Total Synthesis

International Edition: DOI: 10.1002/anie.201600637
German Edition: DOI: 10.1002/ange.201600637

Stereoselective Substrate-Controlled Asymmetric Syntheses of both 2,5-*cis*- and 2,5-*trans*-Tetrahydrofuranoid Oxylipids: Stereodivergent Intramolecular Amide Enolate Alkylation

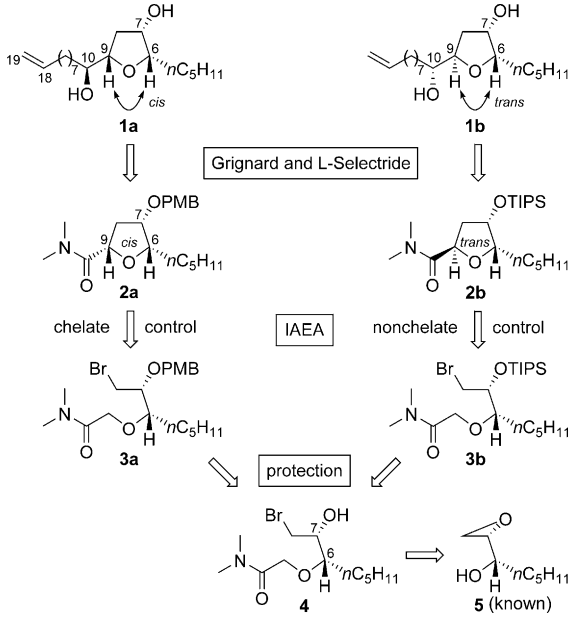
Hongjun Jang[+], Iljin Shin[+], Dongjoo Lee, Hyoungsu Kim, and Deukjoon Kim*

Dedicated to Professor Steven M. Weinreb on the occasion of his 75th birthday

Abstract: *The concise, highly stereoselective, substrate-controlled asymmetric total syntheses of both 2,5-cis- and 2,5-trans-tetrahydrofuranoid nematocidal oxylipids from the Australian brown algae Notheia anomala have been accomplished in a stereodivergent fashion. The highly stereoselective intramolecular amide enolate alkylation strategy provides access to both stereoisomers of the 3-hydroxy-2,5-disubstituted tetrahydrofuran core of these marine natural products through chelate and nonchelate control, which is driven by the C3-hydroxy protecting group. This approach offers an optional and highly stereoelective access to any of the eight possible stereoisomers of the 2,5-disubstituted-3-oxygenated tetrahydrofuran skeleton, an important structural feature which is present in many biologically active natural products.*

The marine C_{19} oxylipid **1b**, which possesses a 2,5-*trans*-disubstituted tetrahydrofuran (THF) skeleton as shown in Scheme 1, was first isolated from the Australian brown algae *Notheia anomala* in 1980 by Warren et al.[1] The relative and absolute stereochemistry of **1b** was established by single-crystal X-ray analysis on the C18–C19 dihydro derivative, and application of the Horeau method to the C10 monoacetate, respectively. Extensive reinvestigation of the same species by Capon and co-workers in 1998 led to the identification of the diastereomeric 2,5-*cis*-disubstituted oxylipid **1a**.[2] Both **1a** and **1b** possess nematocidal activities.[2]

Since the first synthesis of **1b** by Williams and co-workers in 1984,[3] these oxylipids have served as a testing ground to evaluate strategies for stereoselective construction of the 2,5-disubstituted-3-oxygenated THF motif, which is present as an important structural feature in many biologically active natural products.[4] However, relatively few of the many hitherto published approaches to construct this critical structural unit utilized a carbon–carbon bond-forming cyclization reaction as the key step. Of the approaches involving carbon–carbon bond formation, the elegant pathways attempted to date include the use of a Prins-type cyclization, a Mukaiyama-type reaction, [3+2] cycloaddition, or radical addition, and predominantly generate the 2,5-*cis*-disubstituted THF system.[4m,5]



Scheme 1. Retrosynthetic plan for the oxylipds **1a** and **1b**. IAEA = intramolecular amide enolate alkylation, PMB = *p*-methoxybenzyl, TIPS = triisoproylsilyl.

We describe herein our concise, highly stereoselective, substrate-controlled asymmetric total syntheses of both **1a** and **1b**, which contain 3-hydroxy-2,5-*cis*- and 3-hydroxy-2,5-*trans*-disubstituted THF units, respectively, from a common intermediate based on a stereodivergent intramolecular amide enolate alkylation (IAEA) strategy.[6] This novel strategy was derived from the insights garnered during development of our protecting-group-dependent intermolecular amide enolate alkylation/RCM protocols for the synthesis of medium-ring-ether natural products.[7] We wish to emphasize that our versatile approach offers stereoselective access to any of the eight possible stereoisomers of the 2,5-disubstituted-3-oxygenated THF skeleton.

