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anti-Diols from α-Oxyaldehydes: Synthesis and Stereochemical Assignment of Oxylipins from *Dracontium loretense*

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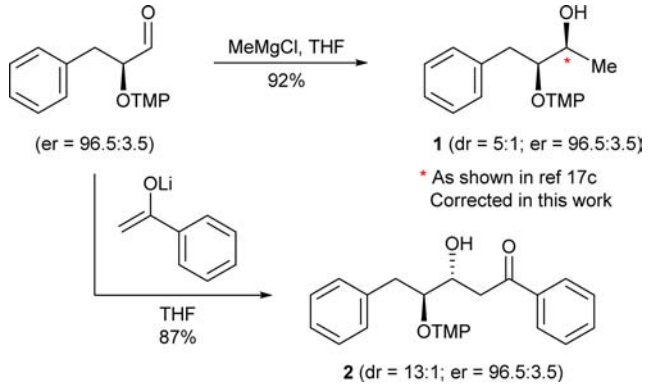
Supporting Information

ABSTRACT: Differentially protected 1,2-diols were synthesized by enantioselective aldehyde α-oxygenation followed by organomagnesium or -lithium addition. Contrary to a previous report, the resultant diols possess an *anti* configuration. Good selectivity was achieved regardless of the hybridization state of the nucleophile or the presence or absence of branching. This method was applied to short syntheses of all possible stereoisomers of two oxylipins from *Dracontium loretense* with incomplete stereochemical assignments. Spectroscopic comparisons between the synthetic and natural oxylipins led to unambiguous assignments.

Chiral 1,2-diols are commonly found in natural products. Sharpless asymmetric dihydroxylation[1] offers a general means to prepare chiral *syn*-1,2-diols from *trans* alkenes but often gives only modest enantioselectivity when preparing *anti*-1,2-diols. Many alternative approaches to chiral *anti*-1,2-diols involve carbon−carbon bond formation. Addition of α-oxycarbonyl compounds[2−4] or functionalized allyl reagents[5,6] to aldehydes forges the central carbon−carbon bond. Addition to α-oxyaldehydes with substrate-,[7,8] reagent-,[9] or catalyst-based[10] stereocontrol constructs the carbon−carbon bond next to the diol. Ring-opening of a hydroxy epoxide[11] (optionally prepared by kinetic resolution of a racemic allylic alcohol[12]) affords carbon−carbon bond formation one position further removed. Other approaches to *anti*-1,2-diols include functional group transformations (e.g., epoxide opening[13] or allylic substitution[14]) and desymmetrization reactions.[15] Addition to α-oxyaldehydes is appealing because of its broad substrate scope, but chiral α-oxyaldehydes often require multiple synthetic steps to prepare. Enantioselective aldehyde α-oxygenation[16,17] offers direct access to α-oxyaldehydes, potentially streamlining the synthesis of *anti*-1,2-diols. Herein we report that aldehyde α-oxygenation followed by organomagnesium or -lithium addition yields differentially masked *anti*-1,2-diols, not the previously reported *syn* diols.[17c] We demonstrate the substrate scope of this process and apply it to the synthesis and stereochemical assignment of oxylipins from the Peruvian plant *Dracontium loretense*.[18]

We selected the imidazolidinone-catalyzed incorporation of TEMPO[17] as our starting point because, unlike nitrosobenzene-based methods,[16] this reaction delivers stable α-oxyaldehydes. MacMillan reported that Grignard reagents (see **1**, Scheme 1) and enolates (see **2**) may be added with no degradation of enantiomeric ratio.[17c] However, we were puzzled that Grignard product **1** appeared to be formed through a chelation-controlled addition, yet aldol product **2** appeared to be the result of a polar Felkin−Anh addition.[19]

Scheme 1. Some Published α-Oxyaldehyde Reactions[a]



[a]See ref 17c. TMP = 2,2,6,6-tetramethylpiperidinyl.

