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Development of a Concise and General Enantioselective Approach to 2,5-Disubstituted-3-hydroxytetrahydrofurans

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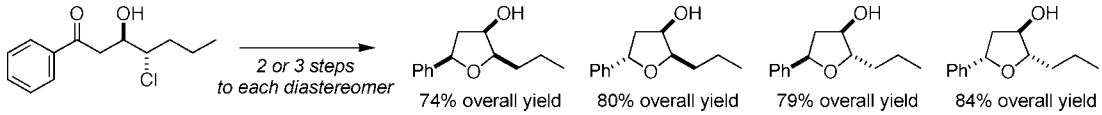
ABSTRACT



Concise syntheses of 2,5-disubstituted-3-hydroxytetrahydrofurans have been developed that provide access to each configurational isomer of this scaffold from a single aldol adduct. Application of these methods to the rapid preparation of (6*S*,7*S*,9*S*,10*S*)- and (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol, two structurally related marine epoxylipids, is reported.

Oxygenated 2,5-disubstituted tetrahydrofurans are common structural scaffolds in biologically active natural products.[1] For example, the diastereomeric brown alga metabolites **1**[2a] and **2**[2b] (Figure 1) possess a C3-oxygenated tetrahydrofuran

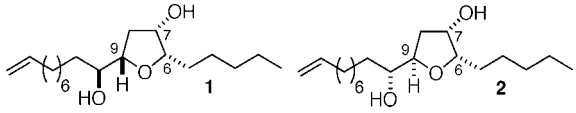


Figure 1. Anthelmintic oxylipids **1** and **2** isolated from the Southern Australian brown alga *Notheia anomala*.

core and have demonstrated nematocidal activity comparable to that of commercially available nematocides.[2a] Not surprisingly then, considerable effort has been invested in the development of methods for the enantio- and diastereoselective synthesis of oxygenated tetrahydrofurans.[3,4] However, these strategies often initiate with chiral pool materials and are consequently designed for the synthesis of a single configurational isomer and are not widely applicable to the production of naturally occurring and stereochemically

(1) For reviews, see: (a) Bermejo, A.; Figadère, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, 269. (b) Dutton, C. J.; Banks, B. J.; Cooper, C. B. *Nat. Prod. Rep.* **1995**, 165.

(2) (a) Capon, R. J.; Barrow, R. A.; Rochfort, S.; Jobling, M.; Skene, C.; Lacey, E.; Gill, J. H.; Friedel, T.; Wadsworth, D. *Tetrahedron* **1998**, *54*, 2227. (b) Warren, R. G.; Wells, R. J.; Blount, J. F. *Aust. J. Chem.* **1980**, *33*, 891.

(3) For recent reviews, see: (a) Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261. (b) Kang, E. J.; Lee, E. *Chem. Rev.* **2005**, *105*, 4348. (c) Miura, K.; Hosomi, A. *Synlett* **2003**, 143. (d) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041. (e) Harmange, J.-C.; Figadère, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711.

(4) For recent examples, see: (a) Mitchell, T. A.; Zhao, C.; Romo, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 5026. (b) Parsons, A. T.; Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2008**, *10*, 2541. (c) Donohoe, T. J.; Williams, O.; Churchill, G. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2869. (d) Chavre, S. N.; Choo, H.; Cha, J. H.; Pae, A. N.; Choi, K. I.; Cho, Y. S. *Org. Lett.* **2006**, *8*, 3617. (e) Blanc, A.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 2096. (f) Chandler, C. L.; Phillips, A. J. *Org. Lett.* **2005**, *7*, 3493. (g) Mertz, E.; Tinsley, J. M.; Roush, W. R. *J. Org. Chem.* **2005**, *70*, 8035.

(5) For enantioselective syntheses of **1**, 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. (c) García, C.; Soler, M. A.; Martín, V. S. *Tetrahedron Lett.* **2000**, *41*, 4127.

