The Catalytic Asymmetric Claisen Rearrangement (CAC) in Natural Product Synthesis: Synthetic Studies Toward (–)-Ecklonialactone B

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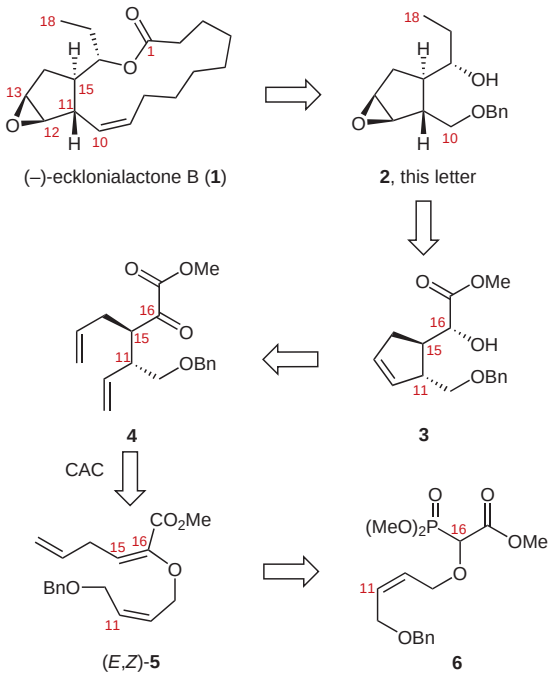
Abstract: A catalytic asymmetric Claisen rearrangement (CAC) in concert with a ring-closing metathesis (RCM) has been utilized in the enantioselective synthesis of the C10–C18 segment of ecklonialactone B.

Key words: total synthesis, natural products, asymmetric catalysis, pericyclic reactions, Lewis acids

(–)-Ecklonialactone B (E_B, **1**), is a carbocyclic C_{18}-oxylipin of marine origin that has been isolated from the brown algae *Ecklonia stolonifera*[1] and *Egregia menziessi*[2] (Scheme 1).[3] E_B is a member of a larger family of ecklonialactones that are distinguished by the number and position of double bonds in the macrolactone ring.[4,5] Furthermore, the cyclopentane segment of ecklonialactones may either be epoxidized (as in E_B) or *trans*-dihydroxylated at the C12/C13 position. The relative configuration of ecklonialactone A ($\Delta^{6,9}$), E_A, has been established by crystal structure analysis.[1] By chemical correlation, it was demonstrated that E_B (Δ^9) possesses the same relative configuration as E_A.[1] The absolute configuration of E_A was later deduced from its chiroptical properties and conferred to E_B based on the similar negative optical rotation values of E_A and E_B.[2]

As part of a program aimed at the exploration of the scope and limitations of the recently developed catalytic asymmetric Claisen rearrangement (CAC)[6] in natural product synthesis,[7] E_B (**1**) was identified as a worthwhile target molecule. Specifically, the proof of the assigned absolute configuration, which has important biosynthetic implications,[2] as well as the study of potential biological activities[3] of **1** and its derivatives appear appealing. In this letter, we report an 11-step synthesis (8% overall yield) of the enantiomerically pure cyclopentanoid **2**, the key building block in the total synthesis of E_B (**1**).

Our retrosynthetic analysis of E_B (**1**) is depicted in Scheme 1. It is apparent that the molecular complexity of **1** materializes at the highly substituted cyclopentane moiety, which features five contiguous stereogenic carbon atoms, and that the cyclopentanoid **2** represents an advanced building block toward E_B (**1**). The first retrosynthetic simplification converts **2** into the cyclopentanoid **3** by removing the epoxide and C18. Subsequent utilization of a ring-closing metathesis transformation and of a redox transformation provides the α-keto ester **4**. The following disconnection rests on the CAC retron present in **4** and provides the achiral *E*,*Z*-configured allyl vinyl ether **5**. The final simplification takes advantage of the availability of an olefination transformation for the diastereoselective synthesis of 2-alkoxycarbonyl-substituted allyl vinyl ethers as **5** from the known phosphonoacetate **6**.[7b]