Intrigued by this stereochemical oddity, we decided to investigate a related Grignard reaction. Toward that end, organocatalytic α-oxygenation of hexanal (**3**) (Scheme 2) gave oxyaldehyde **5** in 77% yield and 89:11 er. Superior enantioselectivity often can be attained using a tryptophan-derived catalyst,[17c] but the more lengthy synthesis of that catalyst encouraged us to use imidazolidinone **4**. Table 1 summarizes our investigations into the conversion of aldehyde **5** into alcohol **6a**. Conducting the addition of *n*-butylmagnesium chloride in ether (Table 1, entry 1) afforded only modest selectivity and yield; significant aldehyde reduction to the corresponding primary alcohol was observed. Changing the solvent to tetrahydrofuran (Table 1, entry 2) gave better selectivity and suppressed primary alcohol formation. Both yield and selectivity improved at lower temperature (Table 1, entry 3). Using *n*-butyllithium in place of *n*-butylmagnesium

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Scheme 2. Assigning Relative Stereochemistry

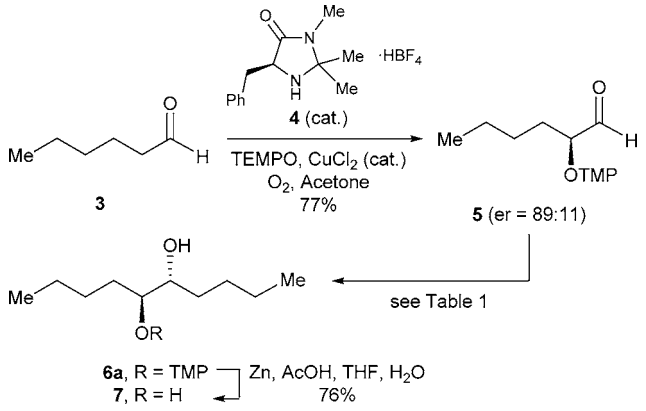
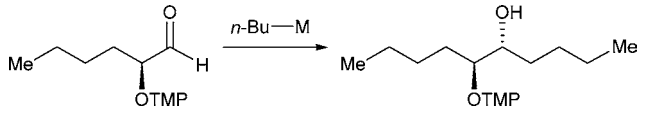


Table 1. Tuning Diastereoselectivity[a]



5 **6a**

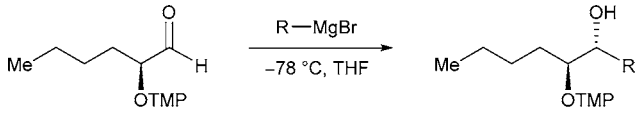
entry	M	solvent	temp (°C)	dr[b]	yield[c] (%)
1	MgCl	Et_2O	0	4:1	60[d]
2	MgCl	THF	0	6:1	70
3	MgCl	THF	−78	10:1	86
4	Li	THF	−78	6:1	81
5	Li	hexanes	−78	12:1	84

[a]0.8−1.0 mmol scale. [b]Determined by ^{1}H NMR analysis of the crude mixture. [c]Isolated yield of a mixture of diastereomers. [d]Estimated by ^{1}H NMR analysis of the crude mixture. The major byproduct was the primary alcohol derived from aldehyde reduction.

chloride (Table 1, entry 4) led to degraded diastereoselectivity, but the selectivity could be rescued by employing hexanes as the solvent (Table 1, entry 5). To determine the relative configuration of differentially masked 1,2-diol **6a**, the 2,2,6,6-tetramethylpiperidinyl (TMP) group was reductively cleaved (Zn, AcOH)[20] to give diol **7** (Scheme 2) in 76% yield. NMR spectroscopic comparisons against the known *syn*[21] and *anti*[22] stereoisomers established the *anti* configuration for diol **7** and its precursor (**6a**).

Since the functional group tolerance of both reactions in this two-step diol synthesis is well established, we focused on evaluating stereoselectivity using different classes of Grignard reagents. Addition of isopropylmagnesium bromide (Table 2, entry 2) gave good diastereoselectivity, but significant reduction of aldehyde **5** to the corresponding primary alcohol was observed. Premixing with cerium(III) chloride[23] (Table 2, entry 3) suppressed formation of the undesired primary alcohol, but also resulted in some degradation of diastereoselectivity. Excellent selectivities were observed in the additions of sp^2 nucleophiles (Table 2, entries 4−6). Selectivity of ethynylmagnesium bromide addition was somewhat lower (Table 2, entry 7), possibly due to reduced steric interactions. The reaction is not only general, but also scalable; in the total synthesis below, a related organolithium addition was performed on 15 mmol scale. Many of the stereoisomer mixtures (**6c−f**) can be separated by routine silica gel flash chromatography; in all of these cases the major product eluted first, facilitating its isolation.

