Organic LETTERS

Letter

pubs.acs.org/OrgLett

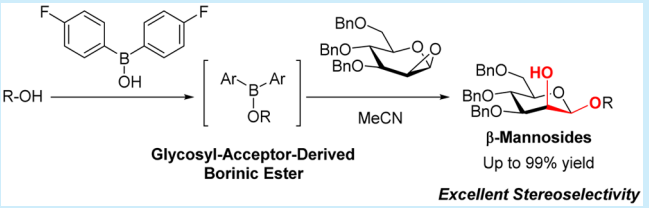
Glycosyl-Acceptor-Derived Borinic Ester-Promoted Direct and β-Stereoselective Mannosylation with a 1,2-Anhydromannose Donor

Masamichi Tanaka, Junki Nashida, Daisuke Takahashi,* and Kazunobu Toshima*

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

Supporting Information

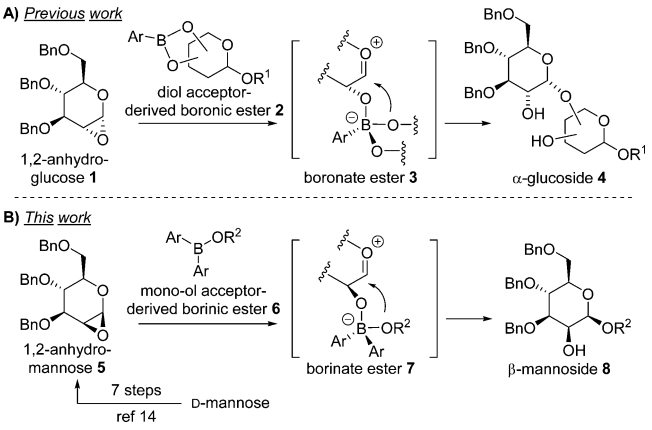
ABSTRACT: β-Stereoselective mannosylations were conducted using a 1,2-anhydromannose donor and mono-ol acceptors in the presence of a glycosyl-acceptor-derived borinic ester. Reactions proceeded smoothly under mild conditions to provide the corresponding β-mannosides with high stereoselectivity in moderate to high yields. In addition, the present glycosylation method was applied successfully to the total synthesis of acremomannolipin A.



β-Mannosides are components of biologically active natural products and natural glycans, such as mannans, glycolipids, and N-linked glycoproteins, which play important roles in biological activities that include cell signaling, protein folding, and immune responses. Therefore, efficient syntheses of these glycosides have attracted much attention.[1] However, the stereoselective synthesis of β-mannosides is difficult due to both the anomeric effect and steric effect of the axial substituent at the C2 position.[2] To overcome these obstacles, efficient indirect[3] and direct[4] methods have been developed. The intramolecular aglycon delivery (IAD) introduced by Hindsgaul et al.[5] is an example of the indirect method that was extended by Stork et al.,[6] as well as Ito and Ogawa.[7] An example of the direct method is the 4,6-*O*-benzylidene method reported by Crich et al.[8] Detailed mechanistic studies[9] suggested that β-mannosylation proceeds via S_N2-like displacement of the triflate anion from α-triflate by a glycosyl acceptor or the functionally indistinguishable β-face attack by a glycosyl acceptor on a transient contact ion pair (CIP). Subsequently, several 4,6-*O*-benzylidene-protected mannosyl donors[10] and a 4,6-*O*-silylene-protected thiomannosyl donor[11] were used successfully for the stereoselective synthesis of β-mannosides. Recently, Demchenko et al. reported β-stereoselective mannosylation involving hydrogen-mediated aglycon delivery (HAD) with 3- and/or 6-*O*-picoloyl thiomannosyl donors that did not have 4,6-*O*-benzylidene protection.[12]

A recent report[13] described regioselective and 1,2-*cis*-α-stereoselective glycosylations using 3,4,6-tri-*O*-benzyl-1,2-anhydroglucose (**1**) and diol glycosyl acceptors in the presence of the corresponding glycosyl-acceptor-derived boronic ester catalyst **2**. In this study, the reactions proceeded smoothly to provide the corresponding α-glucoside **4** with high stereo- and regioselectivity in high yield without any further additives under mild conditions (Scheme 1A). On the basis of previous work, the mono-ol glycosyl-acceptor-derived borinic ester **6** was expected to act as an activator of 1,2-anhydromannose **5**[14] to generate β-mannoside **8** with high stereoselectivity. The present report describes a novel direct and β-stereoselective mannosylation of **5** and a mono-ol glycosyl acceptor utilizing a glycosyl-acceptor-derived borinic ester **6** and its application to the total synthesis of the natural product. The borinic ester **6** was expected to activate **5** without any further additives to afford the tetracoordinate borinate ester **7** involving an oxonium cation moiety. Concomitant glycosylation from the boron-bound oxygen atom in the borinate ester from the same face should provide β-mannoside **8** (Scheme 1B). This is the first example of a direct and highly β-stereoselective mannosylation method using a 1,2-anhydromannose donor.