Scheme 1 Retrosynthesis of (–)-ecklonialactone B (**1**)

The synthesis of the allyl vinyl ether (*E*,*Z*)-**5** is summarized in Scheme 2. Nucleophilic ring opening of tetrahydrofurane by the phenyl selenide anion, that was generated from diphenyl diselenide (**7**) and lithium aluminum hydride (LAH)[8] followed by Parikh–Doering oxidation,[9] provided the aldehyde **8**. Horner–Wadsworth–Emmons olefination[10] of the aldehyde **8** utilizing the 2-allyloxy-substituted trimethyl 2-phosphonoacetate **6**[7b] afforded the allyl vinyl ether **9** as a mixture of vinyl ether double-bond isomers. Subsequent oxidation of the selenide to the selenoxide induced a thermal elimination[11] which provided the required allyl vinyl ether **5** as an

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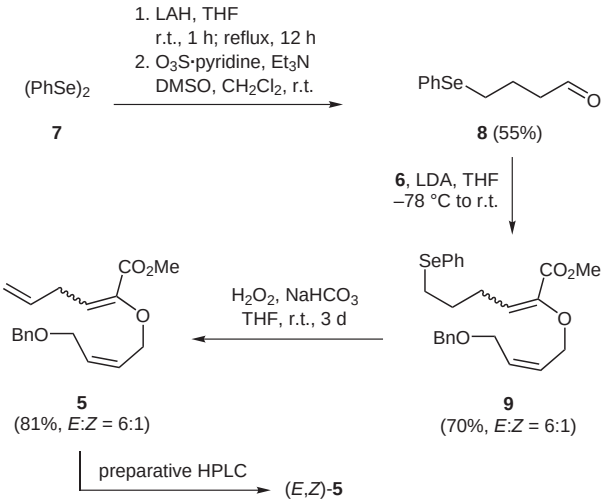
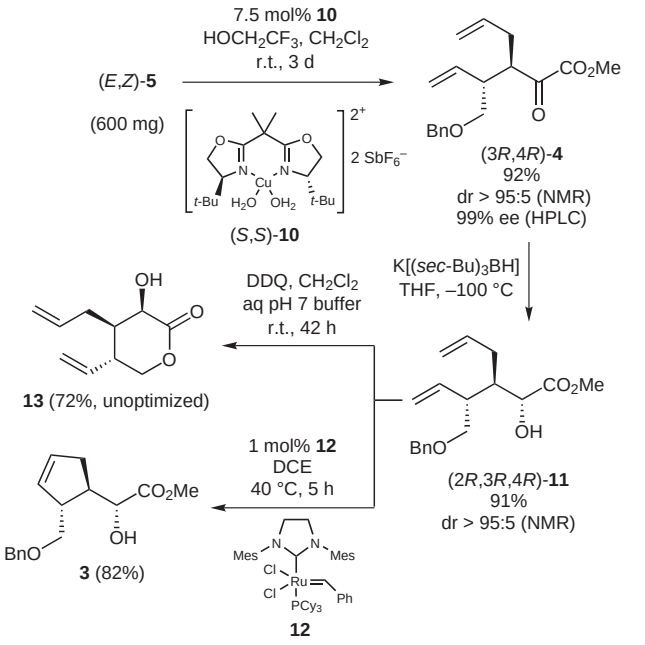


Scheme 2 Synthesis of allyl vinyl ether (*E*,*Z*)-**5**

E:*Z* = 6:1 mixture of double-bond isomers. The diastereomers were conveniently separable by preparative HPLC.[12] Efforts to utilize 3-butenal for the olefination were unsuccessful.[13]

