Organic LETTERS

Letter

pubs.acs.org/OrgLett

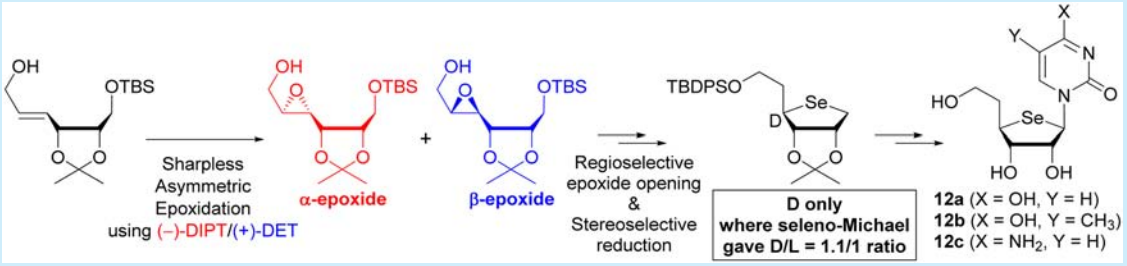
Stereoselective Synthesis of D-5-Homo-4-selenoribose as a Versatile Intermediate for 4′-Selenonucleosides

Gyudong Kim,[†] Yoojin Choi,[†] Pramod K. Sahu,[†] Jinha Yu,[†] Shuhao Qu,[†] Dongjoo Lee,[‡] and Lak Shin Jeong*[,†]

[†]Research Institute of Pharmaceutical Sciences, College of Pharmacy, Seoul National University, Seoul 151-742, Korea

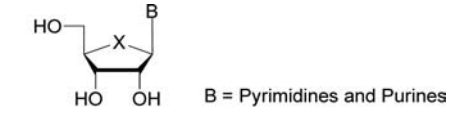
[‡]College of Pharmacy, Ajou University, Suwon 443-749, Korea

Supporting Information



ABSTRACT: Stereoselective synthesis of D-5-homo-4-selenoribose, serving as a versatile intermediate for the synthesis of 4′-selenonucleosides **12a–c**, was accomplished using Sharpless asymmetric epoxidation, regioselective cleavage of the *α,β*-epoxide, and stereoselective reduction of the ketone as the key steps.

4′-Selenonucleosides **1** belong to nonclassical nucleosides in which the furanose ring oxygen is replaced by a selenium (Figure 1).[1,2] They show different sugar puckering from that of



1 (X = Se): 4′-Selenonucleosides
2 (X = O): 4′-Oxonucleosides
3 (X = S): 4′-Thionucleosides

Figure 1. Structures of bioisosteric nucleosides **1–3**.

4′-oxo- (**2**) or 4′-thionucleosides (**3**), possibly due to the bulky selenium atom. For example, 4′-selenouridine adopts the 2′-endo/3′-exo (South) conformation, whereas uridine shows the opposite 2′-exo/3′-endo (North) conformation, indicating that gauche effects are overwhelmed by steric effects, induced by bulky selenium atom.[2g] Recently, oligonucleosides containing 4′-selenonucleosides were successfully synthesized, and they showed promising chemical stability, enough to be studied as biological tools or drugs.[3]

We have synthesized many classes of 4′-selenonucleosides for the development of antiviral and antitumor agents, but most of the synthesized compounds did not exhibit significant antiviral or antitumor activity.[2] It was hypothesized that the lack of biological activity might be attributed to no phosphorylation by cellular kinases because of the steric effects induced by the bulky selenium atom. Thus, we designed and synthesized D-5′-homo-4′-selenonucleosides using a novel seleno-Michael reaction as a key step because it was expected that one-carbon homologation could neutralize the steric effects imparted by the selenium atom.[2j] As expected, D-5′-homo-4′-selenonucleosides exhibited potent antiviral activity, indicating that they could be phosphorylated by cellular kinases, unlike normal 4′-selenonucleosides. From this study, it was discovered that D-5′-homo-4′-selenonucleosides could serve as novel templates for further development of new antiviral or antitumor agents.[2j]