Scheme 1. (A) Regio- and α-Stereoselective Glucosylation Using a Glycosyl-Acceptor-Derived Boronic Ester; (B) β-Stereoselective Mannosylation Using a Glycosyl-Acceptor-Derived Borinic Ester



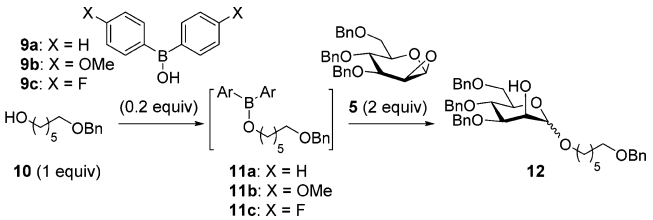
To investigate the hypothesis, 3,4,6-tri-*O*-benzyl-1,2-anhydromannose (**5**) and diphenylborinic acid (**9a**),[15] bis(4-

Received: March 31, 2016

DOI: 10.1021/acs.orglett.6b00926
Org. Lett. XXXX, XXX, XXX−XXX

methoxyphenyl)borinic acid (**9b**),[16] and bis(4-fluorophenyl)-borinic acid (**9c**)[16] were selected as the glycosyl donor and arylborinic acids, respectively. First, glycosylations of **5** and 6-*O*-benzyl-1-hexanol (**10**) were attempted using catalytic amounts of **9a-c** under different reaction conditions. The results show that the glycosylation of **5** and **10** using **9a** in THF at −40 °C for 24 h proceeded to give glycoside **12** in 60% yield with a 42:58 α/β ratio (Table 1, entry 1). To improve β-

Table 1. Glycosylations of 5 and 10 Using Borinic Acids 9a–c under Several Reaction Conditions



entry	borinic acid	solvent	temp (°C)	time (h)	yield of **12** (%)	α/β ratio of **12**
1	**9a**	THF	−40	24	60	42:58
2	**9b**	THF	−40	24	68	81:19
3	**9c**	THF	−40	24	64	17:83
4	**9c**	toluene	−40	24	38	α only
5	**9c**	CH_2Cl_2	−40	24	54	α only
6	**9c**	MeCN	−40	24	73	8:92
7	**9c**	MeCN	−20	24	81	β only
8	**9c**	MeCN	0	24	90	β only
9	**9c**	MeCN	0	3	73	β only
10	**9c**	MeCN	0	6	77	β only
11	**9c**	MeCN	0	12	82	β only

stereoselectivity, the electrostatic effect of the substituents on the benzene ring in the borinic esters was investigated using **9b** and **9c**. When **9b**, which possesses an electron-donating methoxy group, was used, undesired α-stereoselectivity was observed (Table 1, entry 2). In contrast, when **9c**, which possesses an electron-withdrawing fluorine group, was used, glycoside **12** was obtained in 64% yield with good β-stereoselectivity, along with recovered **10** in 20% yield (Table 1, entry 3). The anomeric configuration of **12*α*** and **12*β*** was determined by $^1J_{CH}$ coupling constants, 171 and 155 Hz, respectively.[17] These results suggest that the electron-donating group in **11b** reduces the Lewis acidity of the boron atom, which causes weak activation of **5** by **11b**, and intermolecular S_N2 type substitution of **10** from the α-face of **5** (Figure 1a). However, the electron-withdrawing group in **11c** increases the Lewis acidity of the boron atom, which causes activation of **5** by **11c**, formation of the oxonium cation, and S_N1 type intramolecular nucleophilic attack of the boron-bound oxygen atom in the borinate ester from the same β-face of the oxonium cation (Figure 1b).