The pivotal sequence for the generation of the two stereogenic carbon atoms C11 and C15 as well as the cyclopentene moiety from an acyclic precursor is depicted in Scheme 3. The chosen route to the key building block **3** hinges upon the methodology recently developed in our laboratory.[6,7] The CAC of the allyl vinyl ether (*E*,*Z*)-**5** in the presence of the chiral Lewis acid {Cu[(*S*,*S*)-*tert*-Bu-box]}$(H_2O)_2(SbF_6)_2$[14] (**10**) afforded the α-keto ester (3*R*,4*R*)-**4**[15] as single stereoisomer based on NMR and HPLC analysis. The absolute configuration of **4** was assigned based on the previously established stereochemical course of the CAC.[6,7] Judging from our experience with structurally related allyl vinyl ethers, the CAC of (*E*,*Z*)-**5** was unexpectedly slow requiring 7.5 mol% of **12** and 3 days reaction time to proceed to completion. Nevertheless, the chemo- and stereoselectivity of this catalytic asymmetric C–C-connecting transformation is impressive and reproducible, even on a synthetically useful scale. Studies are underway to further optimize the reaction conditions.

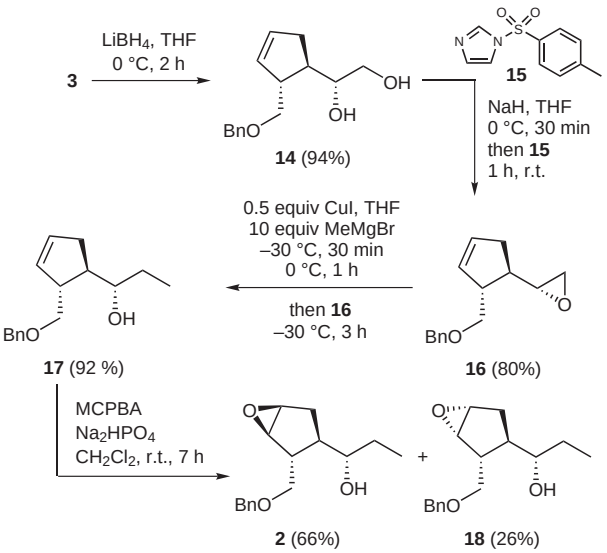
In accordance with previous work from our laboratory, reduction of the α-keto ester **4** with K-selectride provided the α-hydroxy ester (2*R*,3*R*,4*R*)-**11** as a single diastereomer based on NMR analysis (Scheme 3).[6b,7b] The configuration of the newly generated stereogenic carbon atom C2 may be explained by the Cram–Felkin–Anh model.[16] Oxidative cleavage[17] of the benzyl ether in **11** followed by in situ lactonization provided the corresponding δ-lactone **13**. NOE studies on the δ-lactone **13** support the assignment of the relative configuration. The ring-closing metathesis of the diene **11** was catalyzed by the second-generation Grubbs catalyst[18] (**12**) at slightly increased temperature to afford the cyclopentenoid **3**.[19]



Scheme 3 The sequence of two stereodifferentiating reactions and a ring-closing metathesis provides enantiomerically pure **3**

The sequence required for the conversion of cyclopentenoid **3** into the C10–C18 segment **2** of E_B (**1**) is depicted in Scheme 4.

Reduction of **3** to the diol **14** followed by one-step epoxidation[20] enabled the introduction of the yet missing C18. Copper-mediated ring opening of the epoxide **16** with methyl magnesium bromide provided the alcohol **17**.[21] The diastereoselective epoxidation of the cyclopentanoid **17** employing *meta*-chloroperbenzoic acid (MCPBA) provided the desired C10–C18 segment **2**[22] of E_B (**1**) along with its diastereomer **18**.[23] The diastereomers were easily separable by flash chromatography. NOE studies on both diastereomers unambiguously support the assignment of the relative configuration. Efforts aimed at



Scheme 4 Introduction of the C18 methyl group and epoxidation of the cyclopentene double bond

the improvement of the diastereoselectivity of the epoxidation are ongoing.

In summary, we have once again demonstrated the power of the catalytic asymmetric Claisen rearrangement (CAC) of 2-alkoxycarbonyl-substituted allyl vinyl ethers in natural product synthesis. The CAC provides access to stereoisomerically pure acyclic α-keto esters. Various functional groups are tolerated. The strategic positioning of double bonds allows access to cyclic building blocks for the total synthesis of enantiomerically pure carbocyclic natural products. Work aimed at the completion of the total synthesis of E_B (**1**) is currently underway and will be reported in due course.