(6) For enantioselective syntheses of **2**, see: (a) de la Pradilla, R. F.; Castellanos, A. *Tetrahedron Lett.* **2007**, *48*, 6500. (b) Mori, Y.; Sawada, T.; Furukawa, H. *Tetrahedron Lett.* **1999**, *40*, 731. (c) Wang, Z.-M.; Shen, M. *J. Org. Chem.* **1998**, *63*, 1414. (d) Chikashita, H.; Nakamura, Y.; Uemura, H.; Itoh, K. *Chem. Lett.* **1993**, 477. (e) Gurjar, M. K.; Mainkar, P. S. *Hetrocycles* **1990**, *31*, 407. (f) Hatakeyama, S.; Sakurai, K.; Saijo, K.; Takano, S. *Tetrahedron Lett.* **1985**, *26*, 1333. See also ref 5c.

(7) For racemic syntheses of **1** and **2**, see: (a) Capon, R. J.; Barrow, R. A.; Skene, C.; Rochfort, S. *Tetrahedron Lett.* **1997**, *38*, 7609. (b) Williams, D. R.; Harigaya, Y.; Moore, J. L.; D'sa, A. *J. Am. Chem. Soc.* **1984**, *106*, 2641.

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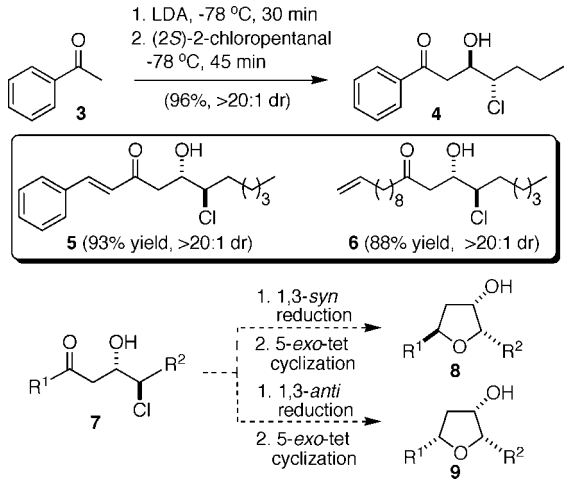
differentiated tetrahydrofurans (e.g., **1** or **2**).[5−7] Herein we report general synthetic methods that provide rapid access to all possible configurational isomers of the 2,5-disubstituted-3-hydroxytetrahydrofuran scaffold, and the application of these methods to short syntheses of both **1** and **2**.

We recently reported a general method for the synthesis of nonracemic *trans*-epoxides that relies on the diastereoselective addition of organolithium reagents to enantioenriched α-chloroaldehydes[8] followed by KOH-promoted epoxide formation.[9] As depicted in Scheme 1, we were pleased to find that lithium

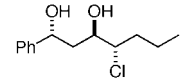
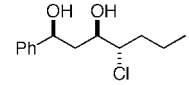
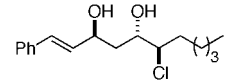
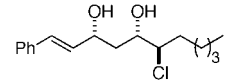
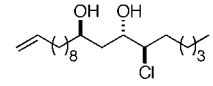
Scheme 1. Lithium Aldol Reaction of α-Chloroaldehydes and a Stereodivergent Strategy for Tetrahydrofuran Synthesis



enolates also couple smoothly with α-chloroaldehydes to provide the corresponding aldol adducts in excellent diastereomeric ratios and yield.[10] For example, treatment of the lithium enolate derived from acetophenone (**3**) with (2*S*)-2-chloropentanal[9] cleanly affords the *anti* chlorohydrin **4** (>20:1 dr). Similarly, the aldol adducts **5** and **6** were produced in excellent yield from the coupling of (2*R*)-2-chloroheptanal[11] with *trans*-4-phenylbuten-2-one and 11-dodecen-2-one, respectively. On the basis of these results we envisaged the conceptually straightforward strategy outlined in Scheme 1, whereby hydroxyl-directed reduction of the ketone function in the aldol adducts, followed by cyclization, would provide rapid access to stereochemically unique tetrahydrofurans (e.g., **8** or **9**). While cognizant of potential problems associated with the reactivity of chlorohydrins,[12] we set out to assess the viability of this stereodivergent route to tetrahydrofuran synthesis.