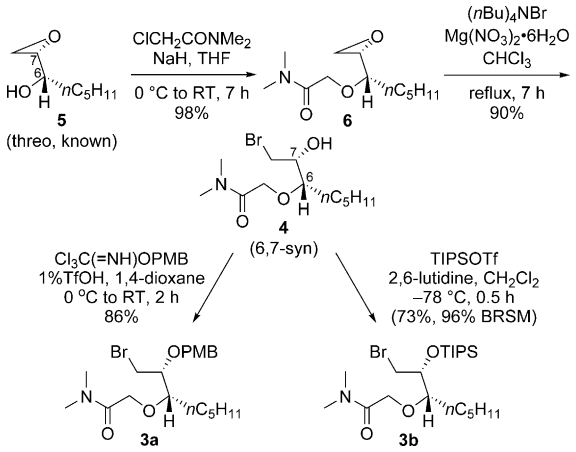
As depicted in our retrosynthetic plan (Scheme 1), we were confident that **1a** and **1b** could be obtained by application of our direct ketone synthesis/L-Selectride reduction protocol[7a,b,d–h,8] to tetrahydrofuranyl α-alkoxy amides **2a**

[*] H. Jang,[+] I. Shin,[+] Prof. Dr. D. Lee, Prof. Dr. H. Kim
College of Pharmacy, Ajou University
Suwon 16499 (Korea)
E-mail: hkimajou@ajou.ac.kr
Prof. Dr. D. Kim
College of Pharmacy, Seoul National University
Seoul 08826 (Korea)
[+] These authors contributed equally to this work.

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201600637.

and **2b**, respectively. We were intrigued by the possibility that the key **2a** and **2b** intermediates might be secured in a stereodivergent fashion by, respectively employing a chelate- and nonchelate-controlled IAEA reaction of the corresponding ω-bromo α-alkoxy amides **3a** and **3b**. These amides **3a** and **3b** have a C7-hydroxy function protected with a chelating (i.e., PMB) and non-chelating protecting group (i.e., TIPS), respectively. We envisioned that **3a** and **3b** could be synthesized from the common hydroxybromoamide intermediate **4** through appropriate protection of the OH group, and **4** in turn could be elaborated from the known epoxy alcohol **5**.[9a]

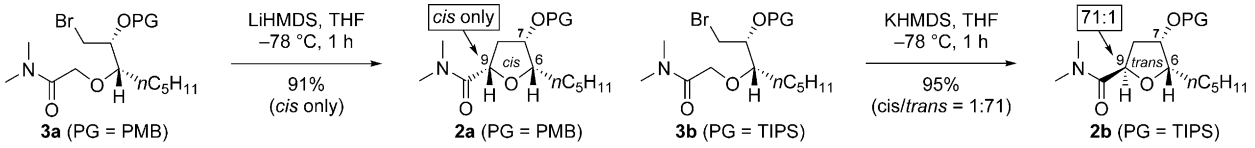
Our asymmetric synthesis of **1a** and **1b** commenced with the preparation of the common synthetic intermediate **4** (Scheme 2). Thus, known the *threo*-epoxy alcohol **5**,[9a] prepared from commercially available (*E*)-oct-2-en-1-ol by a three-step sequence (chlorination,[10] Sharpless asymmetric dihydroxylation,[11] epoxide formation), was subjected to Williamson O-alkylation with *N*,*N*-dimethyl chloroacetamide to deliver the desired epoxy α-alkoxy amide **6** in 98% yield. Regioselective opening of **6** with $(n\mathrm{Bu})_4\mathrm{NBr}$ in the presence of $Mg(NO_3)_2{\cdot}6H_2O$ furnished **4** in good yield (90%).[12] Protection of the hydroxy group in **4** as either the PMB or TIPS ether using the reaction conditions reported by the groups of Bundle[13] and Corey,[14] respectively, afforded the corresponding **3a** and **3b** in good yields.



Scheme 2. Synthesis of the IAEA substrates **3a** and **3b**. BRSM = based on recovered starting material, Tf = trifluoromethanesulfonyl.

