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Total Synthesis of (−)-Ecklonialactone B

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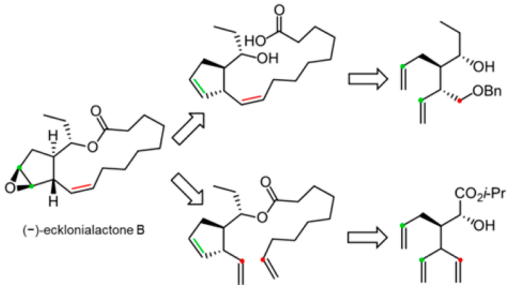
ABSTRACT



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

(1) Kurata, K.; Taniguchi, K.; Shiraishi, K.; Hayama, N.; Tanaka, I.; Suzuki, M. *Chem. Lett.* **1989**, 267–270.

(2) Todd, J. S.; Proteau, P. J.; Gerwick, W. H. *J. Nat. Prod.* **1994**, *57*, 171–174.

(3) Wang, Q.; Millet, A.; Hiersemann, M. *Synlett* **2007**, 1683–1686.

(4) (a) Hickmann, V.; Alcarazo, M.; Fürstner, A. *J. Am. Chem. Soc.* **2010**, *132*, 11042–11044. (b) Hickmann, V.; Kondoh, A.; Gabor, B.; Alcarazo, M.; Fürstner, A. *J. Am. Chem. Soc.* **2011**, *133*, 13471–13480.

(5) (a) Gosteli, J. *Helv. Chim. Acta* **1972**, *55*, 451–460. (b) Rehbein, J.; Hiersemann, M. *J. Org. Chem.* **2009**, *74*, 4336–4342. (c) Rehbein, J.; Leick, S.; Hiersemann, M. *J. Org. Chem.* **2009**, *74*, 1531–1540.

(6) For a recent review on catalyzed Claisen rearrangements, see: Rehbein, J.; Hiersemann, M. *Synthesis* **2013**, *45*, 1121–1159.

(7) (a) Abraham, L.; Czerwonka, R.; Hiersemann, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4700–4703. (b) Abraham, L.; Körner, M.; Schwab, P.; Hiersemann, M. *Adv. Synth. Catal.* **2004**, *346*, 1281–1294. (c) Abraham, L.; Körner, M.; Hiersemann, M. *Tetrahedron Lett.* **2004**, *45*, 3647–3650.

(8) For the synthesis of [Cu{(*S*,*S*)-*tert*-Bu-box}(tfe)$_2$](SbF$_6$)$_2$, see: Jaschinski, T.; Hiersemann, M. *Org. Lett.* **2012**, *14*, 4114–4117.

(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.

10.1021/ol4028418

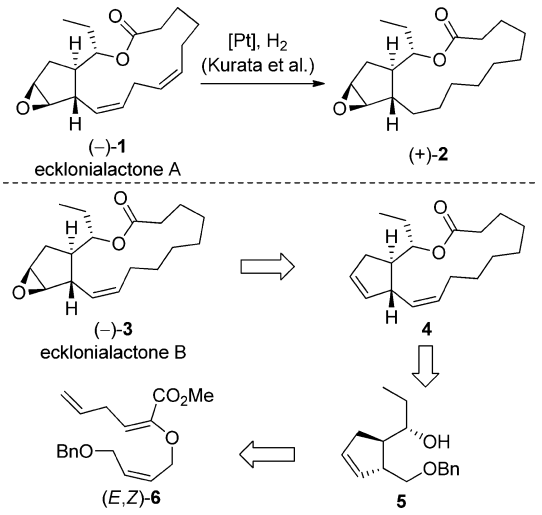


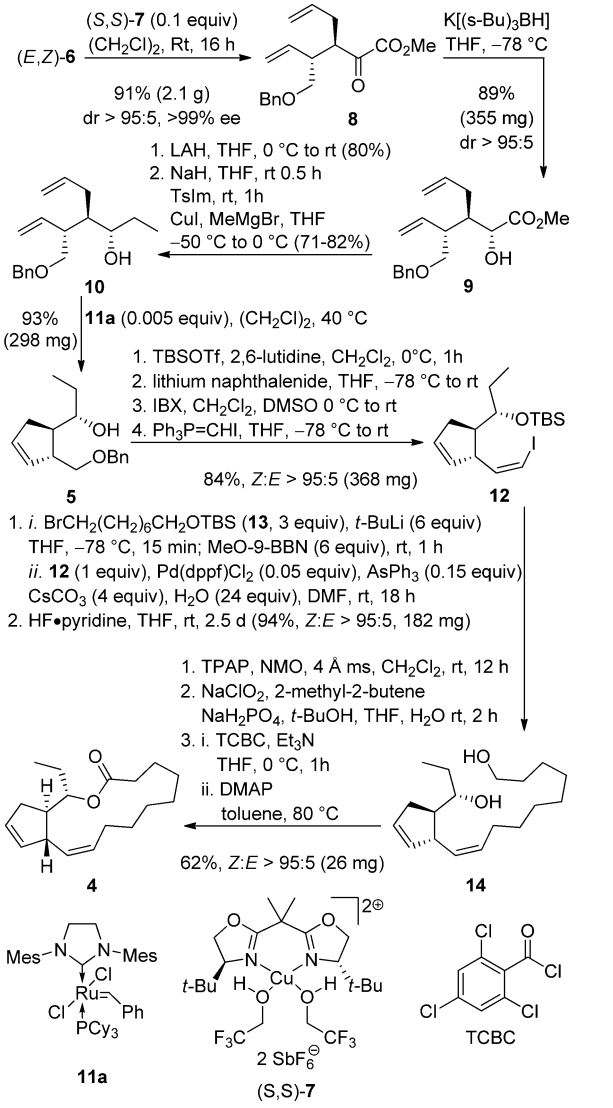
Figure 1. Retrosynthesis.

