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# ENANTIOSELECTIVE PROTECTING-GROUP-FREE SYNTHESIS OF (+)-9,10-DIHYDROECKLONIALACTONE B

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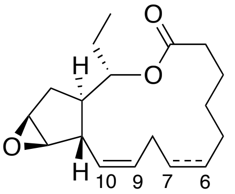
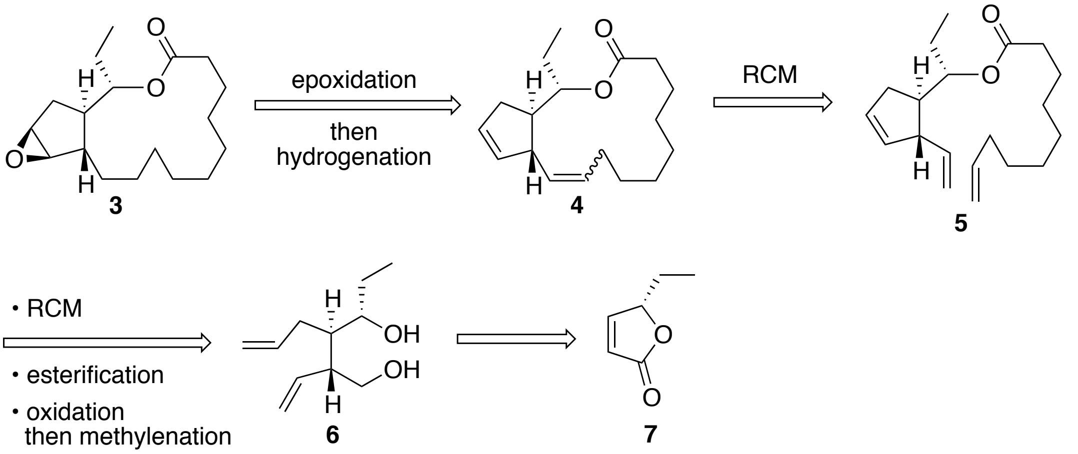
**Abstract** – An enantioselective protecting-group-free route to ecklonialactones, C-18 oxylipins isolated from the brown algae, was demonstrated by the synthesis of (+)-dihydroecklonialactone B from (*E*)-ethyl hex-3-enoate in 17 steps.

As part of our program aimed at the synthesis of natural products having highly substituted cyclopentane rings,[1] we were interested in marine C-18 oxylipins isolated from various brown algae, the parent member of which are ecklonialactone A (**1**) and ecklonialactone B (**2**).[2,3] Although these oxylipins possess characteristic structures consisting of a fused cyclopentane/14-membered macrolactone skeleton with five contiguous stereogenic centers, their biological activities have not been fully examined due to the limited supply from natural sources. Thus, Fürstner's group[4] and Hiersemann's group[5] have undertaken the extensive synthetic studies, resulting in the total syntheses of ecklonialactones A and B and related oxylipins. We report here a novel enantioselective synthesis of (+)-9,10-dihydroecklonialactone B (**3**) without using any protecting groups.[6]



