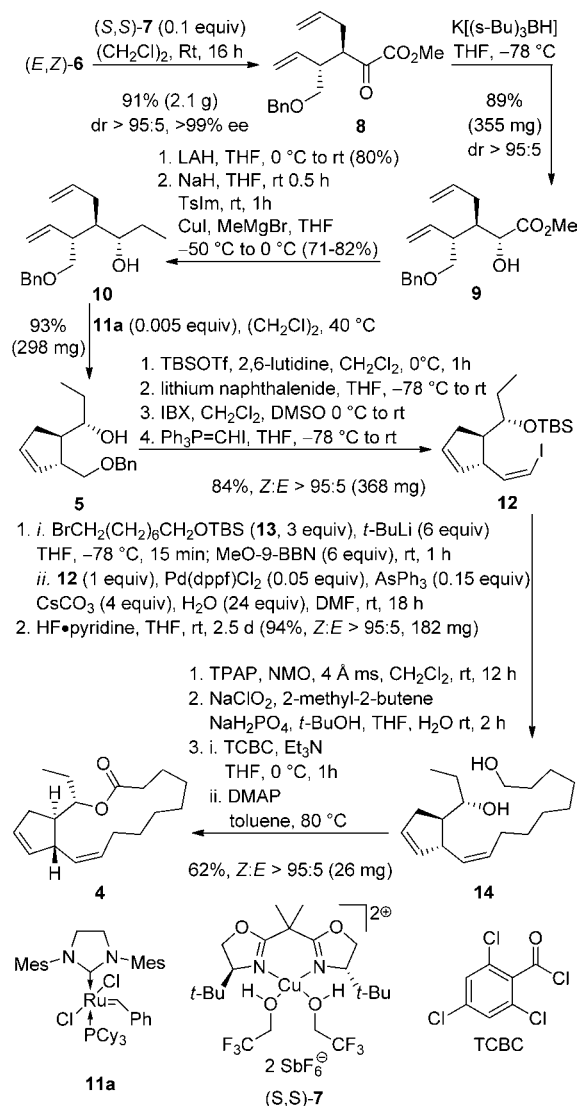
Figure 1. Retrosynthesis.

α -hydroxy ester **9**.^{10–12} Reductive homologation was accomplished by a two-pot reaction sequence: initial LAH reduction afforded the corresponding diol which was isolated and characterized and subsequently converted to the corresponding oxirane using 1-tosyl imidazole (TsIm) and NaH. In situ ring opening of the epoxide employing MeMgBr and CuI, thereafter, provided the alcohol **10**.^{13,14}

Having assembled the unusual stereotriad of the acyclic 1,5-diene **10**, subsequent ring-closing metathesis (RCM) using the Grubbs catalyst **11a**¹⁵ (0.005 equiv) delivered the desired building block **5**. Progressing to the bicyclic diene **4** then required assembly of the 14-membered lactone that included the isolated *Z*-configured double bond.

Accordingly, the secondary hydroxyl group was protected,¹⁶ the benzyl ether reductively cleaved,¹⁷ the unprotected primary alcohol was oxidized,¹⁸ and the resulting aldehyde was subjected to a Wittig-type olefination¹⁹ to

Scheme 1. Synthesis of 12,13-Desepoxy Ecklonialactone

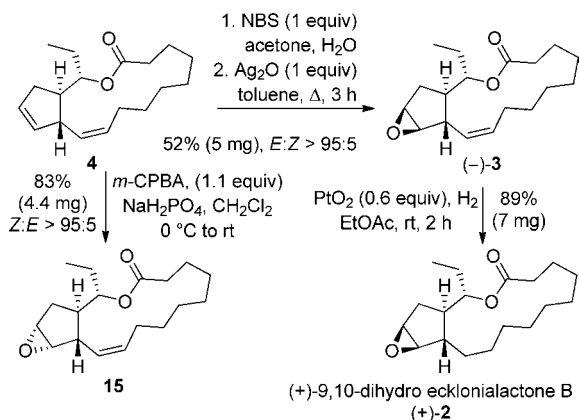


afford the vinyl iodide **12** in excellent overall yield (4 steps, 88%) and a synthetically useful diastereoselectivity (*Z*:*E* > 10:1). Suzuki–Miyaura cross-coupling²⁰ between the vinyl iodide **12** and a *B*-alkyl borate complex, in situ prepared from the alkyl bromide **13**,²¹ *t*-BuLi, and *B*-MeO-9-BBN, and subsequent silyl ether cleavage then delivered the diol **14** in a robust 80% yield as a *Z*:*E* > 10:1 mixture of double bond isomers. Regioselective two-step oxidation^{22,23} of **14** provided the corresponding hydroxy acid which was subjected to a Yamaguchi lactonization²⁴ which furnished the desired 12,13-desepoxy ecklonialactone **4**.

