Organic LETTERS

Letter

pubs.acs.org/OrgLett

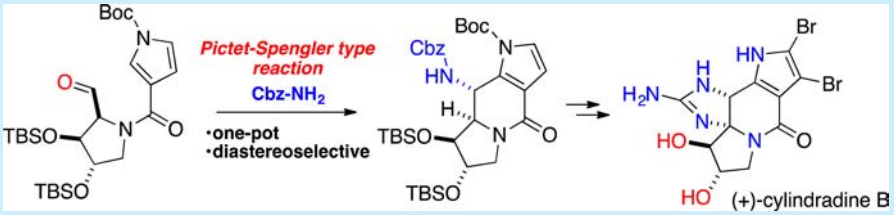
Total Synthesis of Pyrrole−Imidazole Alkaloid (+)-Cylindradine B

Makoto Iwata,[†] Yuko Kamijoh,[†] Eri Yamamoto,[‡] Masahiro Yamanaka,[‡] and Kazuo Nagasawa*[,†]

[†]Department of Biotechnology and Life Science, Tokyo University of Agriculture and Technology, 2-24-16 Naka-cho, Koganei City, Tokyo 184-8588, Japan

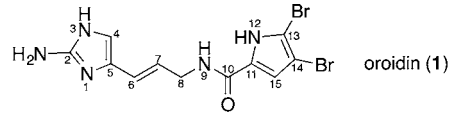
[‡]Department of Chemistry, Faculty of Science, Rikkyo University, 3-34-1 Nishi-Ikebukuro, Toshima-ku, Tokyo 171-8501, Japan

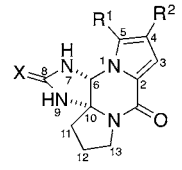
Supporting Information



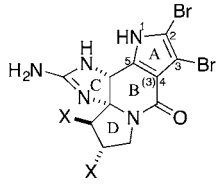
ABSTRACT: Cylindradines A and B are members of the oroidin-derived pyrrole−imidazole alkaloid (PIA) family. They possess a characteristic pyrrole-3-carbamoyl moiety, which is unusual among PIAs. We achieved a total synthesis of (+)-cylindradine B by applying a Pictet−Spengler-type reaction followed by oxidative cyclization in the presence of hypervalent iodine to construct the pyrrole-3-carbamoyl and cyclic guanidine with *N*,*N*′-aminal moieties at C6 and C10.

Pyrrole−imidazole alkaloids (PIAs) are a structurally diverse family of oroidin-derived marine natural products (Figure 1)[1] that can be mainly classified as monomeric, dimeric, and tetrameric derivatives of oroidin (**1**). Unusual biosynthetic pathways have been proposed.[1] Many of the PIA analogues have interesting biological activities, including antitumor, α_{2B} adrenoceptor agonist, and immunosuppressive activities. Thus, PIAs have received much attention from the synthetic and medicinal chemistry communities.[2] Among the monomeric PIAs, many synthetic efforts have been focused on phakellins (**2**−**4**) and phakellstatins (**5** and **6**)[2a−m] because these PIAs possess a characteristic common tetracyclic structure. In 1982,





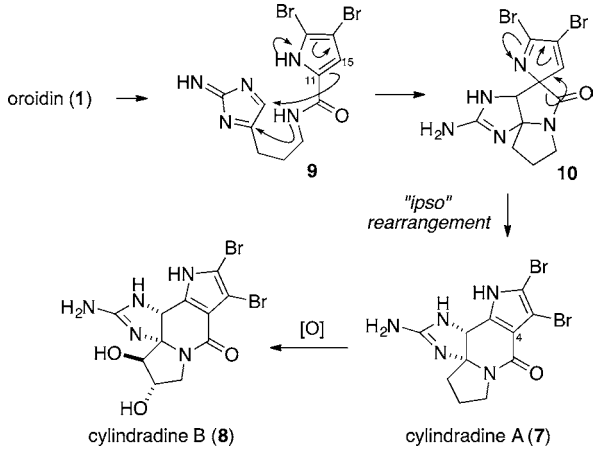
pyrrole-2-carbamoyl type	X	R¹	R²
(+)-dibromophakellin (**2**)	NH	Br	Br
(+)-monobromophakellin (**3**)	NH	H	Br
(+)-phakellin (**4**)	NH	H	H
(+)-dibromophakellstatin (**5**)	O	Br	Br
(+)-phakellstatin (**6**)	O	H	H



pyrrole-3-carbamoyl type	X
(+)-cylindradine A (**7**)	H
(+)-cylindradine B (**8**)	OH

Figure 1. Structures of oroidin (**1**) and oroidin-derived pyrrole−imidazole alkaloids.