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 was cleaved,[17] the unprotected primary alcohol was oxidized,[18] and the resulting aldehyde was subjected to a Wittig-type olefination[19] to

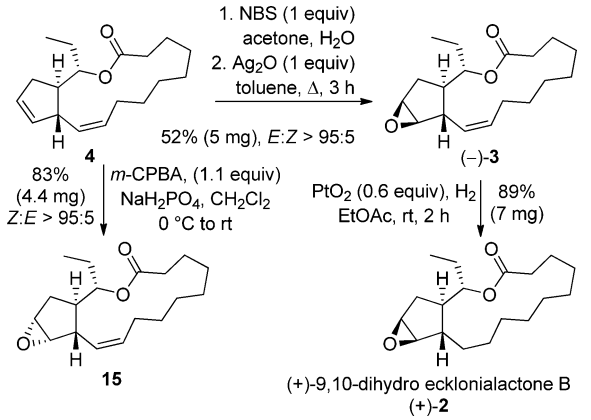
Scheme 1. Synthesis of 12,13-Desepoxy Ecklonialactone



afford the vinyl iodide **12** in excellent overall yield (4 steps, 88%) and a synthetically useful diastereoselectivity (*Z*:*E* > 10:1). Suzuki−Miyaura cross-coupling[20] 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 lactonization[24] which furnished the desired 12,13-desepoxy ecklonialactone **4**.

(10) Brown, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 4100–4102.
(11) Körner, M.; Hiersemann, M. *Org. Lett.* **2007**, *9*, 4979–4982.
(12) Despite being very robust in terms of diastereoselectivity, the reduction is hampered by limited scalability. Attempts to utilize the Corey−Bakshi−Shibata protocol, as described in ref 12a, led to inferior yields or diastereoselectivities, depending on the configuration of the MeCBS catalyst. (a) Gille, A.; Hiersemann, M. *Org. Lett.* **2010**, *12*, 5258–5261. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.
(13) Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 8122–8123.
(14) The reaction conditions for the telescoped process were carefully optimized and controlled, including the screening of various copper salts; however, slightly inconsistent yields and the addition of an excess of CuI (5 equiv) and MeMgBr (10 equiv) were inevitable in our hands.
(15) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
(16) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455–3456.
(17) Liu, H.-J.; Yip, J.; Shia, K.-S. *Tetrahedron Lett.* **1997**, *38*, 2253–2256.
(18) (a) Greenbaum, F. R. *Am. J. Pharm.* **1936**, *108*, 17–22. (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156–4158.
(19) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173–2174.
(20) (a) Miyaura, N.; Ishiyama, T.; Ishikawa, M.; Suzuki, A. *Tetrahedron Lett.* **1986**, *27*, 6369–6372. (b) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014–11015. (c) Schnabel, C.; Hiersemann, M. *Org. Lett.* **2009**, *11*, 2555–2558.
(21) Gill, M.; Rickards, R. W. *J. Chem. Soc., Perkin Trans. 1* **1981**, 599–606.
(22) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625–1627.
(23) (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888–890. (b) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.
(24) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

Scheme 2. Regio- and Diastereoselective Epoxidation



With the diene **4** in hand, opportunities for a regio- and diastereoselective 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 Ag_2O 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-dihydro ecklonialactone 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 catalyst[27] 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 diastereotopos-differentiating RCM[28] 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**.

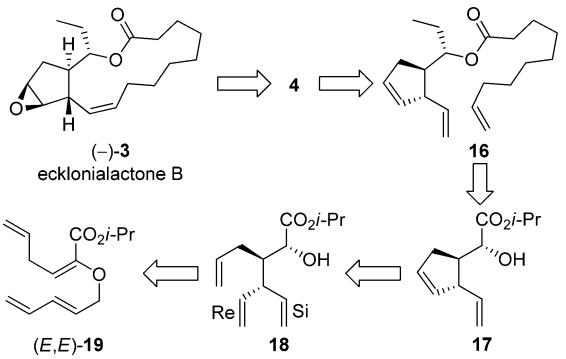


Figure 2. Revised retrosynthesis based on diastereotopos-differentiating RCM.