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Scheme 2. Regio- and Diastereoselective Epoxidation



With the diene **4** in hand, opportunities for a regio- and stereoselective epoxidation of the C12/C13 double bond were explored (Scheme 2). An initial attempt using *m*-CPBA (1 equiv) was highly regioselective. However, the undesired diastereomer **15** was obtained exclusively. This outcome was not unexpected considering the result of Hickmann who obtained the same (12*Re*,13*Si*)-diastereoface differentiation (dr = 7:1) using the corresponding enyne.²⁵ Taking advantage of the intrinsic (12*Re*,13*Si*)-nucleophilicity of the diene **4**, a two-step procedure was then employed to finalize the synthesis. Thus, subjecting the diene **4** to NBS (1 equiv) in aqueous acetone followed by treatment of the isolated and purified bromohydrin intermediate with Ag₂O in toluene at reflux furnished (–)-**3** whose NMR data matched those reported by Kurata as well as Fürstner. At this point, we decided to carry the synthetic material toward the non-natural (+)-9,10-dihydroecklonialactone B (**2**) whose partial synthesis from the natural ecklonialactones A and B had been reported by Kurata.²⁶ Accordingly, (–)-**3** was hydrogenated using Adam's catalyst²⁷ to afford (+)-**2** whose spectroscopic data were in accordance with those reported.

In pursuit of a streamlined synthetic sequence we next implemented a revised retrosynthesis which hinged on the success of a Z-selective RCM for the ring closure of the macrolactone **4** from the triene **16** and a diastereotopodifferentiating RCM²⁸ for formation of the 1,2-*trans*-disubstituted cyclopentenoid **17** from the α -hydroxy ester **18** (Figure 2); **18** would be accessible by a sequence of enantio- and diastereoselective transformations from the Gosteli-type allyl vinyl ether (*E,E*)-**19**.

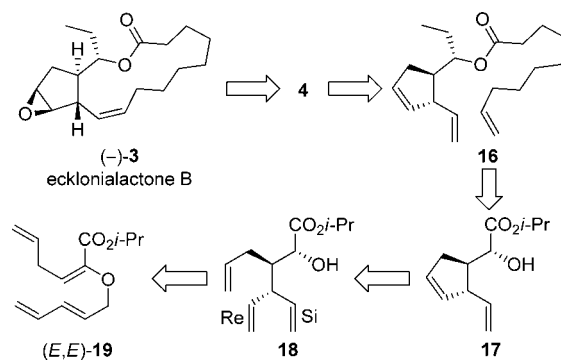


Figure 2. Revised retrosynthesis based on diastereotopos-differentiating RCM.

The synthesis of the Gosteli-type allyl vinyl ether **19** by an aldol condensation approach is outlined in Scheme 3.²⁹ Etherification of 2,4-pentadienol **20** followed by carbodiimide-mediated esterification³⁰ furnished the acetate **21** which was subjected to a stepwise aldol condensation using 4-phenylselenylbutanal³¹ as a synthetic equivalent for 3-butenal to afford the phenylselenides **22** (*Z*:*E* = 3:2) which were separated by preparative HPLC. Oxidation of the selenides (*E,E*)- as well as (*Z,E*)-**22** triggered elimination³² to provide the Gosteli-type allyl vinyl ethers (*E,E*)- and (*Z,E*)-**19**. Subsequent CAGC of (*Z,E*)-**19** delivered the α -keto ester (*S*)-**23** which could serve as a building block for the total synthesis of (+)-ecklonialactone B.

The implementation of the projected nine-step synthetic sequence from (*E,E*)-**19** to (–)-ecklonialactone **B** (**3**) is outlined in Scheme 4. CAGC of (*E,E*)-**19** to the α -keto ester (*R*)-**23** and subsequent reduction by K-Selectride afforded the α -hydroxy ester **24**. The crucial diastereotopos-differentiating RCM was best performed using the Hoveyda–Grubbs catalyst³³ (**11b**, 0.01 equiv) at ambient temperature; we were pleased to discover that the *trans*-1,2-disubstituted cyclopentenoid **25** was thus isolated in very good yield and diastereoselectivity ($\geq 95:5$ according to NMR analysis). Reductive homologation of **25** to the corresponding secondary alcohol was followed by an esterification using the Yamaguchi protocol which delivered the triene **26**. We then turned our attention to devising conditions that would enable the much desired Z-selective RCM of **27** to afford 12,13-desepoxy ecklonialactone (**4**). Disappointingly, however, and despite the screening of