Scheme 1. Proposed Biosynthetic Pathway of Cylindradines

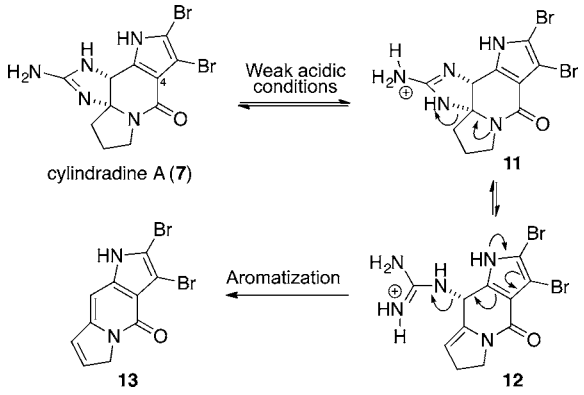


the group of Foley and Büchi independently reported a total synthesis of (±)-dibromophakellin (**2**) based on the proposed biosynthetic pathway;[2a] this was the first synthesis of a monomeric PIA. Subsequently, several total syntheses of racemic phakellins and phakellstatins were reported. Although these alkaloids possess only two asymmetric centers at C6 and C10 (*N*,*N*′-aminal), stereoselective construction of these centers is quite difficult because of their lability toward epimerization under acidic conditions, and to date only Romo's group and our group have reported enantioselective syntheses of phakellins (**2**−**4**)[2k,l] and dibromophakellstatin (**5**).[2j,m]

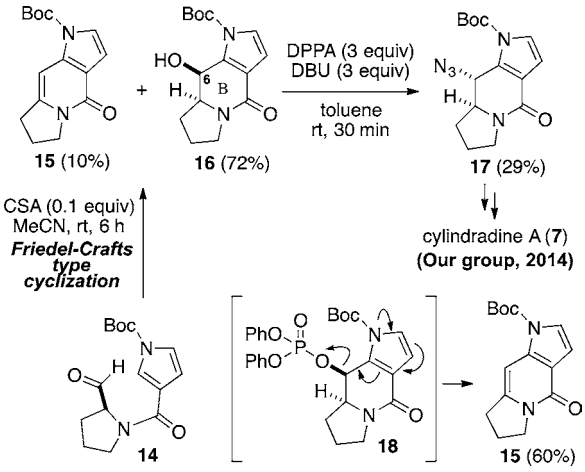
Received: December 13, 2016
Published: January 5, 2017

DOI: 10.1021/acs.orglett.6b03722
Org. Lett. 2017, 19, 420−423

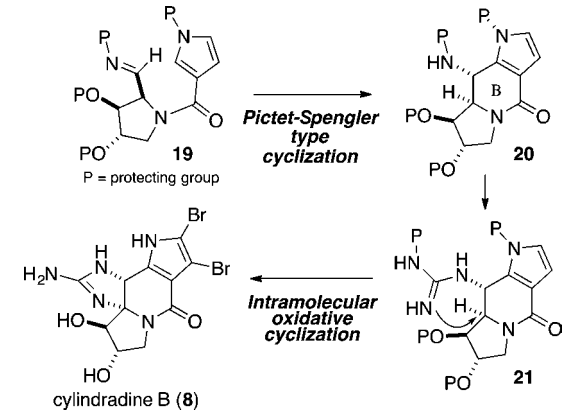
Scheme 2. Decomposition Process of Cylindradine A (7) under Acidic Conditions



Scheme 3. Problematic Steps in the Synthesis of (+)-Cylindradine A (7)



Scheme 4. Synthetic Strategy for Cylindradine B (8)



Cylindradines A (7) and B (8) are monomeric-type PIAs isolated from the marine sponge *Axinella cylindratus* by Kuramoto and co-workers. These compounds show moderate cytotoxicities toward P388 leukemia cells.[3] The cylindradines possess an unusual pyrrole-3-carbamoyl moiety, in contrast to the phakellins and other PIAs, which commonly have a pyrrole-2-carbamoyl structure. A unique biosynthetic pathway for cylindradines was proposed by Kuramoto and co-workers, involving an "ipso" rearrangement process (from **10** into **7** in Scheme 1).