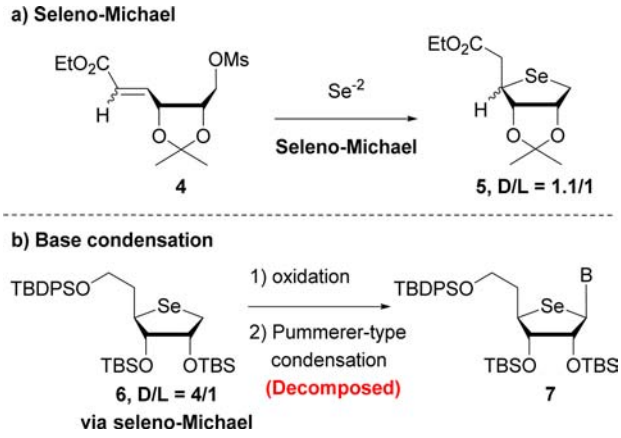
However, as illustrated in Scheme 1, the diastereoselectivity of the novel seleno-Michael reaction of **4** resulted in a 1.1:1 ratio of Michael adducts **5**,[2j] which was not suitable for a comprehensive structure–activity relationship study. In addition, the TBS-protected selenoribose **6** was prepared in a D/L = 4/1 ratio via a seleno-Michael reaction, but it could not afford base-condensed product **7** due to decomposition. Thus, stereoselective formation of acetonide-protected D-5-homo-4-selenoribose **11**[2j] has been highly desirable to search for new therapeutically useful agents from 4′-selenonucleosides.

For the exclusive synthesis of the key intermediate **11**, we decided to employ the Sharpless asymmetric epoxidation (SAE) of **8**, regioselective cleavage of the epoxides **9*α*** and **9*β***, and stereoselective reduction of the ketone **19** using DIBAL-H as the key steps. Herein, we report the stereoselective synthesis of the key intermediate D-5-homo-4-selenoribose **11** from 2,3-*O*-isopropylidene-L-erythrofuranose (**13**)[4a] and its conversion to D-5′-homo-4′-selenonucleosides **12a–c** (Scheme 2).

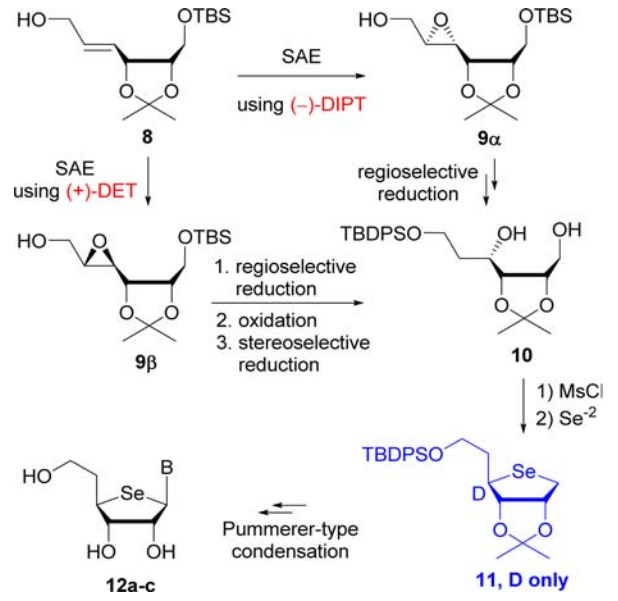
Received: August 19, 2015
Published: September 8, 2015

DOI: 10.1021/acs.orglett.5b02393
Org. Lett. 2015, 17, 4636–4639

Scheme 1. (a) Previously Developed D-5-Homo-4-selenoribose via Seleno-Michael Reaction. (b) Base Condensation of TBS-Protected Selenoribose under Pummerer-Type Conditions



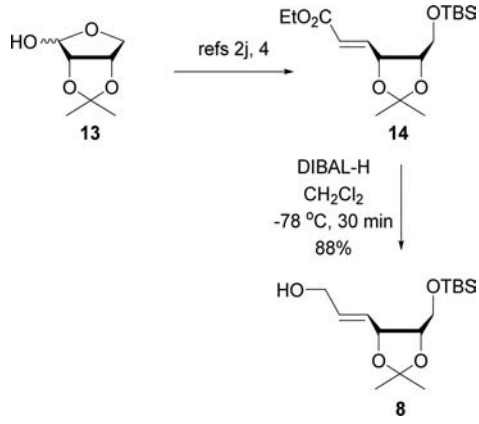
Scheme 2. Key Reactions Developed in This Study