Diastereoselective reductions of ketochlorohydrins are summarized in Table 1. Treatment of **4** with $NaBH_4$ at 0 °C

Table 1. Hydroxyl-Directed Reduction of Ketochlorohydrins

entry	chlorohydrin	conditions[a]	major product[13]	(yield, dr)[b,c]
1	**4**	**A**		**10** (96%, 14:1)
2	**4**	**B**		**11** (97%, 11:1)
3	**4**	**C**		**11** (88%, 20:1)
4	**5**	**A**		**12** (98%, 10:1)
5	**5**	**C**		**13** (72%, >20:1)
6	**6**	**A**		**14** (92%, 9:1)

[a] **A**: $Me_4NBH(OAc)_3$, HOAc/MeCN (1:1.5), −40 °C. **B**: DIBAL-H, THF, −78 °C. **C**: catecholborane, THF, −10 °C. [b] Isolated yield of the chlorodiols, which were inseparable by flash chromatography. [c] Ratio determined by ^{1}H NMR spectroscopic analysis of crude reaction mixtures.

proceeded with poor diastereocontrol[13] (dr = 2.3:1); however, we were encouraged by the apparent stability of the chlorohydrin function under these reaction conditions. Improvement of this diastereomeric ratio was eventually realized through use of $NaBH(OAc)_3$ or $Me_4NBH(OAc)_3$,[14] the latter of which provided the 1,3-*anti* diol **10** as the major component of a 14:1 mixture of diastereomers (entry 1). After some experimentation it was also found that both catecholborane[15] and DIBAL-H provide the epimeric 1,3-*syn* diol **11** in good yield (entries 2 and 3). Following these procedures, the ketochlorohydrins **5** and **6** were also reduced smoothly to afford 1,3-*anti* and 1,3-*syn* chlorodiols **12**−**14** (entries 4−6).[13]

With the chlorodiols **10**−**14** in hand (Table 1), we turned our attention to the key cyclization reaction. Unfortunately, after surveying a wide variety of conditions we were unable to effect the conversion of **10** or **11** into the desired tetrahydrofurans via the direct 5-*exo-tet* cyclization outlined in Scheme 1. For example, under basic conditions (e.g., KOH, KH, NaH, Et_3N), we observed only products of decomposition and/or varying amounts of the corresponding epoxy alcohols (e.g., **15**, Scheme 2). Notably, these latter substances were produced in near quantitative yield by simply treating the chlorodiols with KOH in EtOH. On the basis of this observation, we turned our attention to a Lewis acid catalyzed cyclization of the readily available epoxy alcohols, which would expectedly[6b,16] give rise

(8) For the asymmetric α-chlorination of aldehydes, see: (a) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790. (b) Brochu, M. P.; Brown, S. P.; Macmillan, D. W. *J. Am. Chem. Soc.* **2004**, *126*, 4108. (c) Marquez, C. A.; Fabbretti, F.; Metzger, J. O. *Angew. Chem., Int. Ed.* **2007**, *46*, 6915.

(9) Kang, B.; Britton, R. *Org. Lett.* **2007**, *9*, 5083.

(10) For a theoretical investigation of nucleophilic addition to an α-chloroaldehyde, see: Cee, V. J.; Cramer, C. J.; Evans, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 2920.

(11) (2*R*)-2-Chloroheptanal is available in 97% yield and 84% enantiomeric excess through chlorination of heptanal (NCS, CH_2Cl_2, L-prolinamide) following the procedure described in ref 8a.

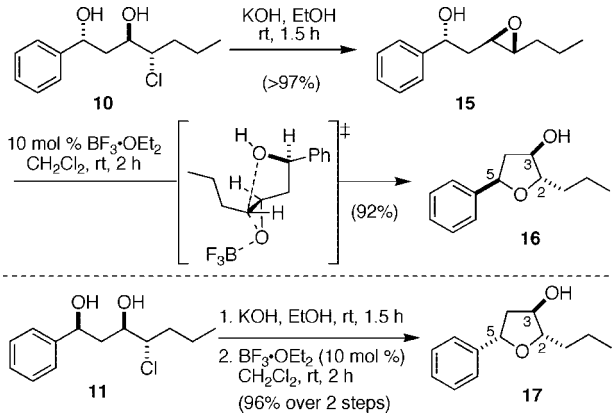
(12) De Kimpe, N.; Verhé, R. *The Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines*; Patai, S.; Rappoport, Z., Eds.; John Wiley and Sons: New York, 1988.

(13) The relative configuration of the formed carbinol stereocenter was confirmed unequivocally by conversion to the corresponding acetonide and subsequent analysis of the ^{13}C NMR spectrum as reported in Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945.