Next, the solvent effect on glycosylation of **5** and **10** was examined in the presence of **9c** using toluene, CH_2Cl_2, and MeCN. The results indicated that complete α-stereoselectivity occurred when toluene and CH_2Cl_2 were used (Table 1, entries 4 and 5). In contrast, the reaction proceeded smoothly to provide **12** in 73% yield with high β-stereoselectivity, along with recovered **10** in 19% yield, when MeCN was used (Table 1, entry 6). These results indicate that MeCN is the best solvent for this reaction. Next, the reaction time and reaction temperature were optimized. When glycosylation was con-

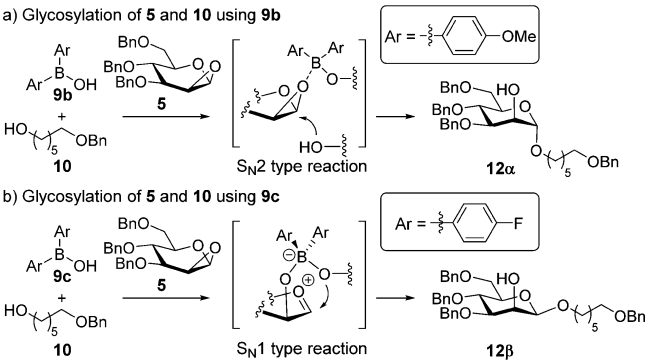
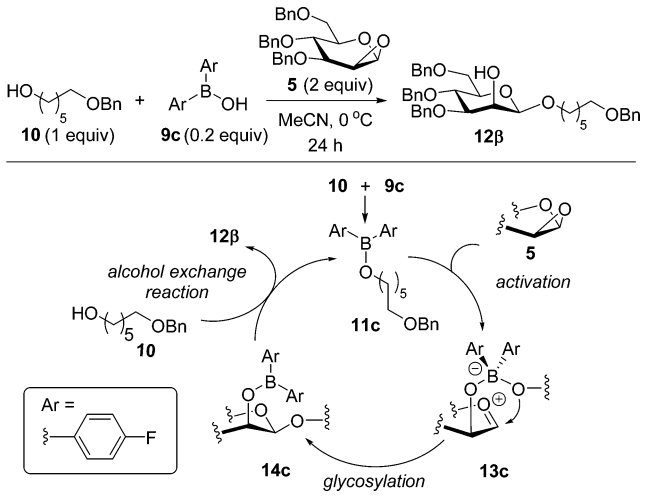


Figure 1. Electrostatic effect of the substituents on the benzene ring in **9b** and **9c** in the glycosylation of **5** and **10**.

ducted at 0 °C for 24 h, the chemical yield of **12** was greater than those obtained at −20 and −40 °C (Table 1, entries 6–8). In addition, a reaction time of 24 h gave the greatest yield of **12** with complete β-stereoselectivity (Table 1, entries 8–11). Thus, glycosylaton of **5** and **10** using **9c** in MeCN at 0 °C for 24 h provided the best result, producing **12*β*** in 90% yield as a single isomer (Table 1, entry 8). These results led to the proposal of the reaction mechanism shown in Scheme 2. First,

Scheme 2. Proposed Catalytic Cycle for Glycosylation of 5 and 10 Using 9c

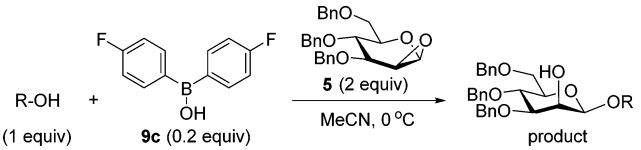


arylborinic acid **9c** reversibly binds to mono-ol acceptor **10**. The resulting glycosyl acceptor-derived borinic ester **11c** activates the 1,2-anhydromannose **5** without any further additives. The oxonium cation intermediate **13c** involving a tetracoordinate borinate ester moiety increases the nucleophilicity of the boron-bound oxygen atom, and concomitant glycosylation from the B–O moiety in the borinate ester affords the corresponding borinic ester **14c**. Finally, an alcohol exchange reaction between **14c** and **10** regenerates the borinic ester catalyst **11c** and provides β-mannoside **12*β***.