With **3a** and **3b** in hand, we first investigated the desired chelate-controlled IAEA reaction of **3a** for the synthesis of **1a**. In the event, treatment of **3a** with LiHMDS in THF at −78 °C for 1 hour led to exclusive formation of the desired 6,9-*cis*-THF **2a** in 91% yield (entry 2 in Scheme 3), presumably via a chelated transition state geometry (**A**).[1b] The ROE (rotating-frame Overhauser effect) interaction between protons on C6 and C9 in **2a** was supportive of the assigned *cis* relative stereochemistry. As shown in the table in Scheme 3, neither the solvent (entries 6 and 7) nor the cation of the base used (entries 2, 4, and 6) seemed to affect the yield and diastereoselectivity in a significant manner. Meanwhile, a lower reaction temperature was found to improve the yield appreciably (0 versus −78 °C; entries 3 and 5 versus 4 and 6, respectively).

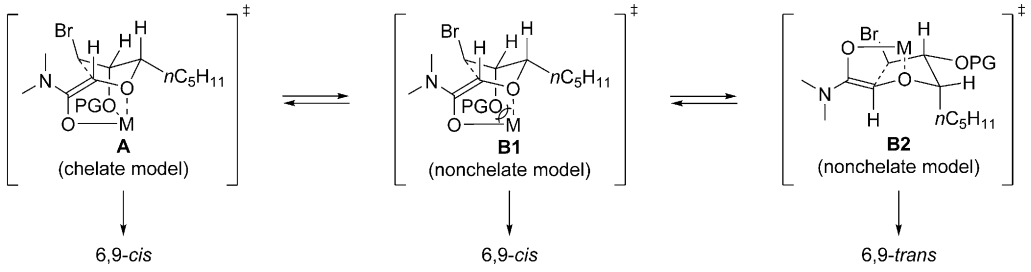
Having accomplished a highly stereoselective synthesis of **2a**, we next turned our attention to construction of **2b** for the synthesis of **1b**. Thus, subjection of **3b**, with a TIPS-protected alkoxy group at C7, to KHMDS in THF at −78 °C for 1 hour gave rise to **2b** as the major isomer (*cis*/*trans* = 1:71) in excellent yield (95%; entry 10 in Scheme 3). The TIPS-protected alkoxy group is known to be a poor coordinating



Entry	Protecting group: PG	Base	Solvent	*T* [° C]	Yield [%][a]	d.r.[b] (*cis*/*trans*)
1	PMB	LiHMDS	THF	0	87	>174:1
2	PMB	LiHMDS	THF	–78	91	*cis* only
3	PMB	NaHMDS	THF	0	53	>178:1
4	PMB	NaHMDS	THF	–78	94	*cis* only
5	PMB	KHMDS	THF	0	71	>135:1
6	PMB	KHMDS	THF	–78	94	>105:1
7	PMB	KHMDS	toluene	–78	94	*cis* only

Entry	Protecting group: PG	Base	Solvent	*T* [° C]	Yield [%][a]	d.r.[b] (*cis*/*trans*)
8	TIPS	LiHMDS	THF	–78	77	1:4
9	TIPS	NaHMDS	THF	–78	86	1:7
10	TIPS	KHMDS	THF	–78	95	1:71
11	TIPS	KHMDS	toluene	–78	100	1:3
12	TBS	KHMDS	THF	–78	79	1:13
13	TES	KHMDS	THF	–78	90	1:1
14	TMS	KHMDS	THF	–78	42	>10:1[c]

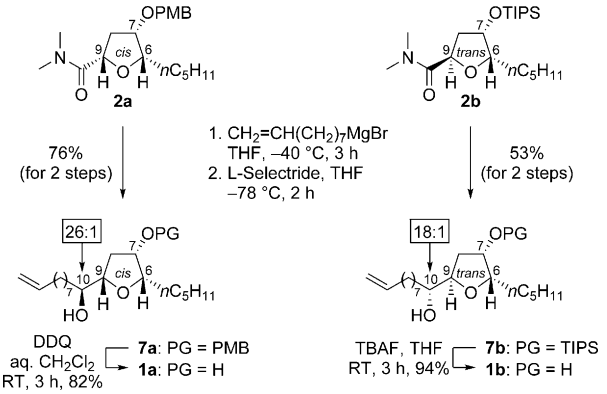
[a] Total yield [b] Determined by ^{1}H NMR spectroscopy [c] After removal of TMS group



Scheme 3. Intramolecular amide enolate alkylation of 6,7-*syn*-bromoamides. HMDS = hexamethyldisilazide, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TMS = trimethylsilyl.