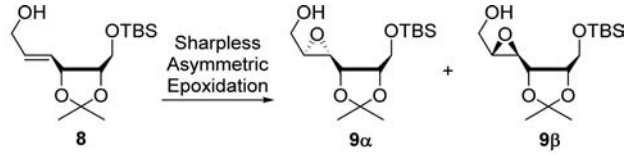
For the synthesis of the substrate **8** for Sharpless asymmetric epoxidation, lactol **13**[4a] was converted to known compound **14**,[4b−d] which was reduced with DIBAL-H to give the desired substrate, (*E*)-allylic alcohol **8** (Scheme 3).

With the key asymmetric epoxidation substrate **8** in hand, Sharpless asymmetric epoxidation[5] of **8** was tried under several conditions, as shown in Scheme 4. Epoxidation (entry 1) using (+)-DET afforded the undesired *β*-epoxide **9*β*** exclusively. Thus, it was thought that the use of (−)-DET might produce the desired *α*-epoxide **9*α*** as a single diastereomer. To our surprise and disappointment, epoxidation of **8** using (−)-DET afforded the undesired **9*β*** as the major isomer (entry 2) and the desired *α*-epoxide **9*α*** with low stereoselectivity (entry 3). The optimal result (entry 4) was obtained using (−)-DIPT at −25 °C, which afforded an inseparable mixture of **9*α*** and **9*β*** in a 3:1 ratio after considerable experimentation (Scheme 4). Epoxidation of **8** with $VO(acac)_2$ (0.1 equiv) and TBHP (3 equiv) in toluene[5a] at reflux or *m*-CPBA (3 equiv) and $NaHCO_3$ (1.5 equiv) in CH_2Cl_2 at room temperature still afforded the undesired **9*β*** as a major isomer. In addition, we

Scheme 3. Synthesis of (*E*)-Allylic Alcohol 8 for Sharpless Asymmetric Epoxidation Substrate



Scheme 4. Sharpless Asymmetric Epoxidation of (*E*)-Allylic Alcohol 8



entry[a]	tartrate	temp (°C)	time (h)	ratio (9α:9β)[b]	yield (%)[c]
1	(+)-DET	−20	16	9β only	74
2	(−)-DET	−20 to 0	100	1 : 2.7	70
3	(−)-DET	−20	112	1.9 : 1	56 (66[d])
4	(−)-DIPT	−25	40	3 : 1	75

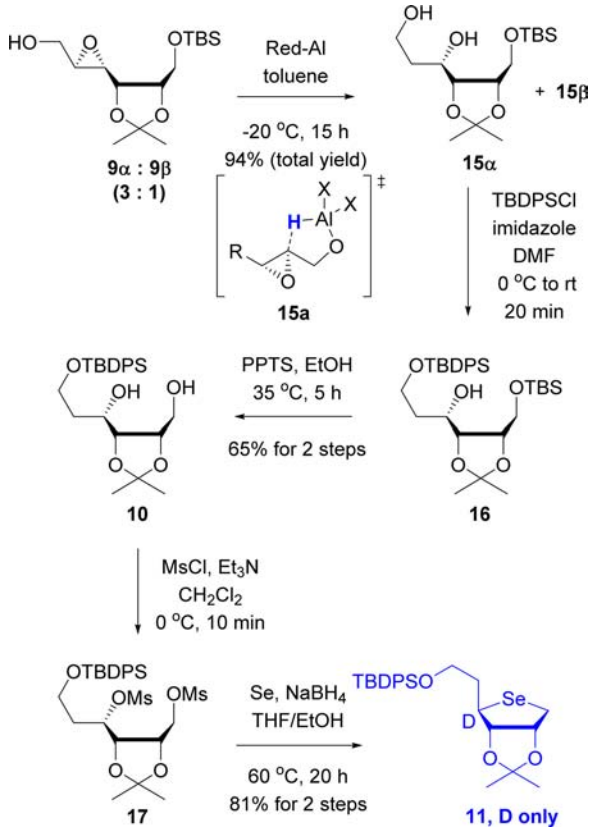
[a]Reaction conducted using chiral tartrate (1.2 equiv), $Ti(O\text{-}i\text{-}Pr)_4$ (1.0 equiv), TBHP (4.0 equiv), 4Å-MS, CH_2Cl_2 (0.5 M). [b]Determined by crude ^1H NMR. [c]Isolated total yield after silica gel chromatography. [d]Based on recovery of starting material.