Next, the scope and limitations of this glycosylation method was investigated using several alcohols. The results indicate that use of the primary alcohols **15**–**19** and the secondary alcohol **20** allowed glycosylation to proceed smoothly under mild conditions to provide the corresponding β-mannosides **23**–**28** in high yields with excellent β-stereoselectivity in the absence of any additives (Table 2, entries 1–6). However, when the secondary alcohol **21** was used, the chemical yield of the

DOI: 10.1021/acs.orglett.6b00926
Org. Lett. XXXX, XXX, XXX–XXX

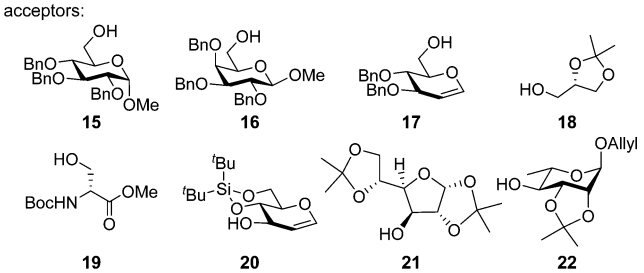
Table 2. Glycosylations of 5 and Alcohols Using a Catalytic Amount of 9c



entry	acceptor[a]	time (h)	product	yield (%)	α/β ratio
1	**15**	4	**23**[18]	99	β only
2	**16**	4	**24**	83	β only
3	**17**	3	**25**	99	β only
4	**18**	2	**26**[19]	96	β only
5	**19**	3	**27**	86	β only
6	**20**	24	**28**	95	β only
7	**21**	24	**29**	64	β only
8	**22**	24	**30**	trace	β only

[a]The acceptors are shown below.

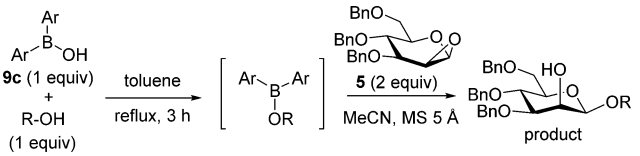
acceptors:



corresponding β-mannoside **29** was less than those of **23**−**28**. In addition, when **22** was used, only a trace amount of **30** was obtained, probably due to the low binding affinities of the relatively hindered **21** and **22** toward **9c** (Table 2, entries 7 and 8). Thus, after mixing **21** and a stoichiometric amount of **9c** in toluene at reflux for 3 h, followed by concentration *in vacuo*, glycosylation of **5** in the presence of MS 5 Å in MeCN at 0 °C for 24 h was examined. The glycosylation proceeded smoothly to give **29** in 85% yield with complete β-stereoselectivity (Table 3, entry 1). This favorable result led to the application of the same reaction conditions to the secondary alcohols **22** and **31**−**33**. The results showed that the corresponding β-mannosides **30** and **34**−**36** were obtained in moderate yields with complete β-stereoselectivity (Table 3, entries 2−5). In all cases, the anomeric configuration of the products was determined by $^1J_{CH}$ coupling constants. These results indicate that (i) the 1,2-*cis*-β-stereoselectivity obtained from this method was consistently very high and (ii) for secondary alcohols the chemical yield depended on the chemical structure of the glycosyl acceptor, probably because of the binding affinity of the glycosyl acceptor to **9c** and because the reactivity of the glycosyl-acceptor-derived borinic ester toward **5** was strongly influenced by the steric effects of the glycosyl acceptor.

Finally, the present glycosylation method was applied to the synthesis of the biologically active natural product, acremomannolipin A. Acremomannolipin A has been isolated[20] from the extract of the filamentous fungus *Acremonium strictum*, as a potential Ca^{2+} signaling modulator, and two total syntheses have been reported.[21] The synthetic scheme of acremomannolipin A is summarized in Scheme 3. Known mannitol derivative

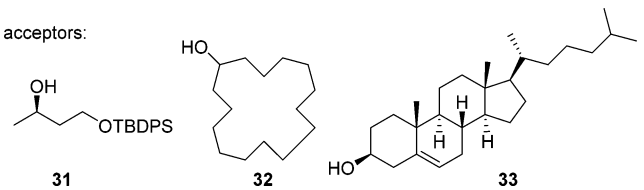
Table 3. Glycosylations of 5 and Several Alcohols Using a Stoichiometric Amount of 9c