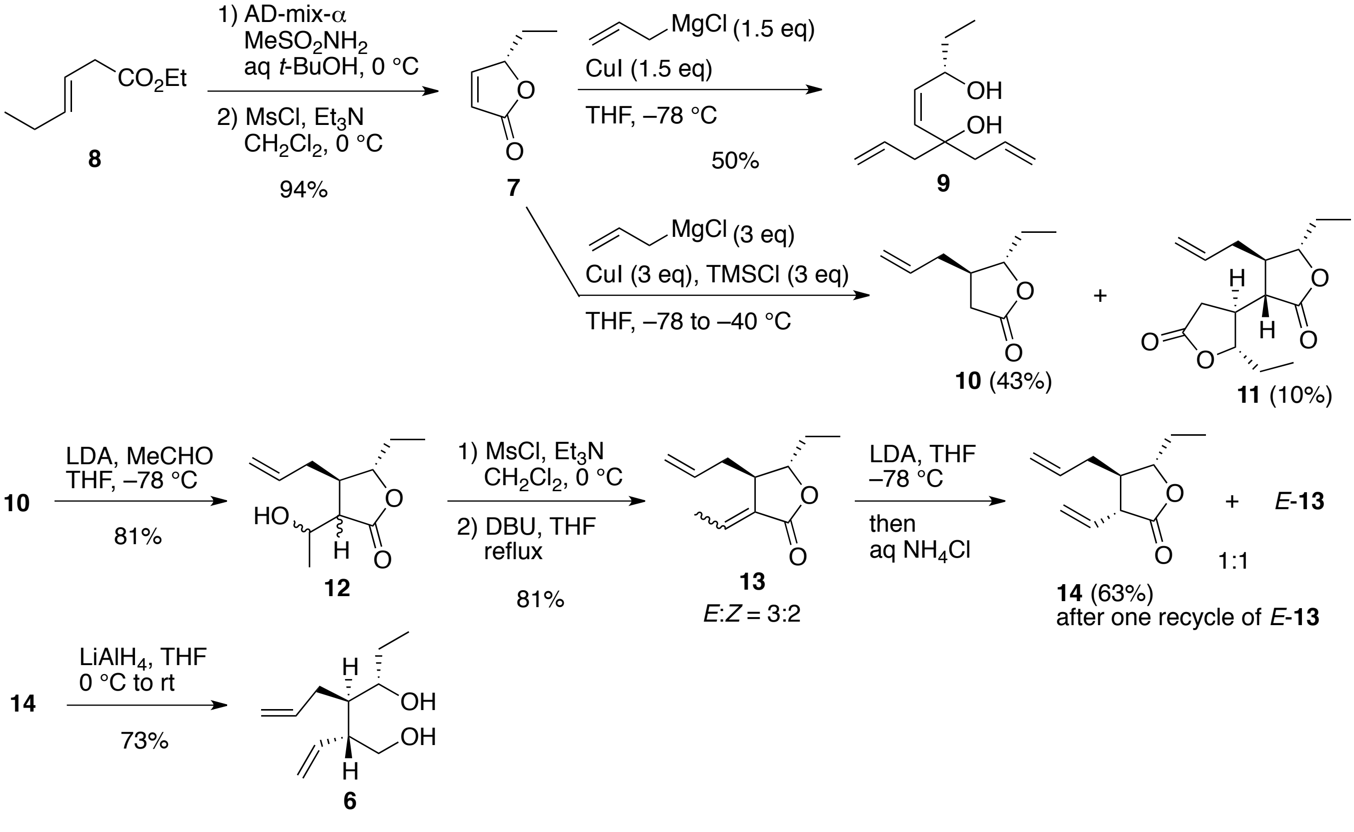
ecklonialactone A (**1**): $\Delta^{6,7}$
ecklonialactone B (**2**)
9,10-dihydroecklonialactone B (**3**)

Since Hiersemann *et al.*[5b,c] demonstrated that the epoxide functionality could be installed on the cyclopentene ring of diene **4** with excellent regio- and stereoselectivity, we selected **4** as a precursor of 9,10-dihydroecklonialactone B (**3**). We envisaged that compound **4** could be obtained from diol **6** via ester **5** by an approach relying on two ring-closing metathesis reactions (Scheme 1). It was assumed that diol **6** would be accessible from known butenolide **7** with high enantiomeric purity by stereoselective installation of vicinal allyl and vinyl groups (Scheme 1).