were unable to introduce the epoxide moiety using the (*Z*)-allylic alcohol under Sharpless asymmetric epoxidation conditions.[5f] The diastereoselectivity of the asymmetric epoxidation has been explained by "reagent-controlled" epoxidation using a chiral tartrate-$Ti(O\text{-}i\text{-}Pr)_4$ complex. Epoxidation of allylic alcohol **8** using (−)-DET (or DIPT) reflects the outcome of consonance (a mismatched pair) of the reagent preference for *α*-attack to afford the threo selectivity, while using (+)-DET, the reagent's preference is switched to the *β*-face (a matched pair) to afford the erythro selectivity.[5g] Epoxidation of carbohydrate-derived *γ*-alkoxy (*E*)-allylic alcohols under various conditions also depends on the structures of the carbohydrate moiety, showing quite different diastereoselectivity.[5g,j]

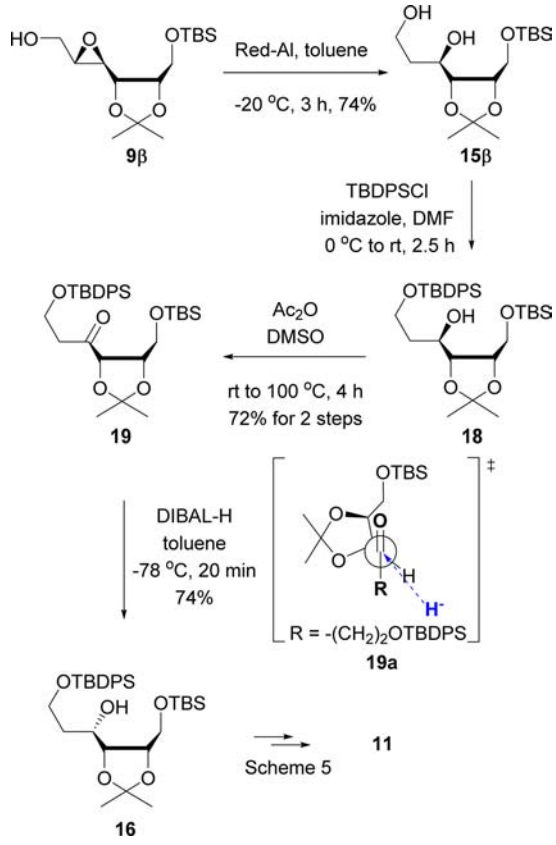
With **9*α*** and **9*β*** in hand, we turned our attention to preparation of the key D-5-homo-4-selenoribose **11** (Scheme 5). Regioselective epoxide cleavage of a 3:1 mixture of **9*α*** and **9*β*** was achieved by Red-Al to obtain **15*α*** and **15*β***, which could be easily separated by silica gel chromatography. The regioselective epoxide cleavage presumably occurs by intramolecular hydride reduction as illustrated in the transition state **15a**[6] (Scheme 5). Diol **15*α*** was transformed into the key intermediate **16** by regioselective TBDPS protection, followed by selective removal of TBS group using PPTS. The diol **10**

DOI: 10.1021/acs.orglett.5b02393
Org. Lett. 2015, 17, 4636−4639

Scheme 5. Stereoselective Synthesis of D-5-Homo-4-selenoribose 11 from a 3:1 Mixture of 9α and 9β



Scheme 6. Stereoselective Synthesis of the Same Intermediate 11 from β-Epoxide 9β