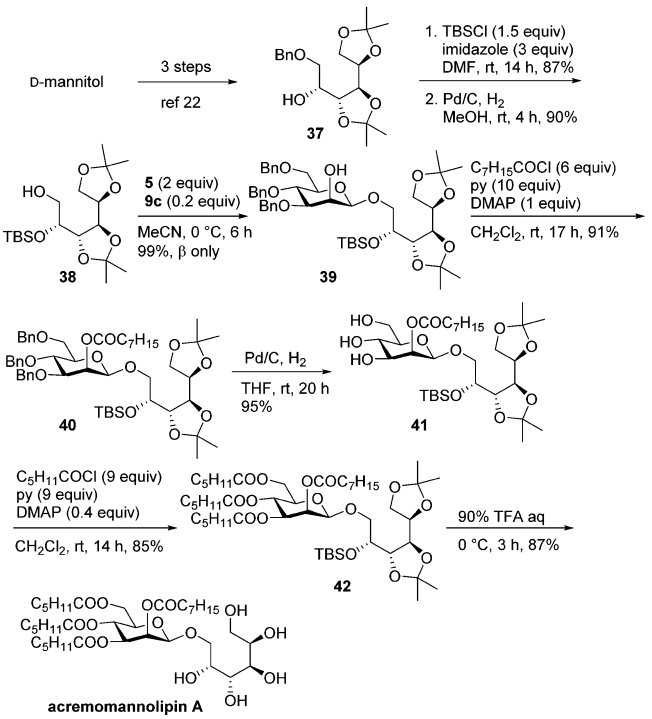
entry	acceptor	time (h)	temp (°C)	product (yield, %)	α/β ratio	recovery yield (%) of acceptor
1	**21**	24	0	**29** (85)	β only	–
2	**22**	24	0	**30** (61)	β only	39
3	**31**	6	−40	**34** (58)	β only	40
4	**32**	24	0	**35** (57)	β only	23
5[a]	**33**	24	0	**36** (56)	β only	31

[a]MeCN/THF = 4/1 was employed as a solvent.

acceptors:



Scheme 3. Total Synthesis of Acremomannolipin A



37 was prepared from D-mannitol according to the reported procedure[22] in three steps. Silylation of **37** followed by removal of benzyl group gave **38**, which was used as a glycosyl acceptor.

Next, the glycosylation of **38** and **5** was carried out using a catalytic amount of **9c** in MeCN at 0 °C for 6 h, which resulted in a 99% yield of the desired β-mannoside **39** ($^1J_{CH}$ = 157 Hz) with excellent β-stereoselectivity. These results also demonstrate the high efficiency and generality of the glycosylation method. In addition, acylation with octanoyl chloride in pyridine gave **40**. Removal of the benzyl groups in **40** followed by acylation with hexanoyl chloride gave **42**. Finally, deprotection of TBS and the acetonide groups in **42** furnished acremomannolipin A. The ^{1}H NMR, ^{13}C NMR, optical rotation, and HRMS (ESI-TOF) data for an analytical sample

DOI: 10.1021/acs.orglett.6b00926
Org. Lett. XXXX, XXX, XXX−XXX

of synthetic acremomannolipin A were identical to those reported.

In conclusion, the first direct and highly β-stereoselective mannosylation of 1,2-anhydromannose and mono-ol acceptors was developed utilizing a glycosyl-acceptor-derived borinic ester under mild conditions. The use of di(4-fluoro)phenylborinic acid (**9c**) in MeCN was effective for glycosylations with several mono-ol acceptors. Furthermore, this glycosylation method was applied successfully to the total synthesis of acremomannolipin A. Detailed mechanistic studies of this method, application to other types of acceptors, and synthetic studies of other biologically active compounds using the present method are now in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00926.

Experimental methods and details; synthetic details, ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: dtak@applc.keio.ac.jp.
*E-mail: toshima@applc.keio.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported in part by the MEXT-supported Program for the Strategic Research Foundation at Private Universities, 2012−2016, from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT).

■ REFERENCES

(1) (a) *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds; Wiley-VCH: Weinheim, 2000; Vols. *1*−*4*. (b) *Glycoscience, Chemistry and Chemical Biology*; Fraser-Reid, B. O., Tatsuta, K., Thiem, J., Eds; Springer: Berlin, 2001.

(2) (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155−173. (b) Demchenko, A. V. *Synlett* **2003**, 1225−1240.

(3) For selected reviews, see: (a) Jung, K.-H.; Müller, M.; Schmidt, R. R. *Chem. Rev.* **2000**, *100*, 4423−4442. (b) Cumpstey, I. *Carbohydr. Res.* **2008**, *343*, 1553−1573. (c) Ishiwata, A.; Lee, Y. J.; Ito, Y. *Org. Biomol. Chem.* **2010**, *8*, 3596−3608. For selected recent examples, see: (d) Partridge, K. M.; Bader, S. J.; Buchan, Z. A.; Taylor, C. E.; Montgomery, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 13647−13650. (e) Ishiwata, A.; Kaeothip, S.; Takeda, Y.; Ito, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 9812−9816.