(14) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

(15) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190.

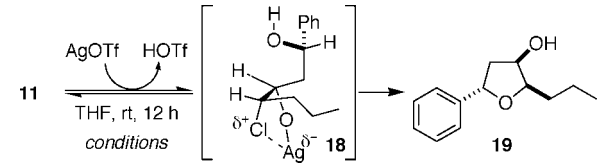
Scheme 2. Synthesis of Tetrahydrofurans **16** and **17**



to the stereoisomeric tetrahydrofurans **16** and **17**. Following this revised strategy, treatment of **15** with BF_3•OEt_2 (10 mol %) at low temperature (−78 °C) effected clean transformation to **16**, albeit with low conversion.[17] Repetition of this experiment at room temperature, however, provided the desired tetrahydrofuran **16** in excellent yield (92%). Likewise, treatment of the epoxy alcohol derived from **11** (not shown) under similar conditions resulted in clean transformation to **17**. Mechanistically, both **16** and **17** are derived from direct opening of the epoxide and inversion of configuration.[18] In both cyclizations, none of the C2 epimer that would arise from an S_N1-type process or the intermediacy of a halohydrin[16d,18] were observed.

While it could be shown that Mitsunobu inversion[19]/hydrolysis of **16** or **17** provides access to the two remaining diastereomers of the 2,5-disubstituted-3-hydroxytetrahydrofuran scaffold,[20] these additional synthetic steps detract from the overall appeal of this route. Thus, we refocused efforts on the direct 5-*exo*-*tet* cyclization outlined in Scheme 1. Bearing in mind that base-promoted cyclizations of **10** and **11** led exclusively to epoxide formation, we envisaged that treatment of the chlorodiols with silver triflate (AgOTf) may lead to a silver alkoxide (e.g., **18**) in which coordination between silver and chlorine would favor a noncompetent conformation for epoxide formation and activate the chloromethine to nucleophilic attack by the distal alcohol function. Table 2 summarizes our efforts toward the realization of this process. As indicated in entry 1, treatment of **11** with AgOTf led to a complex mixture that

Table 2. AgOTf-Promoted Cyclization of Chlorodiol **11**



entry	AgOTf (equiv)	additive (equiv)	% yield **19**[a]
1	1.0	none	0[b]
2	1.0	Ag_2O (1.0)	55
3	0.5	Ag_2O (0.5)[c]	45
4	1.0	Ag_2O (1.0)[d]	90

[a] Isolated yield of **19**. [b] Considerable decomposition of starting material and/or product was observed. [c] Complete consumption of **11** required 24 h. [d] 0 °C to rt overnight.

contained none of the desired tetrahydrofuran **19**. We were encouraged, however, by resonances in the ^1H NMR spectrum of the crude reaction mixture (e.g., δ 5.73 (dd, J = 6.5, 2.5 Hz)) that were consistent with the formation of dihydrofurans, potentially produced via acid-catalyzed dehydration of **19**. Unfortunately, addition of a variety of organic or inorganic bases failed to significantly improve the outcome of this reaction. As AgOTf can be prepared from the reaction of Ag_2O with triflic acid,[21] Ag_2O was screened as a triflic acid scavenger and found to facilitate the formation of **19** in good yield (entry 2).[22] Use of substoichiometric amounts of Ag_2O and AgOTf required extended reaction times and resulted in increased decomposition of **11** and/or **19** and consequently lower isolated yields of the latter substance (entry 3).[23] The most favorable conditions for the conversion of **11** into **19** involved the addition of 1 equiv of both AgOTf and Ag_2O to a THF solution of **11** at 0 °C, followed by the gradual warming of this mixture to room temperature over 12 h (entry 4). On the basis of these results and the epoxide opening route detailed above, each configurational isomer of the 2,5-disubstituted-3-hydroxytetrahydrofuran scaffold can now be accessed in excellent overall yield from a single aldol adduct.

