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An Expeditious Total Synthesis of Both Diastereoisomeric Lipid Dihydroxytetrahydrofurans from *Notheia anomala*

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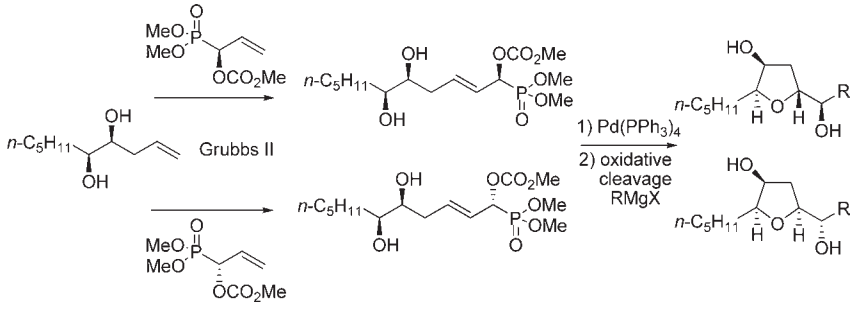
ABSTRACT



Short, high yielding syntheses of both diastereomers of the naturally occurring oxylipids 1 and 2 using a combination of organocatalytic hydroxylation of an aldehyde, alkene cross metathesis, and palladium(0) catalyzed cyclization chemistry (six-step process) are reported. Furthermore, the influence of the catalyst on the cross metathesis reaction of the homoallylic 1,2-diol has been studied in detail.

As new and improved synthetic transformations are discovered, the synthesis of complex organic molecules has become more efficient. The application of new enantio- and chemoselective reactions and new methods of carbon–carbon and carbon–heteroatom bond formation can greatly reduce the number of steps required for a given synthesis.

The nematocidal oxylipids **1** and **2** (Figure 1), isolated from the Australian brown algae *Notheia anomala*,[1] have been targets for synthesis for the past three decades.

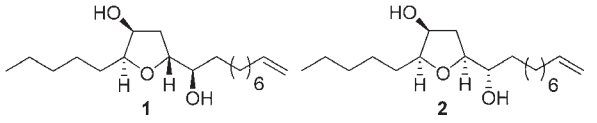


Figure 1. Oxylipids isolated from southern Australian algae *Notheia anomala*.

The biological activity and the challenging 2,5-disubstituted-3-oxygenated tetrahydrofuranyl (thf) motif make them appealing candidates for total synthesis. Perhaps more importantly, the 2,5-disubstituted-3-oxygenated thf motif is an important structural feature found in many biologically active natural products.[2]

Due to the 30 year history, syntheses of the oxy lipids **1** and **2** have evolved with improvements in synthetic methodology. Williams et al. reported the first total synthesis of racemic **1** in 1984.[3] The Williams synthesis required

(1) (a) Capon, R. J.; Barrow, R. A.; Rochfort, S.; Jobling, M.; Skene, C. *Tetrahedron* **1998**, *54*, 2227. (b) Murray, L. M.; Barrow, R. A.; Capon, R. J. *Aust. J. Chem.* **1991**, *44*, 843. (c) Barrow, R. A.; Capon, R. J. *Aust. J. Chem.* **1990**, *43*, 895. (d) Warren, R. G.; Wells, R. J.; Blount, J. F. *Aust. J. Chem.* **1980**, *33*, 891.

(2) For examples, see: (a) Gollner, A; Johann, M. *Org. Lett.* **2008**, *10*, 4701. (b) Li, X.; Li, J.; Mootoo, D. R. *Org. Lett.* **2007**, *9*, 4303. (c) Wang, J.; Pagenkopf, B. L. *Org. Lett.* **2007**, *9*, 3703. (d) Jung, J. H.; Kim, Y. W.; Kim, M. A.; Choi, S. Y.; Chung, Y. K.; Kim, T.-R.; Shin, S.; Lee, E. *Org. Lett.* **2007**, *9*, 3225. (e) Evans, D. A.; Kvaerno, L.; Mudler, J. A.; Raymer, B.; Dunn, T. B.; Beauchamin, A.; Olhava, E. J.; Juhl, M.; Kagechika, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4693. (f) Evans, P. A.; Murthy, V. S.; Roseman, J. D.; Rheingold, A. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 3175.