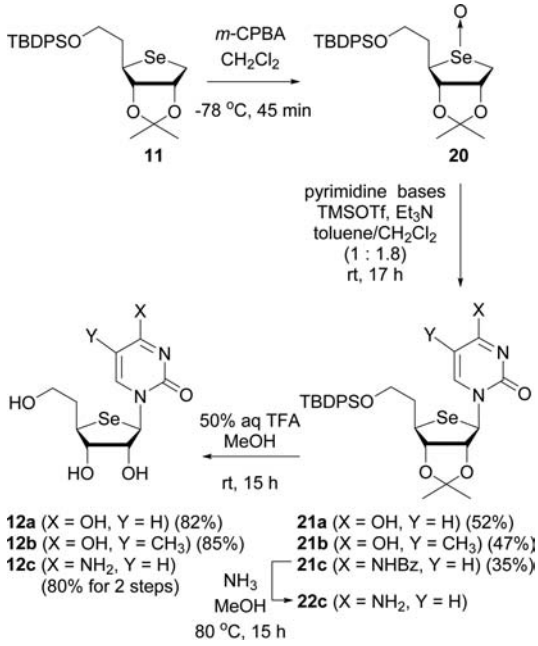


was treated with MsCl to give the dimesylate, which was cyclized using selenium dianion to afford the desired D-5-homo-4-selenoribose **11**[2j] as a single stereoisomer in 81% yield from diol **10**.

The undesired product **9β**, obtained exclusively from Sharpless asymmetric epoxidation (entry 1 in Scheme 4), could be transformed to the same desired D-5-homo-4-selenoribose **11** by the regioselective cleavage of epoxide **9β**, selective protection, and Albright–Goldman oxidation[8] followed by stereoselective reduction of ketone **19** to obtain **16** (Scheme 6). Tactics other than this turned out to be problematic. For instance, Mitsunobu reaction of **18** gave only recovery of starting material. Also, bromination of **18** with inversion of configuration upon exposure to CBr_4 and Ph_3P resulted in the formation of the oxacylized compound accompanied by TBS deprotection. Thus, we turned our attention into stereoselective DIBAL-H reduction of ketone **19**, based on the Felkin–Ahn transition state **19a**[7] as illustrated in Scheme 6. It is noteworthy that during the DIBAL-H reduction in THF as solvent TBS migration was a nuisance, but changing from THF to the nonpolar toluene prevented TBS migration. The key intermediate **16** was converted to the same D-5-homo-4-selenoribose **11** by the method described in Scheme 5.

The key D-5-homo-4-selenoribose **11** was oxidized to selenoxide **20**, which was condensed with pyrimidine bases such as uracil, thymine, and N^4-benzoylcytosine in the presence of TMSOTf and Et_3N to yield the desired β-nucleosides **21a–c** exclusively.[2j] The removal of the benzoyl group of **21c** with methanolic ammonia produced **22c**. Treatment of **21a**, **21b**, and **22c** with 50% aqueous TFA afforded the final nucleosides **12a–c**, respectively[2j] (Scheme 7).

Scheme 7. Stereoselective Synthesis of D-5′-Homo-4′-seleno Nucleosides 12a–c



In conclusion, enantiomerically pure D-5-homo-4-selenoribose **11** was synthesized from 2,3-*O*-isopropylidene-L-erythrofuranose (**13**) using Sharpless asymmetric epoxidation, regioselective cleavage of the epoxide, stereoselective reduction of a ketone, and seleno cyclization. This synthetic protocol,

DOI: 10.1021/acs.orglett.5b02393
Org. Lett. 2015, 17, 4636–4639

resulting in the sole formation of **11**, was superior to the previous method using the seleno-Michael reaction giving only 1.1:1 diastereoselectivity. This result makes it possible for large-scale preparation. The key intermediate **11** was converted to the final 4′-selenonucleosides **12a−c** using a Pummerer-type condensation as the key step. It is expected that the final nucleosides **12a−c** will be utilized as important building blocks for the development of biologically active nucleosides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02393.

^{1}H and ^{13}C NMR spectra of all new compounds and preparation of starting materials (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: lakjeong@snu.ac.kr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the grant from Midcareer Research Program (370C-20130120) of National Research Foundation, Korea

■ REFERENCES

(1) Jordheim, L. P.; Durantel, D.; Zoulim, F.; Dumontet, C. *Nat. Rev. Drug Discovery* **2013**, *12*, 447.