To assess the scope of these cyclization protocols, the syntheses of several 2,5-disubstituted-3-hydroxytetrahydrofurans were undertaken. As summarized in Table 3, alkyl, alkenyl, and phenyl substituents were well tolerated by these processes, and a variety of stereoisomeric tetrahydrofurans were prepared in good to excellent yield. As indicated in eqs 1 and 2, the styryltetrahydrofurans **21**−**24** readily epimerize when treated with BF_3•OEt_2 at room temperature, and consequently, the BF_3•OEt_2-catalyzed rearrangement of epoxyalcohols derived from **12** or **13** (entries 3 and 5) were carried out at −35 °C to minimize epimerization.[24] Notably, the tetrahydrofuran **25** (entry 6), a C-10 deshydroxy analogue of the marine oxylipid **1**, is

(16) For examples of 5-*endo* cyclizations of epoxy alcohols, see: (a) Doan, H. D.; Gallon, J.; Piou, A.; Vatéle, J.-M. *Synlett* **2007**, *6*, 983. (b) Narayan, R. S.; Borhan, B. *J. Org. Chem.* **2006**, *71*, 1416. (c) Smith, A. B., III; Fox, R. J. *Org. Lett.* **2004**, *6*, 1477. (d) Karikomi, M.; Watanabe, S.; Kimura, Y.; Uyehara, T. *Tetrahedron Lett.* **2002**, *43*, 1495. (e) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1997**, *119*, 12150. (f) Mukai, C.; Sugimoto, Y.-i.; Ikeda, Y.; Hanaoka, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1161.

(17) Use of other Lewis acids (e.g., $AlCl_3$ or $EtAlCl_2$) resulted in complex mixtures that contained only minor (<10%) amounts of **16**.

(18) For a theoretical investigation of the 5-*endo* cyclization of epoxy alcohols, see: Coxon, J. M.; Morokuma, K.; Thorpe, A. J.; Whalen, D. *J. Org. Chem.* **1998**, *63*, 3875.

(19) Mitsunobu, O. *Synthesis* **1981**, 1.

(20) Mitusnobu inversion of **16**, **17**, and **19** provided access to *ent*-**19**, *ent*-**20**, and *ent*-**16**, respectively (see Supporting Information for details).

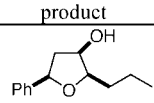
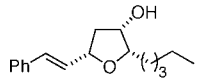
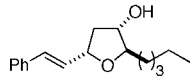
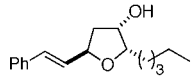
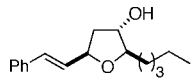
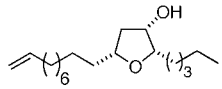
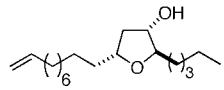
(21) Whitesides, G. M.; Gutowski, F. D. *J. Org. Chem.* **1976**, *41*, 2882.

(22) For AgOTf/Ag_2O promoted oxetane formation from a bromohydrin, see: Popsavin, V.; Radic, J.; Popsavin, M.; Cirin-Novta, V. *J. Serb. Chem. Soc.* **2004**, *69*, 117.

(23) When **11** was treated with Ag_2O (1 equiv) in THF without AgOTf, none of the desired tetrahydrofuran **19** was formed.

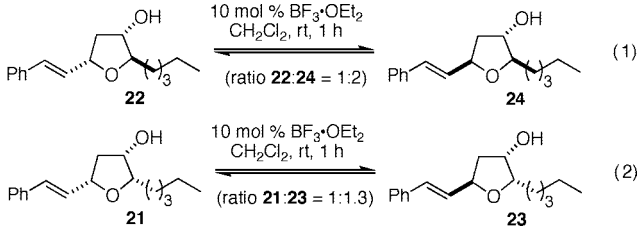
(24) At temperatures below −35 °C these reactions required several days. Repetition of these reactions at temperatures above −20 °C led to serious erosion in diastereomeric purity.