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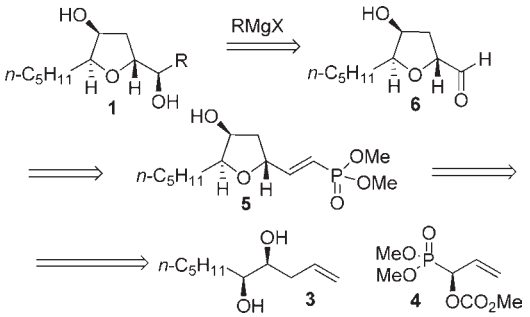
11 steps with an overall yield of 17% from an already advanced intermediate. In addition to a racemic biomimetic synthesis of **1** and **2**,[4] there have been nine unique enantioselective syntheses of **1** with overall yields between 2 and 26% and five enantioselective syntheses of **2** with overall yields between 2 and 37%.[5−8] Only three of these syntheses are able to deliver both naturally occurring diastereoisomers.[7,8] This is not unusual since methods for the synthesis of 2,5-disubstituted tetrahydrofurans are often optimized for either the *cis* or *trans* isomer, but typically not both. Perhaps the most efficient enantioselective synthesis was reported in a 2009 paper by Britton et al., wherein the natural diastereoisomers **1** and **2** were prepared in six steps with 26% and 37% overall yields, respectively.[8]

We recently reported a stereospecific method for the formation of cyclic ethers employing a combination of alkene cross metathesis and Pd(0)-catalyzed cyclization.[9] This method was applied to the synthesis of 2,5-*trans* thf-containing fragments of amphidinolides C and F.[10] Since the cross metathesis and Pd(0)-catalyzed cyclization combination can deliver both the *cis* and *trans* cyclic ethers, it appeared to be ideal for the syntheses of the 2,5-*trans* and 2,5-*cis* oxygenated tetrahydrofuran rings in oxylipids **1** and **2** (Scheme 1). Actually, by careful choice of the coupling partners (e.g., **3** and **4**) in the cross metathesis reaction, any of the 2,5-disubstituted-3-hydroxy thf isomers can be prepared. However, a short enantioselective synthesis of the *syn*-diol **3** was critical to the success of the proposed chemistry.

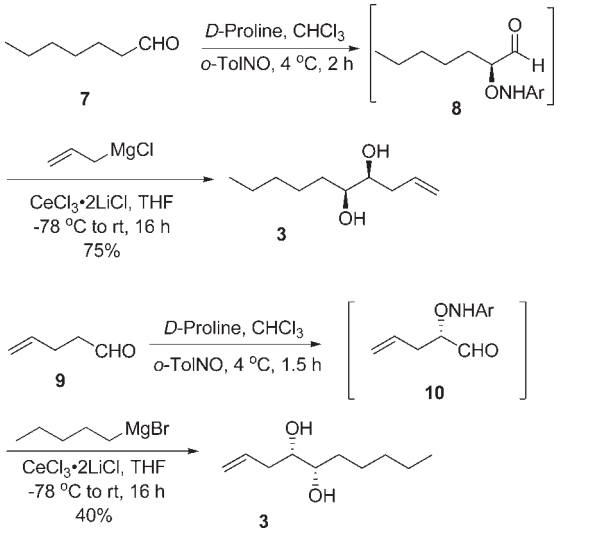
A rapid synthesis of the *syn*-diol **3** was envisaged which employed recent advances in organocatalysis.[11] D-Proline catalyzed nitrosoaldol condensation of heptaldehyde **7** gave the α-aminoxy aldehyde **8**, which was reacted directly with allylmagnesium chloride to furnish the *syn*-diol **3** in 75% isolated yield (Scheme 2) and 5−10% of undesired

Scheme 1. A Retrosynthetic Analysis for the Oxylipids



anti-diol. The diol diastereomers were easily separated by column chromatography.

Scheme 2. Synthesis of *syn*-Diol **3**



Alternatively, *syn*-diol **3** was formed via the D-proline catalyzed nitrosoaldol of 4-pentenal **9** with 2-nitrosotoluene, followed by direct addition of pentylmagnesium bromide to the aminoxy aldehyde **10**. However, in this route the isolated yield of the *syn*-diol **3** was considerably lower (40%).

The cross metathesis reaction between *syn*-diol **3** and the (*S*)-carbonate **4** (> 95% ee) using Grubbs second generation catalyst and CuI as a cocatalyst did not proceed as anticipated (Scheme 3).[9,10,12] Unfortunately, dienal **12** was the major isolated product and the desired cross metathesis product **11** was only a minor component.

