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Total Synthesis of (−)-*N*-Methylwelwitindolinone C Isothiocyanate Based on a Pd-Catalyzed Tandem Enolate Coupling Strategy

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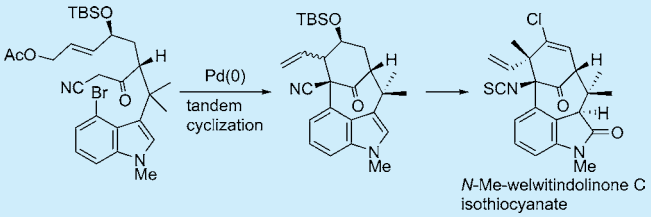
Supporting Information

ABSTRACT: The highly stereocontrolled total synthesis of (−)-*N*-methylwelwitindolinone C isothiocyanate is described, which features the expeditious construction of a bicyclo[4.3.1]-decane ring system by a palladium-catalyzed tandem enolate allylation/arylation reaction.



Moore and co-workers reported the isolation of a series of fascinating welwitindolinone alkaloids from the blue-green algae *Hapalosiphon wetwitschii*, *Westiella intricata*, *Fischerella muscicola*, and *Fischerella major* (Figure 1).[1] These alkaloids exhibit significant biological activities represented by the ability to reverse P-glycoprotein-mediated multidrug resistance in human cancer cells.[2] Most of the welwitindolinones possess a densely functionalized oxindole-fused bicyclo[4.3.1]decane ring system containing two contiguous quaternary centers. The structural challenges coupled with promising pharmacological properties have made these alkaloids attractive targets for synthesis.[3,4] Thus, a number of elegant methodologies to assemble a [4.3.1] bicyclic core have been developed from many research groups[3c,5] but only the Rawal group[6] and the Garg group[7] have succeeded in the total syntheses of [4.3.1] bicyclic welwitindolinones **1**−**6**. Recently, the Martin group[8] also reported the formal syntheses of **2**−**6** though in racemic forms. We now report the novel total synthesis of (−)-*N*-methylwelwitindolinone C isothiocyanate (**2**).

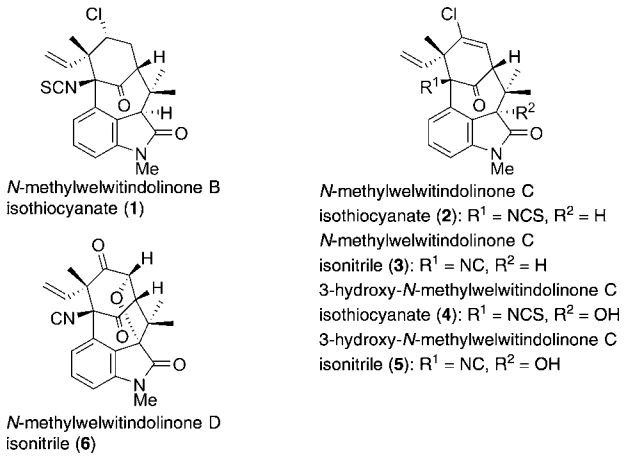
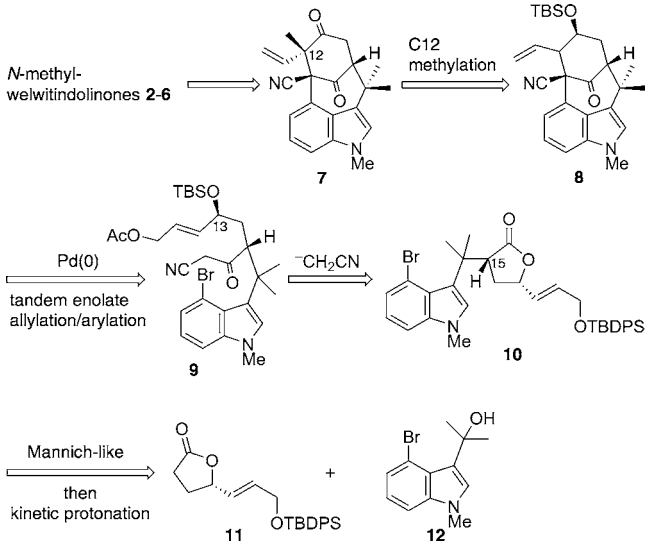


Figure 1. Representative welwitindolinone alkaloids.