group for steric and electronic reasons,[7a,b,d,g,h,15e,h,i,k] and the observed stereoselectivity could be rationalized by invoking a nonchelated transition-state geometry (**B2**) which minimizes steric repulsions present, between the bulky TIPS-protected alkoxy group and the amide enolate moiety, in the alternative nonchelated transition-state (**B1**). Diminished diastereoselectivity was obtained when smaller silyl groups were used. Thus, upon treatment with KHMDS in THF at −78 °C, the *cis*/*trans* diastereoselectivity for the TIPS-, TBS-, and TES-protected cyclization substrates was 1:71, 1:13, and 1:1, respectively (entries 10, 12, and 13). This trend is consistent with a strong steric effect of the silyl group. In the case of the least bulky TMS protecting group, however, a 10:1 mixture of desilylated products was obtained in favor of the *cis* isomer after acid treatment, albeit in low total yield (42 %).[16a] This reversal of stereoselectivity is in accord with observations by Reetz and Hüllmann in their study of nucleophilic addition to α-silyoxyketones. They reported that the TMS-protected alkoxy group led to a surprising degree of chelation-control, thus suggesting that steric factors appear to be more important than any electronic effect because of the silyl group.[15b] It is interesting to note that unlike the intramolecular alkylation of **3a**, that of **3b** exhibited better *trans*/*cis* diastereoselectivity (entries 10 and 11) in more polar solvent, which would favor a nonchelated species. Upon exposure of **3b** to KHMDS at −78 °C, the *trans*/*cis* diastereoselectivity observed in THF and toluene was 71:1 and 3:1, respectively. Likewise, bases with larger cations showed superior *trans*/*cis* selectivity (entry 8–10). With **3b** in THF at −78 °C, the *trans*/*cis* diastereoselectivity observed for KHMDS, NaHMDS, and LiHMDS was 71:1, 7:1, and 4:1, respectively.[16b]

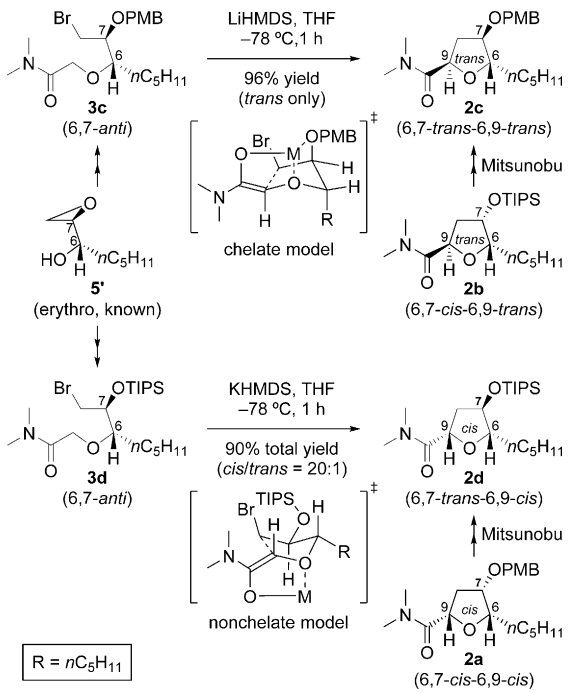
For the completion of the synthesis, application of our direct ketone synthesis protocol[7a,b,d–h,8] to **2a** with CH_2=$CH(CH_2)_7MgBr$, followed by stereoselective L-Selectride reduction[7a,b,d–h,8,17] of the resulting ketone in a Felkin–Anh sense, afforded the desired secondary alcohol **7a** in 76 % overall yield for the two steps (d.r.: 26:1; Scheme 4). Finally, removal of the PMB group in **7a** by treatment with DDQ in wet CH_2Cl_2 under the Yonemitsu conditions[18] delivered the oxylipid **1a** in 82 % yield. The TIPS-protected **2b** could be elaborated to deliver the oxylipid **1b** in 50 % overall yield



Scheme 4. Completion of the synthesis. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TBAF = tetra-*n*-butylammonium fluoride.

(over three steps; d.r.: 18:1) by using a pathway similar to the above-described sequence for **1a**, except that the TIPS protecting group in **7b** was removed by exposure to TBAF. The spectral data and optical rotations of our synthetic **1a** and **1b** were in good agreement with those reported for the natural products as well as other synthetic materials. We draw attention to the fact that the diastereoselectivity observed in our direct ketone synthesis/L-Selectride reduction sequence (26:1 for the 6,9-*cis* series; 18:1 for the 6,9-*trans*) is far superior to that reported in previous syntheses for alternative procedures employing the Grignard addition of CH_2=CH-$(CH_2)_7MgBr$ to tetrahydrofuranyl aldehydes (3:1 to 5.5:1 for the *cis* series with a free hydroxy group at C7;[3o–q] and 2.5:1 to 6:1 for *trans*[3a,b,d,f,g,l–q]).