Although structurally similar diols undergo successful cross metathesis,[13] there are reports of subsequent cleavge

(3) Williams, D. R.; Harigaya, Y.; Moore, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 2641. The method used was capable of forming both the 2,5-*cis* and -*trans* thf isomers.

(4) (a) Capon, R. J.; Barrow, R. A. *J. Org. Chem.* **1998**, *63*, 75. (b) Capon, R. J.; Barrow, R. A.; Skene, C.; Rochfort, S. *Tetrahedron Lett.* **1997**, *38*, 7609.

(5) For enantioselective syntheses of **1**, see: (a) Nesbitt, C. L.; McErlean, C. S. P. *Tetrahedron Lett.* **2009**, *50*, 6318. (b) de la Pradilla, R. F.; Castellanos, A.; Osante, I.; Colomer, I.; Sanchez, M. I. *J. Org. Chem.* **2009**, *74*, 170. (c) de la Pradilla, R. F.; Castellanos, A. *Tetrahedron Lett.* **2007**, *48*, 37. (d) Mori, Y.; Sawada, T.; Furukawa, H. *Tetrahedron Lett.* **1999**, *40*, 731. (e) Chikashita, H.; Nakamura, Y.; Uemura, H.; Itoh, K. *Chem. Lett.* **1993**, 477. (f) Gurjar, M. K.; Mainkar, P. S. *Heterocycles* **1990**, *31*, 407. (g) Hatakeyama, S.; Sakurai, K.; Saijo, K.; Takano, S. *Tetrahedron Lett.* **1985**, *26*, 1333.

(6) For enantioselective syntheses of **2**, see: (a) Gadikota, R. R.; Callam, C. S.; Lowary, T. L. *J. Org. Chem.* **2001**, *66*, 9046. (b) Yoda, H.; Maruyama, K.; Takabe, K. *Tetrahedron: Asymmetry* **2001**, *12*, 1403.

(7) For enantioselective syntheses of both **1** and **2**, see: (a) Nesbitt, C. L.; McErlean, C. S. P. *Org. Biomol. Chem.* **2011**, *9*, 2198. (b) Gracia, C.; Martin, T.; Martin, V. S. *J. Org. Chem.* **2001**, *66*, 1420. (c) Gracia, C.; Soler, M. A.; Martin, V. S. *Tetrahedron Lett.* **2000**, *41*, 4127.

(8) (a) Kang, B.; Mowat, J.; Pinter, T.; Britton, R. *Org. Lett.* **2009**, *11*, 1717. (b) Mowat, J.; Kang, B.; Fonovic, B.; Dudding, T.; Britton, R. *Org. Lett.* **2009**, *11*, 2057.

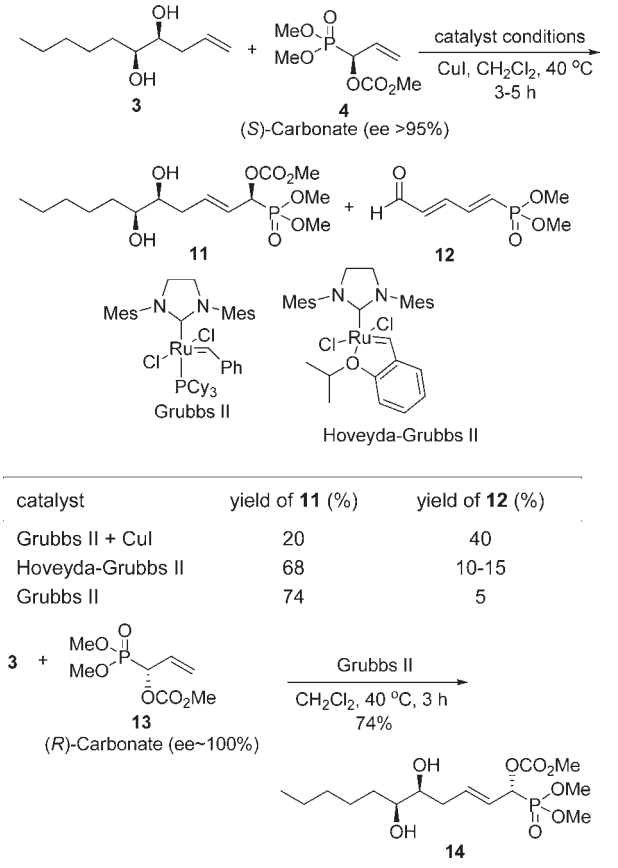
(9) He, A.; Sutivisedsak, N.; Spilling, C. D. *Org. Lett.* **2009**, *11*, 3124.