Acknowledgment

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(12) Preparative HPLC: Nu 50-7, 32 × 250 mm, heptane–EtOAc (95:5), 20 mL/min, t_R (*E*,*Z*)-**5** = 25 min, t_R (*Z*,*Z*)-**5** = 22 min, baseline separation with 100 mg/injection.
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(15) **Synthesis of (3*R*,4*R*)-4**
A stock solution of {Cu[(*S*,*S*)-*tert*-Bu-box]}$(H_2O)_2(SbF_6)_2$ (**10**) in CF_3CH_2OH (1 mL, 0.1 M, 86 mg, 0.1 mmol, 0.05 equiv) was dissolved in CH_2Cl_2 (5 mL). The allyl vinyl ether (*E*,*Z*)-**5** (0.59 g, 2.0 mmol, 1 equiv) was then added and the solution was stirred over night at r.t. At this point, additional {Cu[(*S*,*S*)-*tert*-Bu-box]}$(H_2O)_2(SbF_6)_2$ (0.5 mL, 0.1 M in CF_3CH_2OH, 43 mg, 0.05 mmol, 0.025 equiv) was added. The reaction mixture was stirred for 3 d at r.t. and then concentrated under reduced pressure. The catalyst was removed by filtering the crude product mixture through a short path silica gel column. Subsequent flash chromatography (hexane–EtOAc, 50:1) afforded the α-keto ester **4** (0.54 g, 1.8 mmol, 92%) as a light yellow oil. TLC: R_f = 0.72 (hexane–EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32–2.36 (m, 2 H), 2.83 (ddd, J_1 = 19.1 Hz, J_2 = 9.5 Hz, J_3 = 4.8 Hz, 1 H), 3.32 (dd, J_1 = J_2 = 9.7 Hz, 1 H), 3.39–3.47 (m, 2 H), 3.54 (s, 3 H), 4.27 (d, *J* = 12.1 Hz, 1 H), 4.31 (d, *J* = 12.1 Hz, 1 H), 4.90–4.97 (m, 2 H), 5.13–5.17 (m, 2 H), 5.52 (ddd, J_1 = 17.4 Hz, J_2 = J_3 = 9.5 Hz, 1 H), 5.64 (dddd, J_1 = 17.1 Hz, J_2 = 10.0 Hz, J_3 = 7.1, J_4 = 7.0 Hz, 1 H), 7.19–7.31 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.7 (CH_2), 48.2 (CH), 48.2 (CH), 52.4 (CH_3), 72.5 (CH_2), 72.6 (CH_2), 117.2 (CH_2), 118.9 (CH_2), 127.5 (3 × CH), 128.2 (2 × CH), 134.7 (CH), 135.4 (CH), 137.3 (C), 161.2 (C), 194.7 (C). IR (in substance): 3080-2860, 1730, 1640 cm^{-1}. Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.5; H, 7.3. Found: C, 71.5; H, 7.1. $[\alpha]_D^{25}$ +46.8 (*c* 0.68, $CHCl_3$).
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(19) **Synthesis of 3**
Diene **11** (36.4 mg, 0.12 mmol, 1 equiv) was dissolved in DCE (2.5 mL) in a septum-sealed round-bottomed flask. The flask was twice evacuated (20 mbar, 2 min) and ventilated with argon. The Grubbs catalyst **12** (1.0 mg, 1.2 μmol, 0.01 equiv) was then added to the solution and the flask was again twice evacuated and ventilated with argon. The reaction mixture was then stirred for 5 h at 40 °C. Silica gel (120 mg) was subsequently added and the heterogeneous mixture was stirred for several minutes. The solid was then removed by filtration and the solvents were evaporated at reduced pressure. The crude product was purified by flash chromatography (hexane–EtOAc, 20:1 to 10:1) to afford the cyclopentenoid **3** (27.6 mg, 0.10 mmol, 84%) as a light yellow oil. TLC: R_f = 0.17 (hexane–EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (ddd, J_1 = 15.9 Hz, J_2 = 6.0 Hz, J_3 = 2.1 Hz, 1 H), 2.41 (ddd, J_1 = 15.1 Hz, J_2 = J_3 = 6.3 Hz, 1 H), 2.51 (ddd, J_1 = 15.8 Hz, J_2 = J_3 = 2.3 Hz, 1 H), 2.96–2.98 (m, 1 H), 3.20 (dd, J_1 = J_2 = 8.7 Hz, 1 H), 3.51 (dd, J_1 = 8.8 Hz, J_2 = 5.0 Hz, 1 H), 3.66 (s, 3 H), 4.10 (d, *J* = 6.8 Hz, 1 H), 4.50 (d, *J* = 12.2 Hz, 2 H), 4.55 (d, *J* = 12.2 Hz, 1 H), 5.50 (ddd, J_1 = 3.8 Hz, J_2 = J_3 = 1.9 Hz, 1 H), 5.70 (dd, J_1 = 5.5 Hz, J_2 = 2.3 Hz, 1 H), 7.25–7.35 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.7 (CH_2), 45.9 (CH), 48.8 (CH), 52.0 (CH_3), 73.2 (CH_2), 73.5 (CH_2), 74.0 (CH), 127.7 (3 × CH), 128.4 (2 × CH), 130.1 (CH), 130.9 (CH), 137.6 (C), 174.4 (C). IR (in substance): 3445, 3060–2855, 1738 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.5; H, 7.3. Found: C, 69.3; H, 7.6. $[\alpha]_D^{25}$ –58.9 (*c* 0.56, $CHCl_3$).