Table 2. Varying the Carbon Nucleophile[a]



5 **6a−f**

entry	**6**, R	dr[b]	yield[c] (%)
1[d]	**6a**, *n*-Bu	10:1	86
2	**6b**, *i*-Pr	10:1	35[e]
3[f]	**6b**, *i*-Pr	6:1	85
4	**6c**, CH=CH_2	>20:1	89 (78)[g]
5	**6d**, C(Me)=CH_2	>20:1	84 (79)[g]
6	**6e**, Ph	14:1	77 (73)[g]
7	**6f**, C≡CH	8:1	83 (67)[g]

[a]1.0 mmol scale. [b]Determined by ^{1}H NMR analysis of the crude mixture. [c]Isolated yield of a mixture of diastereomers. [d]Used *n*-butylmagnesium chloride. [e]Estimated by ^{1}H NMR analysis. Major product was primary alcohol derived from aldehyde reduction. [f]1.5 equiv of $CeCl_3$ added. [g]Isolated yield of a single diastereomer.

Surprisingly, the hydroxyl proton of compounds **6a−f** consistently appeared in the ^{1}H NMR spectrum in $CDCl_3$ at ca. 2 ppm for the major diastereomer (**6a**, 2.03 ppm) and at ca. 7 ppm for the minor diastereomer (*epi*-**6a**, 7.28 ppm). We therefore assigned the *anti* configuration to all six major products. We also used this built-in stereochemical probe to correct the stereochemistry of Grignard product **1** (Scheme 1) (hydroxyl proton at 2.14 ppm) and confirm the stereochemistry of aldol product **2** (hydroxyl proton at ca. 2.9 ppm).

The above chemistry was applied to the synthesis of all stereoisomers of oxylipin **16** (Scheme 3) in order to assign the stereochemistry of two isomeric natural products from *D. loretense* with incomplete stereochemical assignments. One oxylipin has an *anti* diol at C9 and C10 (as in Scheme 3) and is an immunostimulant; the other has a *syn* diol (as in Scheme 4) and is inactive.[18] Despite four prior syntheses,[24] the configurations of these oxylipins remained in doubt. The unfortunate choice by three groups[24a−c] to obtain NMR spectra of their synthetic material in a solvent ($CDCl_3$) different from that used by the isolation team (CD_3OD) made comparisons with the natural oxylipins impossible. Recently, one group[24d] obtained NMR spectra in CD_3OD but compared their spectroscopic data only against data for another synthetic oxylipin.

Our synthesis commenced with organocatalytic α-oxygenation of decanal (**8**). The low cost of decanal and the expectation of a second enantioenriching step encouraged us to again select imidazolidinone **4** over more expensive alternatives. Along with cupric chloride, imidazolidinone **4** catalyzed oxidative incorporation of TEMPO to give α-oxyaldehyde **9** in 79% yield and 86:14 er (20 mmol scale).[25] Addition of lithio species **11**[26] afforded alcohol **12** as an 8:1 mixture of chromatographically separable isomers; the major product was isolated in 79% yield (15 mmol scale) with no degradation of enantiomeric ratio. Scrupulous removal of oxygen was critical to the lithiation of distannane **10**. Use of distannane **10** that had previously been exposed to air and not deoxygenated afforded a reactant that evolved a gas (not yet identified) upon exposure to electrophiles (e.g., aldehyde **9** or water).

Silylation of alcohol **12** and Stille cross-coupling[27] with acid chloride **13** afforded enone **14** in 77% yield over two steps. Asymmetric enone reduction was effected by borane−dimethyl