(10) Roy, S.; Spilling, C. D. *Org. Lett.* **2010**, *12*, 5326.

(11) Jiao, P.; Kawasaki, M.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 3333.

(12) (a) He, A.; Yan, B.; Thanavaro, A.; Spilling, C. D. *J. Org. Chem.* **2004**, *69*, 8643. (b) Rivard, M.; Blechert, S. *Eur. J. Org. Chem.* **2003**, 2225. (c) Voigtritter, K; Ghorai, S.; Lipshutz, B. H. *J. Org. Chem.* **2011**, *76*, 4697.

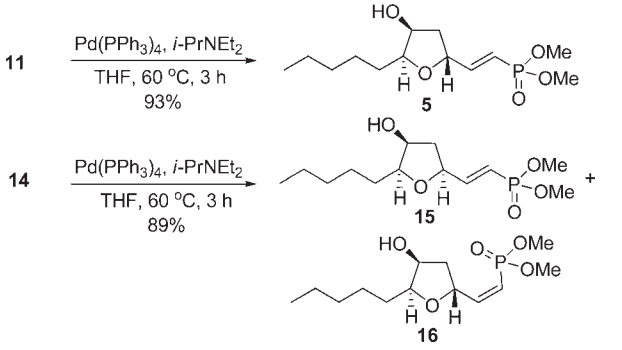
Scheme 3. Oxidative Cleavage of the *syn*-Diol **3** by Grubbs II–CuI Catalyst System



of the diol.[14–16] We use CuI as a cocatalyst to improve the reaction rate of cross metathesis with the phosphono allylic carbonate **4**.[9,10] It is thought that CuI acts as a phosphine scavenger to produce a 14-electron ruthenium species, but this also destabilizes the active metal alkylidene species in the process leading to decomposition.[12c,17] The ruthenium species formed as a result of decomposition can, in the presence of an oxidant, cleave the diol.[14b] It appeared that the solution would be the use of a more robust catalyst system.

Cross metathesis (CM) of *syn*-diol **3** and phosphono allylic carbonate **4** using a Hoveyda–Grubbs II catalyst led to a slower reaction but with significantly improved product distribution. The oxidative cleavage was reduced to < 15% (Scheme 3). Perhaps more surprisingly, the CM reaction of **3** and **4** using Grubbs II (and no CuI) resulted in further improvement in the yield of the product **11** to 74% and diminished the oxidative cleavage to < 5%. Likewise, the CM reaction with the Grubbs II catalyst between *syn*-diol **3** and (*R*)-carbonate **13** yielded 74% of the diastereomeric phosphono allylic carbonate **14** (Scheme 3).

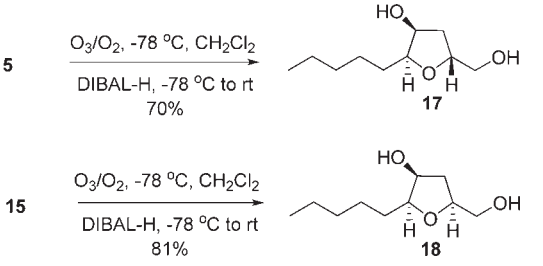
Scheme 4. Synthesis of the 2,5-*trans* and 2,5-*cis*-Thf Vinyl Phosphonates



Palladium(0)-catalyzed cyclization of **11** proceeded smoothly to give the 2,5-*trans*-tetrahydrofuranyl-(*E*)-vinyl phosphonate **5** in 93% isolated yield. Similarly, 2,5-*cis*-tetrahydrofuranyl-(*E*)-vinyl phosphonate **15** was formed in 89% isolated yield, along with 5% of the 2,5-*trans*-tetrahydrofuranyl-(*Z*)-vinyl phosphonate **16** (Scheme 4), which was separated by column chromatography.

The tetrahydrofuranyl vinyl phosphonates were converted into the corresponding tetrahydrofuranyl alcohols for complete characterization (Scheme 5). The alcohols are also potentially useful intermediates. The vinyl phophonates **5** and **15** were subjected to ozonolysis followed by treatment of the ozonide with a large excess of DIBAL-H to furnish the diols **17** and **18** in 70% and 81% isolated yields, respectively. Reduction of the ozonide derived from vinyl phosphonate **5** with an excess of $NaBH_4$ was faster and higher yielding, but 5% of the C(9) epimer of **17** was also formed.