Scheme 5. Synthesis of Aminal 25

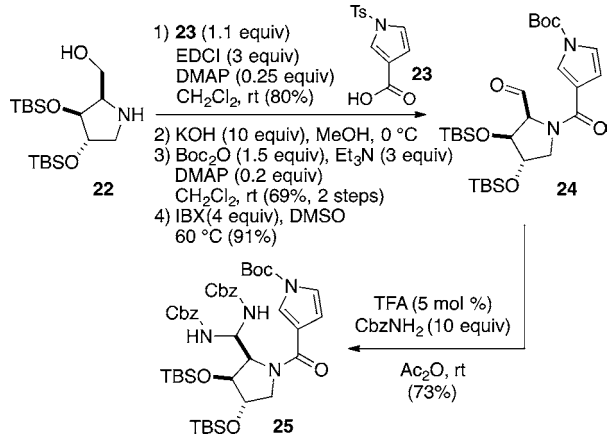
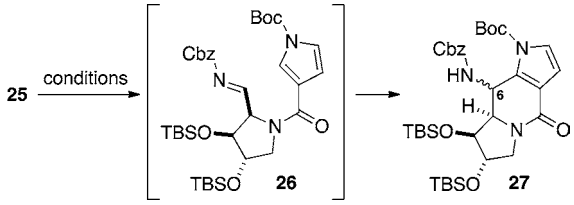


Table 1. Pictet–Spengler-Type Reaction of 25 in the Presence of Acids or Lewis Acids as Catalysts



entry	acid (10 mol %)	solvent	temp (°C)	time (h)	yield of 27 (%)	α:β
1	TFA	THF	rt	48	5	9:1
2	TFA	CH_2Cl_2	rt	48	6	10:1
3	TFA	toluene	rt	48	8	8:1
4	TFA	toluene	100	48	70	>99:1
5	AcOH	toluene	100	48	7	20:1
6	(±)-**28**	toluene	100	7	93	>99:1
7	$Cu(OTf)_2$	toluene	100	1	50	4:1
8	AgOTf	toluene	100	3	68	3:1

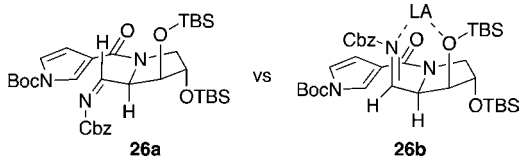
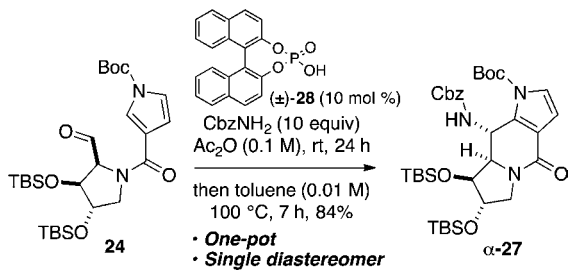


Figure 2. Plausible transition state model in the acid-mediated Pictet–Spengler-type reaction of **26**.

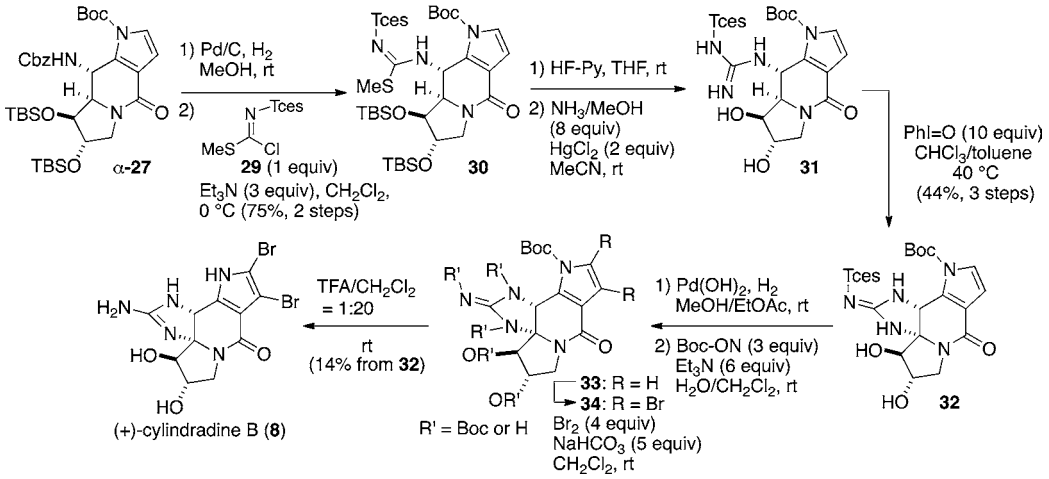
Scheme 6. One-Pot Formation of α-27 from Aldehyde 24