To further demonstrate the potential of our IAEA approach, we embarked upon the synthesis of the 6,9-*cis*- and 6,9-*trans*-THF skeletons with the complementary 6,7-*trans* relative stereochemistry, as summarized in Scheme 5. In



Scheme 5. Intramolecular amide enolate alkylation of 6,7-*anti*-bromo-amides.

the event, we were pleased to find that the IAEA reaction of the PMB- (**3c**) and TIPS-protected (**3d**) 6,7-*anti*-bromo α-alkoxy amides, derived from the known *erythro*-epoxy alcohol **5′**[19] using a protocol similar to the above-described sequence for **5**, led to the corresponding 6,7-*trans*-6,9-*trans*- (**2c**) and 6,7-*trans*-6,9-*cis*-THF (**2d**) products through chelate and nonchelate control, respectively, with high stereoselectivity in good yield. Since both enantiomers of the *threo*- (**5**) and *erythro*-epoxy (**5′**) alcohols are readily accessible through asymmetric dihydroxylation[9a,4n] and Sharpless kinetic resolution,[19] respectively, the present IAEA reactions of 6,7-*anti*-bromo α-alkoxy amides, coupled with those of 6,7-*syn*-amides (Scheme 3), provide optional access to any of the eight

possible 2,5-disubstituted-3-oxygenated THF stereoisomers in a highly stereoselective fashion. It is worth mentioning that the application of a deprotection/Mitsunobu sequence on **2a** and **2b** also proceeded without incident to give the corresponding Mitsunobu products, which were then further converted into **2d** and **2c**, respectively, for structure correlation purposes (see the Supporting Information for details).[20]

In conclusion, we have accomplished concise, highly stereoselective substrate-controlled asymmetric total syntheses of both nematocidal oxylipids **1a** and **1b** which contain the 3-hydroxy-2,5-*cis*- and 3-hydroxy-2,5-*trans*-disubstituted THF unit, respectively, in a stereodivergent fashion from the common intermediate **4**. These routes, which proceed in seven steps from known epoxy alcohol **5**, provide stereoselective access to both 2,5-*cis*- (**2a**) and 2,5-*trans*-THF (**2b**) stereoisomers by a highly efficient intramolecular amide enolate alkylation of **3a** and **3b**, respectively, through corresponding chelate and nonchelate control. To the best of our knowledge, our approach holds the distinction of being the only extant synthesis in which the respective 2,5-*cis* and 2,5-*trans* relative stereochemistry in the THF core of **1a** and **1b** was established with high stereoselectivity through a carbon–carbon bond-forming cyclization in a stereodivergent fashion from a common intermediate. Furthermore, our IAEA-based approach offers optional, highly stereoselective access to any of the eight possible 2,5-disubstituted-3-oxygenated THF stereoisomers.

Acknowledgments

This work was supported by Basic Science Research Program through National Research Foundation of Korea, funded by the Ministry of Science, ICT & Future Planning (NRF-2014R1A1A2056603).

Keywords: alkylations · cyclizations · heterocycles · natural products · total synthesis

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 6497–6501
Angew. Chem. **2016**, *128*, 6607–6611

[1] a) R. G. Warren, R. J. Wells, J. F. Blount, *Aust. J. Chem.* **1980**, *33*, 891–898; b) the numbering used to describe the key structural unit is 2,5-*trans* and 2,5-*cis*, while a different numbering scheme that corresponds to the natural product structure is used when referring to compounds as a whole.

[2] R. J. Capon, R. A. Barrow, S. Rochfort, M. Jobling, C. Skene, E. Lacey, J. H. Gill, T. Friedel, D. Wadsworth, *Tetrahedron* **1998**, *54*, 2227–2242.