Scheme 5. Ozonolysis of the Vinyl Phosphonates



Finally, suitable conditions for the transformation of the vinyl phosphonates to their respective furanyl aldehydes were investigated with the goal of achieving a short and

(13) (a) Kim, S.-G.; Park, T.-H.; Kim, B. J. *Tetrahedron Lett.* **2006**, *47*, 6369. (b) Roulland, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3762.

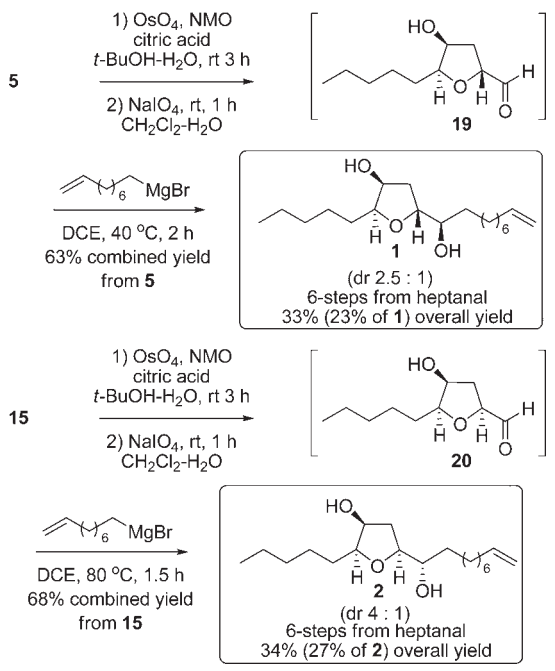
(14) (a) Chunguang, H.; Uemura, D. *Tetrahedron Lett.* **2008**, *49*, 6988. (b) Ma, C.; Schiltz, S.; Le Goff, X. F.; Prunet, J. *Chem.—Eur. J.* **2008**, *14*, 7314.

(15) The oxidative cleavage is believed to be mediated by a high oxidation state ruthenium complex derived from Grubbs II catalyst in the presence of an oxidant; see ref 14b.

(16) We believe aldehyde **12** is formed by oxidative cleavage of the gycol in **11**, followed by elimination of the methyl carbonate.

(17) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887.

Scheme 6. Synthesis of Oxylipids **1** and **2**



efficient total synthesis of oxylipids **1** and **2**. Initially, the vinyl phosphonates were subjected to ozonolysis followed by reduction of the ozonide with various reagents, including Me_2S and polystyrene immobilized PPh_3 (PS-PPh_3). Unfortunately, the results were not satisfactory. Reduction of the ozonide with PS-PPh_3 in CH_2Cl_2/MeOH gave a mixture of stable acetals and hemicaetals, which failed to react with 8-nonenylmagnesium bromide. However, reduction of the ozonide with PS-PPh_3 in CH_2Cl_2, followed by treatment with 8-nonenylmagnesium bromide, did give the desired product **1**, albeit in a low 30% yield.

In an effort to improve the yield of the last step, we switched to oxidative cleavage of the vinyl phosphonate using OsO_4/$NaIO_4$. The typical one pot procedure using a mixture of OsO_4 and $NaIO_4$ in dioxane–water was extremely slow and failed to reach completion after 5 days. However, the two-step process of dihydroxylation of the vinyl phosphonate **5** with OsO_4 and NMO, followed by glycol cleavage using $NaIO_4$ in CH_2Cl_2–H_2O, furnished the aldehyde **19**. The hydroxylated tetrahydrofuranyl aldehydes are highly unstable, and therefore aldehyde **19** was immediately subjected to the addition of 8-nonenylmagnesium bromide without further purification (Scheme 6).[8] The *trans*-thf containing oxylipid **1** was formed as the major product along with its column separable C(10)-epimer in a 2.5:1 ratio and 63% combined yield. Following the same reaction sequence, C9/C10 epimeric natural product **2** was prepared from vinyl phosphonate **15** as the major product along with its column separable C(10)-epimer in a 4:1 ratio in 68% combined yield. The spectral data of the natural products are in complete agreement with those reported in the literature.

In summary, we report short, high yielding syntheses of the oxylipids **1** and **2**. A combination of organocatalytic hydroxylation of an aldehyde, alkene cross metathesis, and palladium(0) cyclization provides very efficient syntheses (six steps) of the natural diastereomeric oxylipids **1** and **2** in 23% and 27% overall yield, respectively.

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Supporting Information Available. Detailed experimental procedures and full spectroscopic data for all new compounds. The material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.