**Scheme 1**. Retrosynthetic analysis

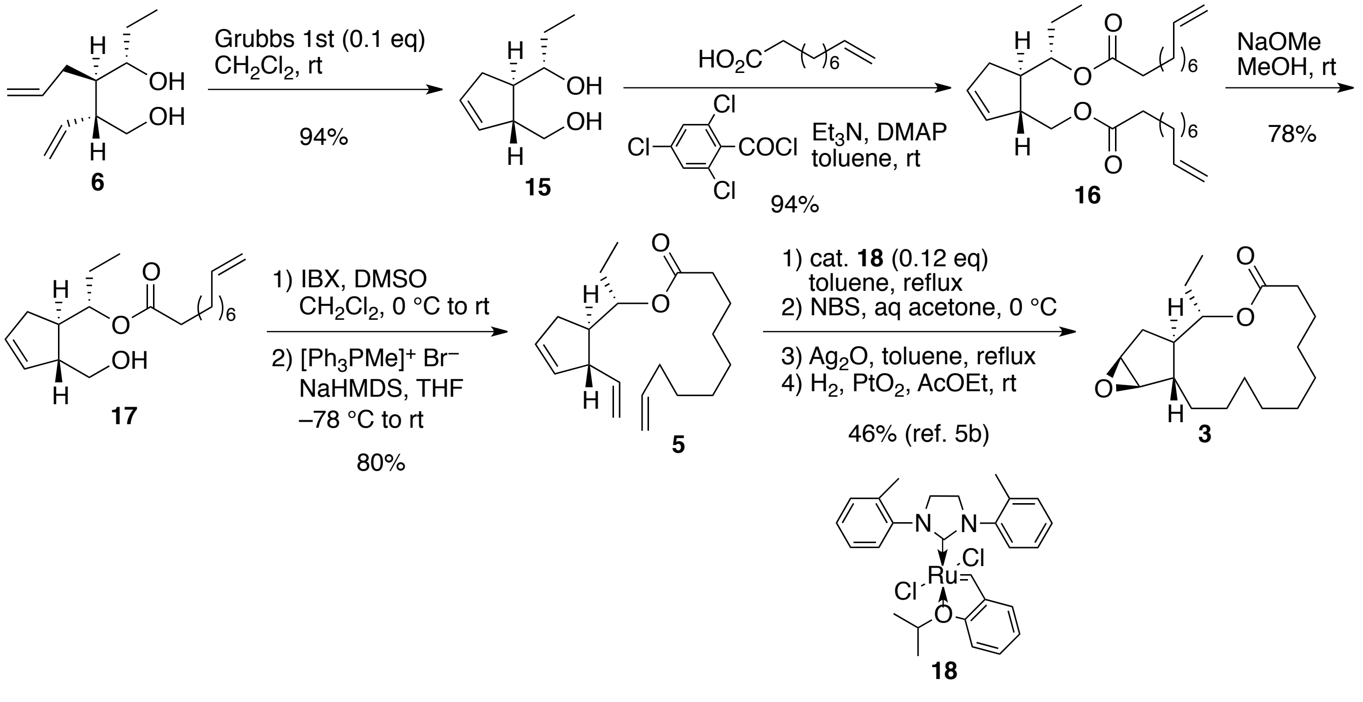
Butenolide **7** was prepared in high enantiomeric purity[7] from ethyl (*E*)-3-hexenoate by asymmetric dihydroxylation using AD-mix-α followed by dehydration of the resulting hydroxy-γ-butyrolactone according to the literature procedure (Scheme 2).[8] We then explored the conjugate addition of an allyl group under various conditions. When the allylation was carried out using allylmagnesium chloride (1.5 eq) in the presence of CuI (1.5 eq) in THF at –78 °C, 1,2-addition product **9** was obtained in 50% yield. On the other hand, when this reaction was conducted using allylmagnesium chloride (3 eq), CuI (3 eq), and trimethylsilyl chloride (3 eq) in THF at –40 °C according to Lipschutz's protocol,[9,10] the desired



**Scheme 2**. Synthesis of diol **6**

1,4-addition product **10** of *trans* configuration[11] was obtained in 43% yield together with bislactone **11**[12] (10% yield). In this particular case, *cis*-isomer of **10** was not isolated. Compound **10** was then converted to α,β-unsaturated lactone **13** as a 3:2 *E*/*Z*-mixture[13] in 67% overall yield by aldol reaction with acetaldehyde followed by dehydration of **12** via the mesylate. Treatment of **13** with LDA at –78 °C in THF followed by quenching of the resulting lithium dienolate gave a 1:1 mixture of **14** and *E*-**13**. These compounds were separated by silica gel column chromatography and the latter was again subjected to the kinetic protonation conditions. As a result of this sequence, **14**[11,14] was obtained in 63% yield from **13**. Compound **14** thus obtained was reduced with $LiAlH_4$ to give diol **6** in 73% yield.

Ring-closing metathesis of diol **6**[15] was found to be promoted cleanly by Grubbs 1st catalyst in $CH_2Cl_2$ at room temperature to deliver cyclopentene **15**[16] in 94% yield (Scheme 3). It is important to note that ring closing metathesis of lactone **14** met with failure under various conditions, possibly due to the appreciable ring strain caused by a five-five *trans*-fused ring system. Condensation of **15** with 9-decenoic acid using 2,4,6-trichlorobenzoyl chloride under Yamaguchi's esterification conditions[17] produced diester **16** in 94% yield, which, upon selective methanolysis with NaOMe in MeOH, provided monoester **17** in 78% yield. IBX oxidation of **17** followed by Wittig olefination of the resulting aldehyde allowed us to obtain Hiersemann's intermediate **5**[5b,18] in 80% yield. Finally, following Hiersemann's procedure,[5b,c] compound **5** was converted to (+)-9,10-dihydroecklonialactone B (**3**) via **4** (2:1 *E*/*Z*-mixture) by a four-step sequence involving ring-closing metathesis, selective epoxidation via a bromohydrin, and hydrogenation. Our synthetic compound **3**[19] exhibited spectral properties identical in all respects to those reported.[5b,c]



**Scheme 3**. Synthesis of 9,10-dihydroecklonialactone B

In conclusion, we have developed an effective method for the enantioselective construction of the fused cyclopentane/14-membered macrolactone skeleton of ecklonialactones, which avoids any protecting group manipulations. The syntheses of ecklonialactones A and B are currently under investigation along our developed methodology.