Table 3. Synthesis of 3-Hydroxytetrahydrofurans

entry	chlorodiol	conditions[a]	product	yield[b]
1	**10**	**A**		**20** (83%)
2	**12**	**A**		**21** (84%)
3	**12**	**B**		**22** (73%)[c]
4	**13**	**A**		**23** (77%)
5	**13**	**B**		**24** (82%)[d]
6	**14**	**A**		**25** (91%)
7	**14**	**C**		**26** (91%)

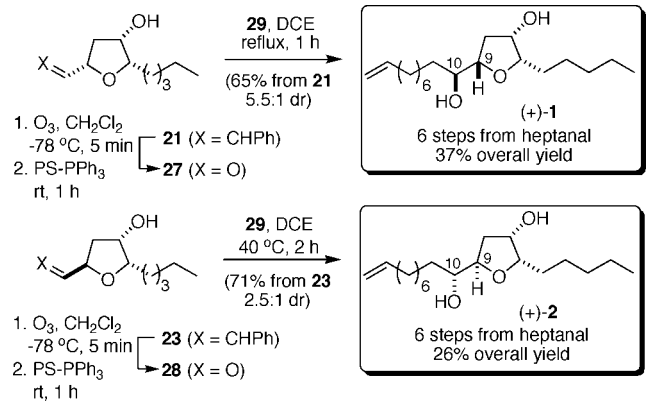
[a] **A**: AgOTf, Ag_2O, THF, 0 °C to rt, 12 h. **B**: (i) KOH, EtOH, rt, 1.5 h; (ii) $BF_3{\cdot}OEt_2$ (10 mol %), CH_2Cl_2, −35 °C, 24 h. **C**: (i) KOH, EtOH, rt, 1.5 h; (ii) $BF_3{\cdot}OEt_2$ (10 mol %), CH_2Cl_2, rt, 24 h. [b] Isolated yield. [c] Produced as a separable 5:1 mixture of **22**:**24**. [d] Produced as a separable 8:1 mixture of **24**:**22**.

available in four steps (64% overall yield) from heptanal following this strategy.



Finally, this concise approach to 3-hydroxytetrahydrofurans was exploited in short total syntheses of the marine oxylipids (+)-**1** and (+)-**2**. As depicted in Scheme 3, oxidative cleavage of the alkene function in **21** with ozone followed by reductive workup with polymer-supported triphenylphosphine (PS-PPh_3) and filtration provided the crude aldehyde **27**.[25] Direct reaction of **27** with an excess of 8-nonenylmagnesium bromide (**29**)[26] in DCE at reflux[27] provided (+)-**1** as the major component of a separable 5.5:1 mixture of C10 epimeric alcohols. A similar

Scheme 3. Synthesis of Marine Oxylipids (+)-**1** and (+)-**2**



sequence of reactions carried out on the tetrahydrofuran **23** afforded the C9/C10 epimeric natural product (+)-**2**. The spectral data derived from these substances were in complete agreement with those reported in the literature.[5,6,28]

In summary, we have developed efficient routes to all configurational isomers of the 2,5-disubstituted-3-hydroxytetrahydrofuran scaffold that initiate with a single aldol adduct. Key to the success of this work is a high yielding, chemoselective, AgOTf-promoted cyclization of chlorodiols that represents a stereochemical compliment to epoxy alcohol formation−Lewis acid catalyzed rearrangement. In addition we have applied these processes to concise syntheses of the anthelmintic marine oxylipids **1** and **2**. Notably, the overall yield for **1** (37%) and **2** (26%) from heptanal and the total number of synthetic steps required compare well with the reported asymmetric syntheses of these substances.[5,6] Importantly, the functional group tolerance and stereochemical flexibility of this new approach should allow rapid access to derivatives of **1** and **2** as well as a wide variety of naturally occurring and biologically active oxygenated tetrahydrofurans, work that is currently underway in our laboratory.

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Supporting Information Available: Experimental and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) The aldehydes **27** and **28** decomposed on silica gel, and consequently the crude aldehydes were used without further purification.

(26) For the addition of **29** to derivatives of **27** and **28** in which the alcohol function is protected, see refs 5a, 6b, 6c and 7b.

(27) Addition of Grignard reagents to **27** at lower temperatures required extended reaction times and proceeded with lower diastereoselectivity, resulting in decreased production of **1**.

(28) The specific rotation for synthetic (+)-**1** ($[\alpha]_D$ = +20.0, *c* 0.5, $CHCl_3$) was consistent with the value reported in ref 5a ($[\alpha]_D$ = +24.3, *c* 0.3, $CHCl_3$), and the specific rotation for synthetic (+)-**2** ($[\alpha]_D$ = +14.5, *c* 1.1, $CHCl_3$) was consistent with the value reported in ref 6d ($[\alpha]_D$ = +15.0, *c* 0.46, $CHCl_3$).