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(22) **Synthesis of 2**
To a solution of the olefin **17** (79.6 mg, 0.32 mmol, 1 equiv) in CH_2Cl_2 (12 mL) was added Na_2HPO_4 (137.7 mg, 0.97 mmol, 3 equiv) and MCPBA (77% purity, 108.7 mg, 0.49 mmol, 1.5 equiv) at 0 °C. The reaction mixture was then stirred for 7 h at r.t. and subsequently quenched with sat. aq Na_2SO_3 solution. The layers were separated and the aq phase was extracted three times with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (hexane–EtOAc, 20:1 to 10:1) afforded the epoxide **2** (56 mg, 0.21 mmol, 66%) and its diastereomer **18** (22 mg, 0.08 mmol, 26%). TLC (hexane–EtOAc, 2:1): R_f(**18**) = 0.41, R_f(**2**) = 0.31.
Compound **2**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (dd, $J_1 = J_2$ = 7.4 Hz, 3 H), 1.26 (ddq, J_1 = 14.2, J_2 = 7.3 Hz, J_3 = 7.1 Hz, 1 H), 1.41 (ddd, J_1 = 13.9 Hz, J_2 = 9.1 Hz, J_3 = 0.7 Hz, 1 H), 1.47–1.59 (m, 2 H), 2.12–2.19 (m, 2 H), 3.26 (ddd, J_1 = 8.5 Hz, J_2 = 8.3 Hz, J_3 = 1.9 Hz, 1 H), 3.40–3.41 (m, 2 H), 3.53 (dd, J_1 = 9.3 Hz, J_2 = 9.1 Hz, 1 H), 3.81 (dd, J_1 = 9.1 Hz, J_2 = 4.5 Hz, 1 H), 4.15 (OH, 1 H), 4.54 (d, J = 12.1 Hz, 1 H), 4.62 (d, J = 12.1 Hz, 1 H), 7.26–7.29 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.2 (CH_3), 28.0 (CH_2), 32.4 (CH_2), 44.7 (CH), 45.6 (CH), 55.6 (CH), 59.1 (CH), 71.5 (CH_2), 73.5 (CH_2), 75.8 (CH), 127.8 (3 × CH), 128.4 (2 × CH), 137.0 (C). IR (in substance): 3430, 3090–2875, 1715 cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_2$: C, 73.3; H, 8.5. Found: C, 72.9; H, 8.6. $[\alpha]_D^{25}$ –55.1 (*c* 0.55, $CHCl_3$).
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