(4) For selected reviews, see: (a) Gridley, J. J.; Osborn, H. M. I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1471−1491. (b) Crich, D. *J. Org. Chem.* **2011**, *76*, 9193−9209. (c) Nigudkar, S. S.; Demchenko, A. V. *Chem. Sci.* **2015**, *6*, 2687−2704. For a selected recent example, see: (d) Zhu, Y.; Yu, B. *Chem. - Eur. J.* **2015**, *21*, 8771−8780.

(5) Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc.* **1991**, *113*, 9376−9377.

(6) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087−1088.

(7) Ito, Y.; Ogawa, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1765−1767.

(8) (a) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 4506−4507. (b) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198−1199. (c) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321−8348.

(9) (a) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217−11223. (b) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435−436. (c) Crich, D. *J. Carbohydr. Chem.* **2002**, *21*, 663−686. (d) Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5386−5389. (e) Huang, M.; Garrett, G. E.; Birlirakis, N.; Bohé, L.; Crich, D. *Nat. Chem.* **2012**, *4*, 663−667. (f) Huang, M.; Retailleau, P.; Bohé, L.; Crich, D. *J. Am. Chem. Soc.* **2012**, *134*, 14746−14749. (g) Adero, P. O.; Furukawa, T.; Huang, M.; Mukherjee, D.; Retailleau, P.; Bohé, L.; Crich, D. *J. Am. Chem. Soc.* **2015**, *137*, 10336−10345. (h) Hosoya, T.; Kosma, P.; Rosenau, T. *Carbohydr. Res.* **2015**, *401*, 127−131.

(10) (a) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435−436. (b) Weingart, R.; Schmidt, R. R. *Tetrahedron Lett.* **2000**, *41*, 8753−8758. (c) Kim, K. S.; Kim, J. H.; Lee, Y. J.; Lee, Y. J.; Park, J. *J. Am. Chem. Soc.* **2001**, *123*, 8477−8481. (d) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015−9020. (e) Tsuda, T.; Sato, S.; Nakamura, S.; Hashimoto, S. *Heterocycles* **2003**, *59*, 509−515. (f) Tanaka, S.; Takashina, M.; Tokimoto, H.; Fujimoto, Y.; Tanaka, K.; Fukase, K. *Synlett* **2005**, 2325−2328. (g) Kim, K. S.; Fulse, D. B.; Baek, J. Y.; Lee, B.-Y.; Jeon, H. B. *J. Am. Chem. Soc.* **2008**, *130*, 8537−8547.

(11) Heuckendorff, M.; Bendix, J.; Pedersen, C. M.; Bols, M. *Org. Lett.* **2014**, *16*, 1116−1119.

(12) Pistorio, S. G.; Yasomanee, J. P.; Demchenko, A. V. *Org. Lett.* **2014**, *16*, 716−719.

(13) Nakagawa, A.; Tanaka, M.; Hanamura, S.; Takahashi, D.; Toshima, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 10935−10939.

(14) Manabe, S.; Marui, Y.; Ito, Y. *Chem. - Eur. J.* **2003**, *9*, 1435−1447.

(15) Lee, D.; Newman, S. G.; Taylor, M. S. *Org. Lett.* **2009**, *11*, 5486−5489.

(16) Mori, Y.; Kobayashi, J.; Manabe, K.; Kobayashi, S. *Tetrahedron* **2002**, *58*, 8263−8268.

(17) Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293−297.

(18) Chayajarus, K.; Chambers, D. J.; Chughtai, M. J.; Fairbanks, A. J. *Org. Lett.* **2004**, *6*, 3797−3800.

(19) Nicotra, F.; Panza, L.; Ronchetti, F.; Russo, G.; Toma, L. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1319−1324.

(20) Sugiura, R.; Kita, A.; Tsutsui, N.; Muraoka, O.; Hagihara, K.; Umeda, N.; Kunoh, T.; Takada, H.; Hirose, D. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6735−6739.

(21) (a) Tsutsui, N.; Tanabe, G.; Kita, A.; Sugiura, R.; Muraoka, O. *Tetrahedron Lett.* **2013**, *54*, 451−453. (b) Sun, P.; Wang, P.; Zhang, Y.; Zhang, X.; Wang, C.; Liu, S.; Lu, J.; Li, M. *J. Org. Chem.* **2015**, *80*, 4164−4175.

(22) Vidyasagar, A.; Sureshan, K. M. *Eur. J. Org. Chem.* **2014**, *2014*, 2349−2356.

DOI: 10.1021/acs.orglett.6b00926
Org. Lett. XXXX, XXX, XXX−XXX