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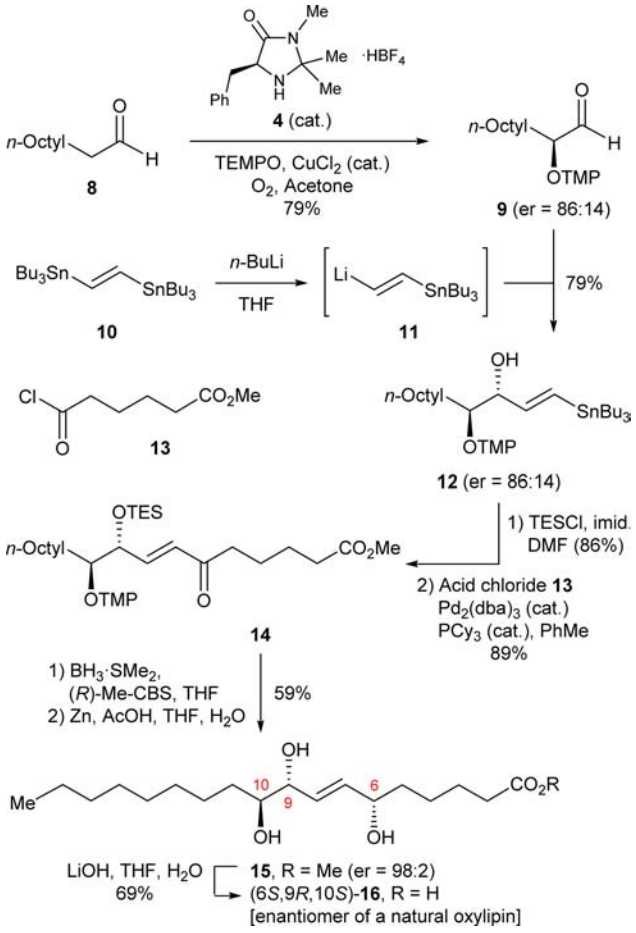
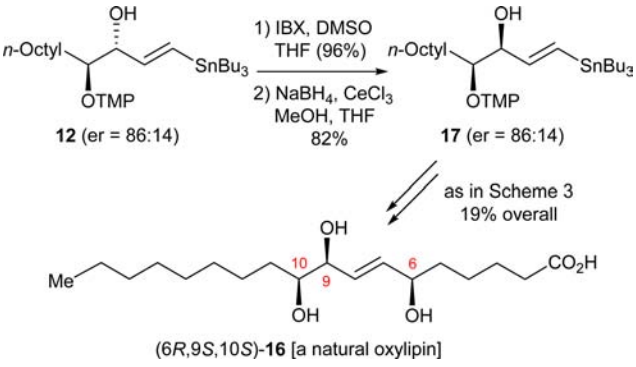
Scheme 3. Synthesis of Oxylipin (6*S*,9*R*,10*S*)-16



Scheme 4. Synthesis of Oxylipin (6*R*,9*S*,10*S*)-16



sulfide complex in the presence of the (*R*)-Me-CBS oxazaborolidine[28] to give a 6:1 mixture of diastereomers.[29] These isomers became chromatographically separable after zinc- and acetic acid-mediated cleavage of the TES and TMP moieties; triol **15** was isolated as a single diastereomer in 59% yield over two steps. The additional enantioenrichment during the CBS reduction delivered material with 98:2 er. Ester hydrolysis (69% yield) completed the synthesis of oxylipin (6*S*,9*R*,10*S*)-**16**. The C6 epimer (6*R*,9*R*,10*S*)-**16** (see the Supporting Information) was prepared similarly. Spectroscopic comparisons of these two C6-epimeric synthetic compounds with the published data for the natural substances revealed one of the natural oxylipins from *D. loretense* to be (6*R*,9*S*,10*R*)-**16** (enantiomer of the compound shown in Scheme 3), not (6*R*,9*R*,10*S*)-**16** as previously claimed.[24c,30,31] Only seven steps long, our synthesis is tied for the shortest[32] to oxylipins containing the 3-en-1,2,5-triol moiety. Furthermore, it is significantly shorter than other syntheses of related oxylipins containing an *anti*-1,2-diol (11−19 linear steps).[24a,c,d,33]

The above diol synthesis currently cannot provide *syn* diols directly. However, *syn* diols can be prepared through an oxidation−reduction sequence. As shown in Scheme 4, IBX oxidation of alcohol **12** followed by Luche reduction (11:1 dr) provided chromatographically separable epimer **17** in 79% yield over two steps with no degradation of enantiomeric ratio. Alcohol **17** was converted into oxylipins (6*R*,9*S*,10*S*)-**16** (shown in Scheme 4) and C6 epimer (6*S*,9*S*,10*S*)-**16** in the same manner as described in Scheme 3 (see the Supporting Information); spectral comparisons revealed one of the natural oxylipins from *D. loretense* to be (6*S*,9*S*,10*S*)-**16**. Thus, the two oxylipins from *D. loretense* are C10 epimers of each other.