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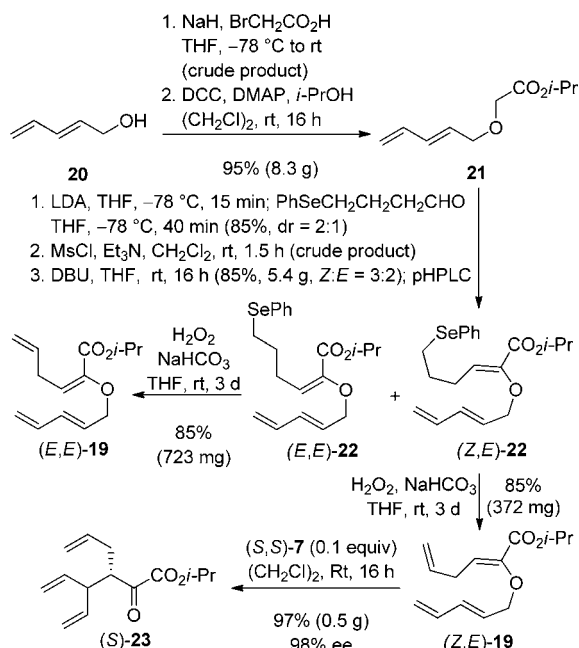
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Scheme 3. Synthesis of Gosteli-Type Allyl Vinyl Ethers and Catalytic Asymmetric Claisen Rearrangement

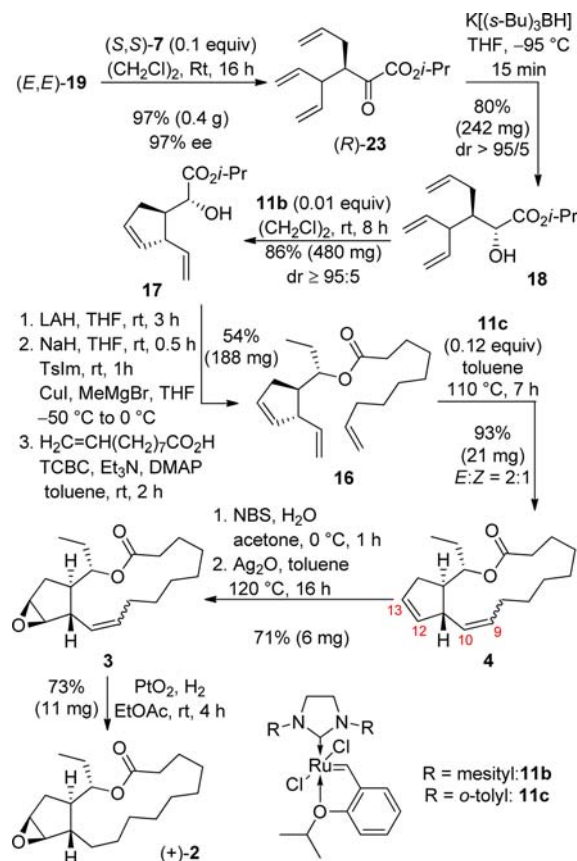


different commercial Ru-based catalysts and conditions, from which in our hands the Stewart–Grubbs catalyst³⁴ (**11c**) was best-performing in terms of yield, the diene **4** was isolated as mixture of $\Delta^{9,10}$ double bond isomers (*E*:*Z* = 1–4:1, depending on the catalyst and conditions).³⁵ Conversion to the oxirane was then performed as described above and proceeded without affecting the ratio of $\Delta^{9,10}$ double bond isomers. Subsequent hydrogenation of the resulting *E*/*Z*-mixture of **3** delivered (+)-**2** whose spectral properties matched those reported by Kurata and those of the synthetic (+)-**2** from our initial synthesis (Scheme 2).

In conclusion, the catalytic asymmetric Claisen rearrangement of the Gosteli-type allyl vinyl ethers **6** and **19** allowed the strategic positioning of double bonds within the chiral acyclic α -keto esters **8** and **23**. Subsequent RCM furnished the cyclopentenoid building blocks **5** and **17** whose availability enabled the total synthesis of

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Scheme 4. Synthesis of (+)-9,10-Dihydro Ecklonialactone B



(–)-ecklonialactone **B** (**3**) (longest linear sequence of 23 steps, 2% overall yield) as well as of the non-natural (+)-9,10-dihydro ecklonialactone **B** (**2**) (protecting-group-free, longest linear sequence of 17 steps, 4% overall yield) via an *E*/*Z*-mixture of (–)-**3**.

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Supporting Information Available. Experimental procedures, spectral and analytical data, copies of ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.