It is noteworthy that the pyrrole-3-carbamoyl moiety in 7 is quite unstable under acidic conditions because irreversible elimination of the guanidine occurs as a result of the electron-donating character of the pyrrole, generating the stable

DOI: 10.1021/acs.orglett.6b03722
Org. Lett. 2017, 19, 420–423

Scheme 7. Total Synthesis of (+)-Cylindradine B (8)



aromatized compound **13** (Scheme 2). We recently overcame a number of synthetic difficulties to achieve a total synthesis of **7**,[4] but some of the steps proceeded in low yield because of the instability of the pyrrole-3-carbamoyl structure, i.e., construction of the B ring and introduction of azide at C6 in **15** (see Scheme 3). Herein we describe the first total synthesis of (+)-cylindradine B (**8**), which has a *trans*-diol on the D ring, based on a modified and improved version of our synthesis of cylindradine A (**7**).

Our previous synthesis of (+)-cylindradine A (**7**), outlined in Scheme 3, utilized an intramolecular Friedel−Crafts-type reaction of aldehyde **14** for construction of the B ring, affording alcohol **16** stereoselectively. However, elimination−aromatization of **16** took place simultaneously to generate **15** in 10% yield as a side product. In addition, the yield upon azidation at C6 was very low (29% yield) because of a concomitant elimination process of the hydroxyl group from intermediate **18** activated by diphenyl phosphoryl azide (DPPA).

With the above points in mind (Scheme 3), we focused on devising a novel approach for the synthesis of cylindradine B (**8**) (Scheme 4). Thus, Pictet−Spengler-type reaction of imine **19** was planned for the formation of the B ring. In this reaction, the amine at C6 would be constructed simultaneously. This strategy should suppress elimination of the amine because of the higher pK_a value of the protonated amino group compared with the hydroxyl group.

The synthesis of aminal **25**, a precursor of imine **26** for the desired Pictet−Spengler-type reaction,[5,6] is illustrated in Scheme 5. The condensation reaction of prolinol **22**[7] with *N*-Ts-protected pyrrole-3-carboxylic acid **23**[8] was carried out using 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide (EDCI) in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) to give the amide in 80% yield. Then the *p*-toluenesulfonyl group on the pyrrole was converted to a Boc group by hydrolysis with potassium hydroxide followed by a reaction with $(Boc)_2O$ in the presence of triethylamine to give the Boc-protected pyrrole in 69% yield over two steps. After oxidation of the alcohol with IBX (91% yield), the resulting aldehyde **24** was reacted with benzyl carbamate in the presence of a catalytic amount of TFA in acetic anhydride to give aminal **25** in 73% yield.

With aminal **25** in hand, the Pictet−Spengler-type reaction was examined under acid-catalyzed conditions to promote in situ formation of imine **26** and subsequent cyclization (Table 1).[5,6] With TFA (10 mol %) as a catalyst, the Pictet−Spengler-type reaction took place to generate *α*-**27** as the major product in a ratio of 8:1−10:1 in THF or dichloromethane or toluene as a solvent, but the yield was extremely low (5−8%) at room temperature (entries 1−3). The yield and selectivity were improved by conducting the reaction at 100 °C in toluene, and *α*-**27** was obtained with 70% stereoselectivity (entry 4). We selected toluene as the solvent at 100 °C and further examined other acid catalysts. In the case of AcOH, *α*-**27** was obtained selectively, but the yield was only 7% (entry 5). The best result was obtained with (±)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (**28**), with which *α*-**27** was obtained as a single diastereomer in 93% yield (entry 6).[9] Interestingly, in the case of Lewis acid catalysts such as $Cu(OTf)_2$ and AgOTf, the diastereoselectivity of **27** decreased to 4:1 and 3:1, respectively (entries 7 and 8). This may be attributed to the formation of a six-membered transition state for **26b** through the metal in the Lewis acid,[10] leading to the undesired *β*-**27**[11] (Figure 2). Under the conditions examined in Table 1, no elimination product of **27** was observed.