[3] a) D. R. Williams, Y. Harigaya, J. L. Moore, A. D′sa, *J. Am. Chem. Soc.* **1984**, *106*, 2641–2644; b) S. Hatakeyama, K. Sakurai, K. Saijo, S. Takano, *Tetrahedron Lett.* **1985**, *26*, 1333–1336; c) M. K. Gurjar, P. S. Mainkar, *Heterocycles* **1990**, *31*, 407–410; d) H. Chikashita, Y. Nakamura, H. Uemura, K. Itoh, *Chem. Lett.* **1993**, 477–480; e) R. J. Capon, R. A. Barrow, C. Skene, S. Rochfort, *Tetrahedron Lett.* **1997**, *38*, 7609–7612; f) Z. M. Wang, M. Shen, *J. Org. Chem.* **1998**, *63*, 1414–1418; g) Y. Mori, T. Sawada, H. Furukawa, *Tetrahedron Lett.* **1999**, *40*, 731–734; h) C. García, M. A. Soler, V. S. Martín, *Tetrahedron Lett.* **2000**, *41*, 4127–4130; i) R. R. Gadikota, C. S. Callam, T. L. Lowary, *J. Org. Chem.* **2001**, *66*, 9046–9051; j) H. Yoda, K. Maruyama, K. Takabe, *Tetrahedron: Asymmetry* **2001**, *12*, 1403–1406; k) C. García, T. Martín, V. S. Martín, *J. Org. Chem.* **2001**, *66*, 1420–1428; l) R. Fernández de la Pradilla, A. Castellanos, *Tetrahedron Lett.* **2007**, *48*, 6500–6504; m) C. L. Nesbitt, C. S. P. McErlean, *Tetrahedron Lett.* **2009**, *50*, 6318–6320; n) R. Fernández de la Pradilla, A. Castellanos, I. Osante, I. Colomer, M. I. Sánchez, *J. Org. Chem.* **2009**, *74*, 170–181; o) B. Kang, J. Mowat, T. Pinter, R. Britton, *Org. Lett.* **2009**, *11*, 1717–1720; p) C. L. Nesbitt, C. S. P. McErlean, *Org. Biomol. Chem.* **2011**, *9*, 2198–2208; q) S. Roy, C. D. Spilling, *Org. Lett.* **2012**, *14*, 2230–2233; r) L. Li, X. Ye, Y. Wu, L. Gao, Z. Song, Z. Yin, Y. Xu, *Org. Lett.* **2013**, *15*, 1068–1071.

[4] For recent reviews on the synthesis of THF-containing natural products, see: a) R. D. Norcrosst, I. Paterson, *Chem. Rev.* **1995**, *95*, 2041–2114; b) A. Bermejo, B. Figadère, M.-C. Zafra-Polo, I. Barrachina, E. Estornell, D. Cortes, *Nat. Prod. Rep.* **2005**, *22*, 269–303; c) E. J. Kang, E. Lee, *Chem. Rev.* **2005**, *105*, 4348–4378; d) J. P. Wolfe, M. B. Hay, *Tetrahedron* **2007**, *63*, 261–290; e) G. Jalce, X. Franck, B. Figadère, *Tetrahedron: Asymmetry* **2009**, *20*, 2537–2581; f) I. B. Spurr, R. C. D. Brown, *Molecules* **2010**, *15*, 460–501; g) B.-G. Wang, J. B. Gloer, N.-Y. Ji, J.-C. Zhao, *Chem. Rev.* **2013**, *113*, 3632–3685; h) A. Lorente, J. Lamariano-Merketegi, F. Albericio, M. Álvarez, *Chem. Rev.* **2013**, *113*, 4567–4610; i) N. S. Sheikh, *Org. Biomol. Chem.* **2014**, *12*, 9492–9504; for recent examples of the synthesis of THF-containing natural products, see: j) D. J. Shepherd, P. A. Broadwith, B. S. Dyson, R. S. Paton, J. W. Burton, *Chem. Eur. J.* **2013**, *19*, 12644–12648; k) M. T. Holmes, R. Britton, *Chem. Eur. J.* **2013**, *19*, 12649–12652; l) T. Umezawa, Y. Oguri, H. Matsuura, S. Yamazaki, M. Suzuki, E. Yoshimura, T. Furuta, Y. Nogata, Y. Serisawa, K. Matsuyama-Serisawa, T. Abe, F. Matsuda, M. Suzuki, T. Okino, *Angew. Chem. Int. Ed.* **2014**, *53*, 3909–3912; *Angew. Chem.* **2014**, *126*, 3990–3993; m) J. Lee, J. S. Panek, *J. Org. Chem.* **2015**, *80*, 2959–2971; n) A. Boyer, *J. Org. Chem.* **2015**, *80*, 4771–4775; o) M. Yamakawa, T. Kurachi, Y. Yoshikawa, M. Arisawa, Y. Okino, K. Suzuki, H. Fujioka, *J. Org. Chem.* **2015**, *80*, 10261–10277; p) S. Gahalawat, Y. Garg, S. K. Pandey, *Asian J. Org. Chem.* **2015**, *4*, 1025–1029; q) M. Holmes, D. Kwon, M. Taron, R. Britton, *Org. Lett.* **2015**, *17*, 3868–3871; r) V. Mullapudi, C. V. Ramana, *Tetrahedron Lett.* **2015**, *56*, 3933–3935; s) U. Nookaraju, P. Kumar, *RSC Adv.* **2015**, *5*, 63311–63317.