## ACKNOWLEDGEMENTS

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## SUPPORTING INFORMATION

$^1$H and $^{13}$C NMR spectra of compounds **3-7**, **10**, **13-17** are available.

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7. The specific rotation ($[\alpha]_D^{26}$ +103.9 (*c* 0.80, $CHCl_3$)) was identical with that reported for the sample of >96% ee ($[\alpha]_D^{26}$ +103 (*c* 2.71, $CHCl_3$)). Cf) S. Tsuboi, J. Sakamoto, H. Yamashita, T. Sakai, and

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11. Determined based on the NOESY spectrum.
12. The stereochemistry was tentatively assigned based on mechanistic consideration.
13. Determined based on the $^1$H NMR spectrum.
14. Compound **14**: a clear oil. $[\alpha]_D^{25}$ –14.6 (*c* 1.97, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.80-5.70 (m, 2H), 5.38-5.08 (m, 4H), 4.03 (td, *J* = 8.6, 3.6 Hz, 1H), 3.01 (m, 1H), 2.38-2.21 (m, 2H), 2.1 (m, 1H), 1.89-1.80 (m, 1H), 1.65-1.5 (m, 1H), 1.02 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CHCl_3$) δ 176, 134, 132, 120, 118, 84, 50, 46, 35, 27, 10; FTIR (neat) 3079, 2973, 2928, 1773, 1642, 1179 cm$^{-1}$; HRMS (EI) calcd for $C_{11}H_{16}O_2$ ($M^+$) 180.1150, found 180.1149.
15. For a similar ring closing metathesis, see: H. Miyaoka, Y. Hara, I. Shinohara, T. Kurokawa, and Y. Yamada, *Tetrahedron Lett.*, 2005, **46**, 7945.
16. This compound was correlated to the known TBS ether[5b] by a three-step conversion (i, PivCl, pyridine, $CH_2Cl_2$; ii, TBSCl, imidazole, DMF; iii, DIBAL-H, $CH_2Cl_2$, –78 °C), confirming its absolute structure. The enantiomeric purity was determined to be 94% ee by $^1$H NMR analysis of the corresponding *R*- and *S*-MTPA esters of the above-mentioned TBS ether derivative.
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18. Compound **5**: a clear oil. $[\alpha]_D^{28}$ –113.2 (*c* 1.11, $CHCl_3$) (lit.[5b] $[\alpha]_D^{28}$ –68.3 (*c* 0.98, $CHCl_3$)); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.85-5.66 (m, 3H), 5.49-5.47 (m, 1H), 5.01-4.91 (m, 5H), 3.21 (br s, 1H), 2.47 (dddd, *J* = 16.0, 8.0, 4.0, 2.0 Hz, 1H), 2.27 (t, *J* = 7.6 Hz, 2H), 2.23-2.22 (m, 1H), 2.03 (m, 3H), 1.59 (m, 3H), 1.28 (m, 9H), 0.87 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.0, 143.0, 140.0, 134.0, 130.0, 115.0, 114.0, 78.1, 53.0, 48.0, 36.0, 35.0, 34.0, 29.3, 29.3, 29.01, 29.0, 26.0, 25.0, 9.0; FTIR (neat) 2929, 2856, 1733, 1639, 1459, 1377, 1246, 1175, 1098 cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{20}H_{32}O_2$ ($M^+$) 304.2402, found 304.2400.
19. Compound **3**: a yellow oil. $[\alpha]_D^{28}$ +11.0 (*c* 0.34, $CHCl_3$) (lit.[5b] $[\alpha]_D^{25}$ +12.9 (*c* 0.6, $CHCl_3$)) (lit.[2a] $[\alpha]_D$ +14.5 (*c* 0.55, $CHCl_3$)); $^1$H NMR (500 MHz, $CDCl_3$) δ 4.88 (m, 1H), 3.44 (d, *J* = 2.5 Hz, 1H), 3.31 (d, *J* = 2.0 Hz, 1H), 2.37 (m, 2H), 2.13 (t, *J* = 7.8 Hz, 1H), 1.91-1.82 (m, 3H), 1.82-1.67 (m, 2H), 1.67-1.53 (m, 1H), 1.51-1.21 (m, 15H), 0.81 (t, *J* = 7.5 Hz, 3H ); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.8, 79.1, 61.4, 57.1, 44.3, 39.1, 33.7, 29.1, 28.6, 26.1, 25.8, 25.4, 25.0, 24.9, 24.9, 24.4, 24.3, 8.8; FTIR (neat) 2936, 2857, 1731, 1456, 1363, 1219, 1174, 1084 cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{18}H_{30}O_3$ ($M^+$) 294.2195, found 294.2198.