In conclusion, aldehyde α-oxygenation followed by addition of an organomagnesium or -lithium reagent is a promising means to access differentially masked *anti*-1,2-diols from simple aldehydes. The utility of this approach and the suitability of the 2,2,6,6-tetramethylpiperidinyl moiety as an alcohol masking group were demonstrated in the concise synthesis of all possible diastereomers of the oxylipins isolated from *D. loretense*. This synthetic work led to unambiguous stereochemical assignment of the natural oxylipins. Efforts are under way to extend this method to the use of other carbon nucleophiles and to improve the stereochemical flexibility so that both *syn*- and *anti*-1,2-diols may be prepared directly.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and graphical NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

(2) Selected methods featuring chiral auxiliaries: (a) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1984**, 753−756. (b) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem.* **1992**, *57*, 1961−1963. (c) Crimmins, M. T.; McDougall, P. J. *Org. Lett.* **2003**, *5*, 591−594.

(3) Selected methods featuring chiral small molecule catalysts: (a) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386−7387. (b) Yoshikawa, N.; Suzuki, T.; Shibasaki, M. *J. Org. Chem.* **2002**, *67*, 2556−2565. (c) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152−2154.

(d) Denmark, S. E.; Chung, W.-j. *Angew. Chem., Int. Ed.* **2008**, *47*, 1890−1892.
(4) Enzymatic method: Fessner, W.-D.; Sinerius, G.; Schneider, A.; Dreyer, M.; Schulz, G. E.; Badia, J.; Aguilar, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 555−558.
(5) Selected methods featuring chiral auxiliaries: (a) Barrett, A. G. M.; Malecha, J. W. *J. Org. Chem.* **1991**, *56*, 5243−5245. (b) Roush, W. R.; Grover, P. T. *Tetrahedron* **1992**, *48*, 1981−1998. (c) Brown, H. C.; Narla, G. *J. Org. Chem.* **1995**, *60*, 4686−4687. (d) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1996**, *61*, 105−108. (e) Hunt, J. A.; Roush, W. R. *J. Org. Chem.* **1997**, *62*, 1112−1124. (f) Yamamoto, Y.; Miyairi, T.; Ohmura, T.; Miyaura, N. *J. Org. Chem.* **1999**, *64*, 296−298. (g) Chen, M.; Handa, M.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *131*, 14602−14603.
(6) Method featuring chiral catalyst: Han, S. B.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 1760−1761.
(7) (a) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828−5835. (b) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199−2204. (c) Anh, N. T.; Eisenstein, O.; Lefour, J.-M.; Dâu, M.-E. T. H. *J. Am. Chem. Soc.* **1973**, *95*, 6146−6147.
(8) (a) Banfi, L.; Bernardi, A.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Org. Chem.* **1984**, *49*, 3784−3790. (b) Iio, H.; Mizobuchi, T.; Tsukamoto, M.; Tokoroyama, T. *Tetrahedron Lett.* **1986**, *27*, 6373−6376. (c) Savall, B. M.; Powell, N. A.; Roush, W. R. *Org. Lett.* **2001**, *3*, 3057−3060. (d) Sa-ei, K.; Montgomery, J. *Org. Lett.* **2006**, *8*, 4441−4443.
(9) (a) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017−3020. (b) Marshall, J. A.; Eidam, P. *Org. Lett.* **2004**, *6*, 445−448.
(10) Luanphaisarnnont, T.; Ndubaku, C. O.; Jamison, T. F. *Org. Lett.* **2005**, *7*, 2937−2940.
(11) Selected recent examples: (a) O'Sullivan, T. P.; Vallin, K. S. A.; Shah, S. T. A.; Fakhry, J.; Maderna, P.; Scannell, M.; Sampaio, A. L. F.; Perretti, M.; Godson, C.; Guiry, P. J. *J. Med. Chem.* **2007**, *50*, 5894−5902. (b) Garbe, L.-A.; Morgenthal, K.; Kuscher, K.; Tressl, R. *Helv. Chim. Acta* **2008**, *91*, 993−1007. (c) Singh, S.; Guiry, P. J. *J. Org. Chem.* **2009**, *74*, 5758−5761. (d) Show, K.; Gupta, P.; Kumar, P. *Tetrahedron: Asymmetry* **2011**, *22*, 1212−1217.
(12) (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237−6240. (b) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687−5696.
(13) (a) Lim, S. M.; Hill, N.; Myers, A. G. *J. Am. Chem. Soc.* **2009**, *131*, 5763−5765. (b) Albrecht, L.; Jiang, H.; Dickmeiss, G.; Gschwend, B.; Hansen, S. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 9188−9196.