The Pictet−Spengler-type reaction for the synthesis of amine **27** was eventually successfully accomplished in a one-pot reaction with aldehyde **24**. Thus, reaction of aldehyde **24** with benzyl carbamate in the presence of (±)-**28** and heating at 100 °C in toluene (0.01 M) gave *α*-**27** selectively in 84% yield (Scheme 6).

Our total synthesis of cylindradine B (**8**) was achieved from *α*-**27** (Scheme 7). Deprotection of the Cbz group from **27** with hydrogen in the presence of 10% Pd/C was followed by a reaction with *S*-methyl *N*-(2,2,2-trichloroethoxysulfonyl)-carbon-chloroimidothioate (**29**)[12] in the presence of triethylamine, which gave **30** in 75% yield (two steps). The two TBS groups in **30** were removed with HF·pyridine, and the *S*-methyl isothiourea was converted into guanidine **31** by reaction with NH_3/MeOH in the presence of $HgCl_2$. Then oxidative cyclization of **31** was carried out by reaction with the hypervalent iodine reagent iodosobenzene (PhIO) to give cyclic guanidine **32** in 44% yield (three steps).[4] The Tces group on the guanidine was changed to a Boc group prior to bromination of the pyrrole, since removal of Tces in the presence of the dibromopyrrole moiety at the final stage was troublesome.[4] Thus, the reaction of **32** with hydrogen in the presence of $Pd(OH)_2$ in a mixed solvent of methanol and ethyl

DOI: 10.1021/acs.orglett.6b03722
Org. Lett. 2017, 19, 420−423

acetate followed by reaction with Boc-ON[13] in the presence of triethylamine gave a mixture of tris- and tetra-Boc-protected **33**, as confirmed by mass spectrometric analysis.[14] Then bromination of the pyrrole moiety in **33** was carried out with bromine in the presence of sodium bicarbonate to give Boc-protected cylindradine B (**34**). Finally, all of the Boc groups in **34** were removed with TFA to afford (+)-cylindradine B (**8**) in 14% yield from Tces-protected tetracyclic guanidine **32**. The ^{1}H and ^{13}C NMR and HRMS data for synthetic **8** were in good agreement with reported values.[9]

We have presented the first total synthesis of (+)-cylindradine B (**8**), a structurally unique monomeric PIA analogue. In this synthesis, the B ring was constructed by a Pictet–Spengler-type reaction with an aminal in the presence of a phosphoric acid catalyst. A one-pot reaction using aldehyde **24** and benzyl carbamate enabled the stereochemistry at C6 to be simultaneously controlled without generation of the elimination product. Further oxidative cyclization of protected guanidine **31** with hypervalent iodine constructed the cyclic *N*,*N*′-aminal structure, and this was followed by bromination to furnish (+)-cylindradine B (**8**).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03722.

Experimental procedures, spectroscopic data, results of DFT calculations, and ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*knaga@cc.tuat.ac.jp

ORCID

Masahiro Yamanaka: 0000-0001-7978-620X

Kazuo Nagasawa: 0000-0002-0437-948X

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Prof. Dr Makoto Kuramoto (Ehime University) for helpful discussions. This work was financially supported in part by a Grant-in-Aid for Middle Molecular Strategy from JSPS (JP16H01134), a Grant-in-Aid for Scientific Research on Innovative Areas “Advanced Molecular Transformations by Organocatalysts” from The Ministry of Education, Culture, Sports, Science and Technology, Japan (23105013), and a grant from the Uehara Memorial Foundation. M.I. is a research fellow of the JSPS (DC2, 16J07367).

■ REFERENCES

(1) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753–1783.