[5] For selected examples of 2,5-disubstituted-3-oxygenated THF syntheses by C–C bond-forming cyclization, see: a) M. J. Brown, T. Harrison, L. E. Overman, *J. Am. Chem. Soc.* **1991**, *113*, 5378–5384; b) E. Lee, S.-K. Yoo, H. Choo, H. Y. Song, *Tetrahedron Lett.* **1998**, *39*, 317–318; c) P. A. Evans, V. S. Murthy, J. D. Roseman, A. L. Rheingold, *Angew. Chem. Int. Ed.* **1999**, *38*, 3175–3177; *Angew. Chem.* **1999**, *111*, 3370–3372; d) T.-P. Loh, Q.-Y. Hu, K.-T. Tan, H.-S. Cheng, *Org. Lett.* **2001**, *3*, 2669–2672; e) L. E. Overman, L. D. Pennington, *J. Org. Chem.* **2003**, *68*, 7143–7157; f) J. H. Jung, Y. W. Kim, M. A. Kim, S. Y. Choi, Y. K. Chung, T.-R. Kim, S. Shin, E. Lee, *Org. Lett.* **2007**, *9*, 3225–3228; g) S. Kollmann, R. Fröhlich, D. Hoppe, *Synthesis* **2007**, 883–892; h) S. N. Chavre, H. Choo, J. K. Lee, A. N. Pae, Y. Kim, Y. S. Cho, *J. Org. Chem.* **2008**, *73*, 7467–7471; i) S.-H. Kim, S.-J. Oh, P.-S. Ho, S.-C. Kang, K.-J. O, C.-M. Yu, *Org. Lett.* **2008**, *10*, 265–268; j) P. D. Pohlhaus, S. D. Sanders, A. T. Parsons, W. Li, J. S. Johnson, *J. Am. Chem. Soc.* **2008**, *130*, 8642–8650.

[6] For a recent review of intramolecular enolate alkylation, see: a) D. Kim, *Synlett* **2014**, *25*, 35–57; For examples of tetrahydropyran ring synthesis by intramolecular glycolate alkylation, see: b) T. Fujisawa, Y. Okumura, K. Morita, Y. Ukaji, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3487–3489; c) H. Ohrui, M. Morita, H. Meguro, *Carbohydr. Res.* **1992**, *224*, 319–325; d) S. Knapp, V. V. Thakur, M. R. Madduru, K. Malolanarasimhan, G. J. Morriello,

G. A. Doss, *Org. Lett.* **2006**, *8*, 1335 – 1337; e) M. Latif, J. I. Yun, K. Seshadri, H. R. Kim, C. H. Park, H. Park, H. Kim, J. Lee, *J. Org. Chem.* **2015**, *80*, 3315 – 3320.

[7] a) H. Lee, H. Kim, T. Yoon, B. Kim, S. Kim, H.-D. Kim, D. Kim, *J. Org. Chem.* **2005**, *70*, 8723 – 8729; b) J. Park, B. Kim, H. Kim, S. Kim, D. Kim, *Angew. Chem. Int. Ed.* **2007**, *46*, 4726 – 4728; *Angew. Chem.* **2007**, *119*, 4810 – 4812; c) B. Kim, G. Cheon, J. Park, H. Lee, H. Kim, S. Kim, D. Kim, *Heterocycles* **2007**, *74*, 171 – 175; d) W. Jeong, M. J. Kim, H. Kim, S. Kim, D. Kim, K. J. Shin, *Angew. Chem. Int. Ed.* **2010**, *49*, 752 – 756; *Angew. Chem.* **2010**, *122*, 764 – 768; e) B. Kim, T. Sohn, S. Kim, D. Kim, J. Lee, *Heterocycles* **2011**, *82*, 1113 – 1118; f) B. S. Dyson, J. W. Burton, T. Sohn, B. Kim, H. Bae, D. Kim, *J. Am. Chem. Soc.* **2012**, *134*, 11781 – 11790; g) M. J. Kim, T. Sohn, D. Kim, R. S. Paton, *J. Am. Chem. Soc.* **2012**, *134*, 20178 – 20188; h) T. Sohn, D. Kim, R. S. Paton, *Chem. Eur. J.* **2015**, *21*, 15988 – 15997; for application of the asymmetric alkylation/RCM strategy in the synthesis of medium-ring ether natural products, see: i) M. T. Crimmins, E. A. Tabet, *J. Am. Chem. Soc.* **2000**, *122*, 5473 – 5476 and references therein.

[8] a) H. Kim, W. J. Choi, J. Jung, S. Kim, D. Kim, *J. Am. Chem. Soc.* **2003**, *125*, 10238 – 10240 and references therein; b) H. Lee, H. Kim, S. Baek, S. Kim, D. Kim, *Tetrahedron Lett.* **2003**, *44*, 6609 – 6612; c) S. Baek, H. Jo, H. Kim, H. Kim, S. Kim, D. Kim, *Org. Lett.* **2005**, *7*, 75 – 77.