(2) (a) Inagaki, Y.; Minakawa, N.; Matsuda, A. *Nucleic Acids Symp. Ser.* **2007**, *51*, 139. (b) Jeong, L. S.; Tosh, D. K.; Kim, H. O.; Wang, T.; Hou, X.; Yun, H. S.; Kwon, Y.; Lee, S. K.; Choi, J.; Zhao, L. X. *Org. Lett.* **2008**, *10*, 209. (c) Tosh, D. K.; Choi, W. J.; Kim, H. O.; Lee, Y.; Pal, S.; Hou, X.; Choi, J.; Choi, S.; Jeong, L. S. *J. Org. Chem.* **2008**, *73*, 4259. (d) Jayakanthan, K.; Johnston, B. D.; Pinto, B. M. *Carbohydr. Res.* **2008**, *343*, 1790. (e) Jeong, L. S.; Choi, Y. N.; Tosh, D. K.; Choi, W. J.; Kim, H. O.; Choi, J. *Bioorg. Med. Chem.* **2008**, *16*, 9891. (f) Jeong, L. S.; Tosh, D. K.; Choi, W. J.; Lee, S. K.; Kang, Y.-J.; Choi, S.; Lee, J. H.; Lee, H.; Lee, H. W.; Kim, H. O. *J. Med. Chem.* **2009**, *52*, 5303. (g) Varughese, A.; Choi, W. J.; Chun, J.; Kim, H. O.; Jeon, J. H.; Tosh, D. K.; Lee, H. W.; Chandra, G.; Choi, J.; Jeong, L. S. *Org. Lett.* **2010**, *12*, 2242. (h) Taniike, H.; Inagaki, Y.; Matsuda, A.; Minakawa, N. *Tetrahedron* **2011**, *67*, 7977. (i) Yu, J.; Kim, J.-H.; Lee, H. W.; Alexander, V.; Ahn, H.-C.; Choi, W. J.; Choi, J.; Jeong, L. S. *Chem. - Eur. J.* **2013**, *19*, 5528. (j) Sahu, P. K.; Kim, G.; Yu, J.; Ahn, J. Y.; Song, J.; Choi, Y.; Jin, X.; Kim, J.; Lee, S. K.; Park, S.; Jeong, L. S. *Org. Lett.* **2014**, *16*, 5796.

(3) (a) Inagaki, Y.; Minakawa, N.; Matsuda, A. *Nucleic Acids Symp. Ser.* **2008**, *52*, 329. (b) Watts, J. K.; Johnston, B. D.; Jayakanthan, K.; Wahba, A. S.; Pinto, B. M.; Damha, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8578. (c) Tarashima, N.; Hayashi, K.; Terasaki, M.; Taniike, H.; Inagaki, Y.; Hirose, K.; Furukawa, K.; Matsuda, A.; Minakawa, N. *Org. Lett.* **2014**, *16*, 4710.

(4) (a) Murali Krishna, U.; Deodhar, K. D.; Trivedi, G. K. *Tetrahedron* **2004**, *60*, 4829. (b) Nagarapu, L.; Karnakanti, S.; Bantu, R. *Tetrahedron* **2012**, *68*, 5829. (c) Kitamoto, K.; Nakayama, Y.; Sampei, M.; Ichiki, M.; Furuya, N.; Sato, T.; Chida, N. *Eur. J. Org. Chem.* **2012**, *2012*, 4217. (d) The (*Z*)-isomer was isomerized to the (*E*)-isomer **14** in the presence of a RhH(CO) $(PPh_3)_3$ catalyst (ref 2j).

(5) (a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136. (b) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (c) Katsuki, T.; Lee, W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373. (d) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337. (e) Valverde, S.; Herradon, B.; Rabanal, R. M.; Martin-Lomas, M. *Can. J. Chem.* **1987**, *65*, 332. (f) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (g) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A.; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245. (h) Sarabia, F.; Sanchez-Ruiz, A. *J. Org. Chem.* **2005**, *70*, 9514. (i) Kumar, K. S.; Reddy, C. S. *Org. Biomol. Chem.* **2012**, *10*, 2647. (j) Kim, G.; Sohn, T.; Kim, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 272.

(6) (a) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437. (b) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719.

(7) Gallos, J. K.; Stathakis, C. I.; Salapassidou, M. J.; Grammatoglou, C. E.; Koumbis, A. E. *Carbohydr. Res.* **2007**, *342*, 744.

(8) Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1965**, *87*, 4214.

DOI: 10.1021/acs.orglett.5b02393
Org. Lett. 2015, 17, 4636−4639