(2) (a) Foley, L. H.; Buchi, G. *J. Am. Chem. Soc.* **1982**, *104*, 1776–1777. (b) Wiese, K. J.; Yakushijin, K.; Horne, D. A. *Tetrahedron Lett.* **2002**, *43*, 5135–5136. (c) Feldman, K. S.; Skoumbourdis, A. P. *Org. Lett.* **2005**, *7*, 929–931. (d) Feldman, K. S.; Skoumbourdis, A. P.; Fodor, M. D. *J. Org. Chem.* **2007**, *72*, 8076–8086. (e) Jacquot, D. E. N.; Zoellinger, M.; Lindel, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 2295–2298. (f) Zöllinger, M.; Mayer, P.; Lindel, T. *J. Org. Chem.* **2006**, *71*, 9431–9439. (g) Jacquot, D. E. N.; Zoellinger, M.; Lindel, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 2295–2298. (h) Zöllinger, M.; Mayer, P.; Lindel, T. *J. Org. Chem.* **2006**, *71*, 9431–9439. (i) Hewlett, N. M.; Tepe, J. *Org. Lett.* **2011**, *13*, 4550–4553. (j) Poullennec, K. G.; Romo, D. *J. Am. Chem. Soc.* **2003**, *125*, 6344–6345. (k) Wang, S.; Romo, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1284–1286. (l) Imaoka, T.; Iwamoto, O.; Noguchi, K. I.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3799–3801. (m) Imaoka, T.; Akimoto, T.; Iwamoto, O.; Nagasawa, K. *Chem. - Asian J.* **2010**, *5*, 1810–1816. (n) Yamaguchi, J.; Seiple, I. B.; Young, I. S.; O'Malley, D. P.; Maue, M.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3578–3580. (o) O'Malley, D. P.; Yamaguchi, J.; Young, I. S.; Seiple, I. B.; Baran, P. S. *Angew. Chem.* **2008**, *120*, 3637–3639. (p) Su, S.; Seiple, I. B.; Young, I. S.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 16490–16491. (q) Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1095–1098. (r) Seiple, I. B.; Su, S.; Young, I. S.; Nakamura, A.; Yamaguchi, J.; Jørgensen, L.; Rodriguez, R. A.; O'Malley, D. P.; Gaich, T.; Köck, M.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 14710–14726. (s) Ma, Z.; Wang, X.; Wang, X.; Rodriguez, R. A.; Moore, C. E.; Gao, S.; Tan, X.; Ma, Y.; Rheingold, A. L.; Baran, P. S.; Chen, C. *Science* **2014**, *346*, 219–224. (t) Namba, K.; Takeuchi, K.; Kaihara, Y.; Oda, M.; Nakayama, A.; Nakayama, A.; Yoshida, M.; Tanino, K. *Nat. Commun.* **2015**, *6*, 8731.

(3) Kuramoto, M.; Miyake, N.; Ishimaru, Y.; Ono, N.; Uno, H. *Org. Lett.* **2008**, *10*, 5465–5468.

(4) Iwata, M.; Kanoh, K.; Imaoka, T.; Nagasawa, K. *Chem. Commun.* **2014**, *50*, 6991–6994.

(5) Kano, T.; Yurino, T.; Asakawa, D.; Maruoka, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 5532–5534.

(6) Mulcahy, J. V.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 12630–12631.

(7) Ryu, Y.; Kim, G. *J. Org. Chem.* **1995**, *60*, 103–108.

(8) Huffman, J. W.; Smith, V. J.; Padgett, L. W. *Tetrahedron* **2008**, *64*, 2104–2112.

(9) See the Supporting Information.

(10) Stanton, G. R.; Koz, G.; Walsh, P. J. *J. Am. Chem. Soc.* **2011**, *133*, 7969–7976.

(11) The diastereomeric mixture of α-**27** and β-**27** was not separable by regular silica gel column chromatography, and spectral data for pure β-**27** were not obtained.

(12) Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J. *Org. Lett.* **2006**, *8*, 1073–1076.

(13) Itoh, M.; Hagiwara, D.; Kamiya, T. *Tetrahedron Lett.* **1975**, *16*, 4393–4394.

(14) The positions protected by Boc groups were not determined.

DOI: 10.1021/acs.orglett.6b03722
Org. Lett. 2017, 19, 420–423