(14) (a) Park, J. K.; McQuade, D. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 2717−2721. (b) Kim, D.; Lee, J. S.; Kong, S. B.; Han, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 4203−4206.
(15) (a) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67−70. (b) Arai, T.; Mizukami, T.; Yanagisawa, A. *Org. Lett.* **2007**, *9*, 1145−1147. (c) Hartung, J.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2014**, *53*, 3885−3888.
(16) (a) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247−4250. (b) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808−10809. (c) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293−8296.
(17) (a) Sibi, M. P.; Hasegawa, M. *J. Am. Chem. Soc.* **2007**, *129*, 4124−4125. (b) Van Humbeck, J. F.; Simonovich, S.; Knowles, R. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 10012−10014. (c) Simonovich, S. P.; Van Humbeck, J. F.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 58−61.
(18) Benavides, A.; Napolitano, A.; Bassarello, C.; Carbone, V.; Gazzerro, P.; Malfitano, A. M.; Saggese, P.; Bifulco, M.; Piacente, S.; Pizza, C. *J. Nat. Prod.* **2009**, *72*, 813−817.
(19) While this manuscript was being prepared, the MacMillan group reported the use of related aldol reactions to synthesize pentoses: Peifer, M.; Berger, R.; Shurtleff, V. W.; Conrad, J. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 5900−5903.
(20) Boger, D. L.; Garbaccio, R. M.; Jin, Q. *J. Org. Chem.* **1997**, *62*, 8875−8891.
(21) Plietker, B. *Org. Lett.* **2004**, *6*, 289−291.
(22) Rosatella, A. A.; Afonso, C. A. M. *Adv. Synth. Catal.* **2011**, *353*, 2920−2926.
(23) Imamoto, T. *Pure Appl. Chem.* **1990**, *62*, 747−752.
(24) (a) Chatterjee, S.; Kanojia, S. V.; Chattopadhyay, S.; Sharma, A. *Tetrahedron: Asymmetry* **2011**, *22*, 367−372. (b) Wadavrao, S. B.; Ghogare, R. S.; Narsaiah, A. V. *Tetrahedron Lett.* **2012**, *53*, 3955−3958. (c) Saikia, B.; Devi, T. J.; Barua, N. C. *Tetrahedron* **2013**, *69*, 2157−2166. (d) Yadav, J. S.; Shankar, K. S.; Reddy, A. N.; Reddy, B. V. S. *Helv. Chim. Acta* **2014**, *97*, 546−555.
(25) 90:10 er on 2 mmol scale.
(26) (a) Corey, E. J.; Wollenberg, R. H. *J. Am. Chem. Soc.* **1974**, *96*, 5581−5583. (b) Renaldo, A. F.; Labadie, J. W.; Stille, J. K. *Org. Synth.* **1989**, *67*, 86−88.
(27) (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636−3638. (b) Milstein, D.; Stille, J. K. *J. Org. Chem.* **1979**, *44*, 1613−1618.
(28) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611−614.
(29) The 86:14 (6:1) er of the starting material is likely a major reason for the moderate dr of this reaction.
(30) Barua and co-workers[24c] apparently interpreted the reported *relative* configuration (9*R**,10*S**,7*E*)[18] as an *absolute* assignment. They synthesized a pair of C6 epimers which have opposite signs of optical rotation and incorrectly assigned the stereochemistry of the natural oxylipin based on optical rotation. They did not notice any NMR discrepancies because their spectra were obtained in a different solvent ($CDCl_3$) from that used by the isolation team (CD_3OD).
(31) Yadav and co-workers[24d] prepared (6*S*,9*R*,10*S*)-**16** (enantiomer of the natural product) and obtained NMR spectra in CD_3OD but only compared their synthetic product against the material prepared in the Sharma synthesis (NMR spectra in $CDCl_3$, and no comparison made against the natural product).[24a] They do not address the opposite sign of optical rotation as compared with the natural oxylipin[18] or the discrepancy with the Barua group's stereochemical assignment.[24c]
(32) Miura, A.; Kuwahara, S. *Tetrahedron* **2009**, *65*, 3364−3368.
(33) (a) Shirahata, T.; Sunazuka, T.; Yoshida, K.; Yamamoto, D.; Harigaya, Y.; Nagai, T.; Kiyohara, H.; Yamada, H.; Kuwajima, I.; Ōmura, S. *Bioorg. Med. Chem.* **2003**, *13*, 937−941. (b) Sabitha, G.; Reddy, E. V.; Bhikshapathi, M.; Yadav, J. S. *Tetrahedron Lett.* **2007**, *48*, 313−315.