[9] a) Z.-B. Zhang, Z.-M. Wang, Y.-X. Wang, H.-Q. Liu, G.-X. Lei, M. Shi, *J. Chem. Soc. Perkin Trans. 1* **2000**, 53 – 57; b) the enantiomeric excess for **5** (> 91 % *ee*) was determined by ^{1}H NMR analysis of the corresponding Mosher esters following standard protocols (see J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543 – 2549; J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512 – 519); details are found the Supporting Information; c) for synthesis of the antipode of **5**, see: Ref. [4n].

[10] S. M. Glueck, W. M. F. Fabian, K. Faber, S. F. Mayer, *Chem. Eur. J.* **2004**, *10*, 3467 – 3478.

[11] K. P. M. Vanhesschel, Z.-M. Wang, K. B. Sharpless, *Tetrahedron Lett.* **1994**, *35*, 3469 – 3472.

[12] a) Y.-G. Suh, B.-A. Koo, J.-A. Ko, Y.-S. Cho, *Chem. Lett.* **1993**, *22*, 1907 – 1910; b) difficulties encountered in the opening of epoxy amide **8** using chloride and iodide prevented us from investigating internal alkylation of the corresponding halo α-alkoxy amides.

[13] T. Iversen, D. R. Bundle, *J. Chem. Soc. Chem. Commun.* **1981**, 1240 – 1241.

[14] E. J. Corey, H. Cho, C. Rűcker, D. H. Hua, *Tetrahedron Lett.* **1981**, *22*, 3455 – 3458.

[15] For the effect of silyl protecting groups on chelation, see: a) M. T. Reetz, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556 – 569; *Angew. Chem.* **1984**, *96*, 542 – 555; b) M. T. Reetz, M. Hűllmann, *J. Chem. Soc. Chem. Commun.* **1986**, 1600 – 1602; c) S. D. Kahn, G. E. Keck, W. J. Hehre, *Tetrahedron Lett.* **1987**, *28*, 279 – 280; d) G. E. Keck, S. Castellino, *Tetrahedron Lett.* **1987**, *28*, 281 – 284; e) S. V. Frye, E. L. Eliel, R. Cloux, *J. Am. Chem. Soc.* **1987**, *109*, 1862 – 1863; f) A. J. Stern, J. S. Swenton, *J. Org. Chem.* **1989**, *54*, 2953 – 2958; g) S. Shambayati, J. F. Blake, S. G. Wierschke, W. L. Jorgensen, S. L. Schreiber, *J. Am. Chem. Soc.* **1990**, *112*, 697 – 703; h) X. Chen, E. R. Hortelano, E. L. Eliel, S. V. Frye, *J. Am. Chem. Soc.* **1990**, *112*, 6130 – 6131; i) X. Chen, E. R. Hortelano, E. L. Eliel, S. V. Frye, *J. Am. Chem. Soc.* **1992**, *114*, 1778 – 1784; j) D. A. Evans, J. L. Duffy, M. J. Dart, *Tetrahedron Lett.* **1994**, *35*, 8537 – 8540; k) G. R. Stanton, C. N. Johnson, P. J. Walsh, *J. Am. Chem. Soc.* **2010**, *132*, 4399 – 4408.

[16] a) The TMS group was removed to simplify product analysis because varying amounts of desilylated products were also obtained from the alkylation; b) in the experiments with LiHMDS and NaHMDS (entries 8 and 9 in Scheme 3), the reaction did not proceed beyond 45 and 40 % conversion, respectively.

[17] a) H. Iida, N. Yamazaki, C. Kibayashi, *J. Org. Chem.* **1986**, *51*, 3769 – 3771; b) J. S. Clark, A. B. Holmes, *Tetrahedron Lett.* **1988**, *29*, 4333 – 4336; c) K. Tsushima, A. Murai, *Tetrahedron Lett.* **1992**, *33*, 4345 – 4348.

[18] Y. Oikawa, T. Yoshioka, O. Yonemitsu, *Tetrahedron Lett.* **1982**, *23*, 885 – 888.

[19] H. Wang, I. D. Kozekov, T. M. Harris, C. J. Rizzo, *J. Am. Chem. Soc.* **2003**, *125*, 5687 – 5700 and references therein.

[20] O. Mitsunobu, M. Yamada, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380 – 2382.

Received: January 20, 2016
Revised: March 10, 2016
Published online: April 21, 2016