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 esterification[30] furnished the acetate **21** which was subjected to a stepwise aldol condensation using 4-phenylselenylbutanal[31] 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 elimination[32] 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 catalyst[33] (**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 (≥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

(25) Hickmann, V. A. Schutzgruppenfreie enantioselektive Totalsynthese von Ecklonialacton A und B sowie biologische Tests aktiver Naturstoffe. Ph.D. Dissertation, Technische Universität Dortmund, 2011.

(26) Kurata, K.; Taniguchi, K.; Shiraishi, K.; Suzuki, M. *Phytochemistry* **1993**, *33*, 155–159.

(27) Voorhees, V.; Adams, R. *J. Am. Chem. Soc.* **1922**, *44*, 1397–1405.

(28) (a) Huwe, C. M.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2376–2378. (b) Lautens, M.; Hughes, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 129–131.

(29) Hiersemann, M. *Synthesis* **2000**, 1279–1290.

(30) (a) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069–2076. (b) Neises, B.; Steglich, W. *Angew. Chem.* **1978**, *90*, 556–557.

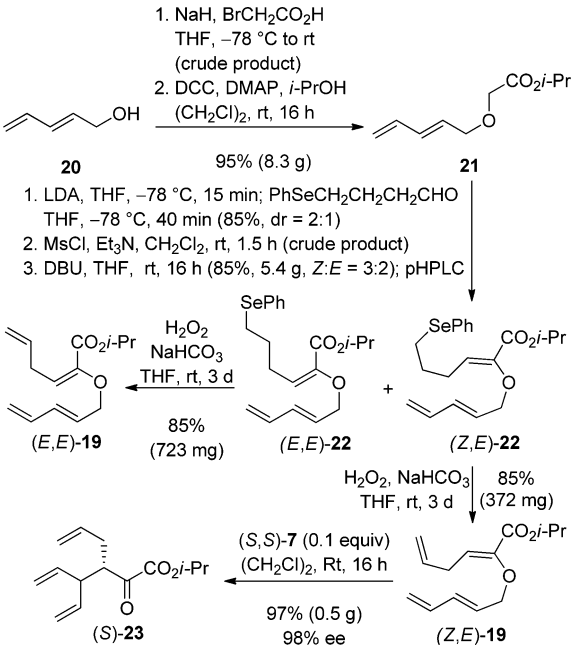
(31) (a) Haraguchi, K.; Tanaka, H.; Hayakawa, H.; Miyasakai, T. *Chem. Lett.* **1988**, 931–934. (b) Haraguchi, K.; Tanaka, H.; Miyasakai, T. *Synthesis* **1989**, 434–436.

(32) (a) Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, *14*, 1979–1982. (b) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697–2699.

(33) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799.

(34) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589–1592.

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

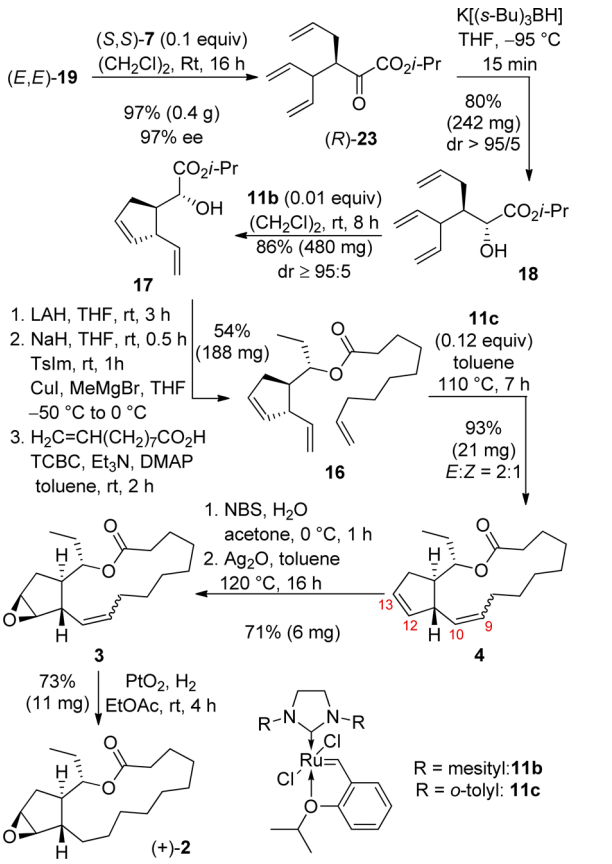


different commercial Ru-based catalysts and conditions, from which in our hands the Stewart–Grubbs catalyst[34] (**11c**) was best-performing in terms of yield, the diene **4** was isolated as mixture of $\Delta^{9,10}$ double bond isomers (*E*:*Z* = 1–4:1, depending on the catalyst and conditions).[35] 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

(35) The search for catalysts that support the selective RCM to macrocyclic 1,2-disubstituted *Z*-cycloalkenes is ongoing; see: (a) Wang, C.; Yu, M.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Chem.—Eur. J.* **2013**, *19*, 2726–2740. (b) Marx, V. M.; Herbert, M. B.; Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2012**, *135*, 94–97.

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 ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.