Scheme 1. Retrosynthesis



For the synthesis of the welwitindolinone alkaloids, we envisioned diketo nitrile **7** as a common precursor (Scheme 1). We expected that compound **7** would be derived from **8** by stereoselective methylation at the C12 center based on Martin's protocol.[8] To expeditiously access **8**, we envisioned a palladium-catalyzed tandem enolate allylation/arylation sequence from **9**, which had not previously been examined for the assembly of a [4.3.1] bicyclic core.[3c,5−8] Considering steric repulsions during the sequential cyclizations, we selected the relatively less bulky cyanoketone functionality[9] and 13*S* configuration[10] for **9**. To stereoselectively synthesize **9**, we considered an approach from **11** of *S* configuration via a Mannich-like reaction with **12** followed by epimerization at C15 under kinetic protonation

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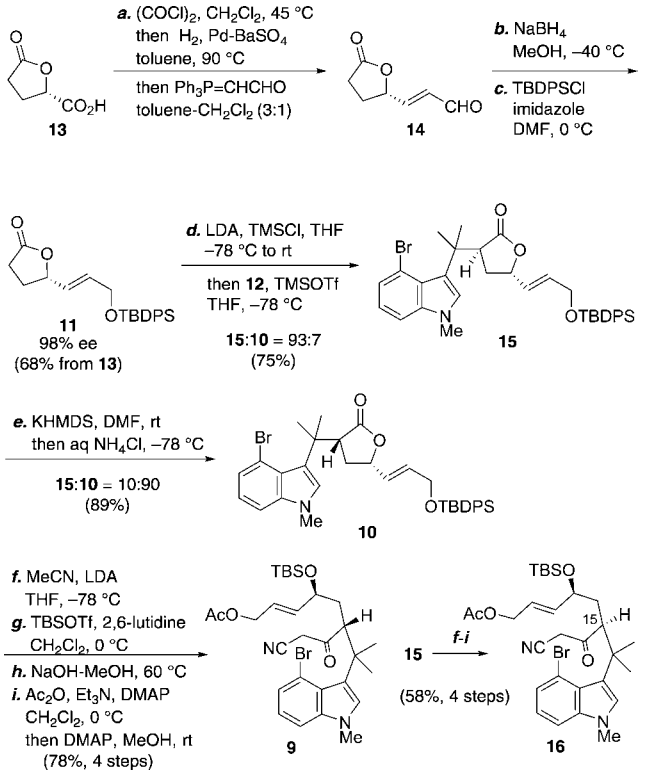
conditions and nucleophilic opening of γ-lactone **10** with the anion of acetonitrile.

Our synthesis thus began with the preparation of **11** with high enantiopurity (Scheme 2). Commercially available carboxylic acid

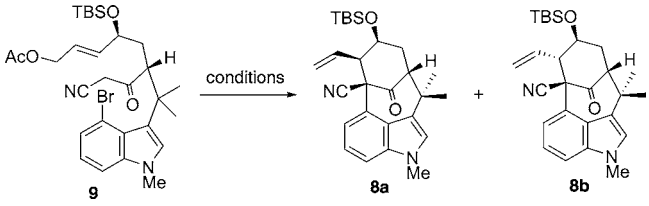
Scheme 2. Synthesis of Cyclization Precursors



13 was first converted to aldehyde **14** by a one-pot procedure[11] involving formation of the acid chloride, Rosenmund reduction, and Wittig reaction. Without purification, **14** was then subjected to $NaBH_4$ reduction followed by silylation to give **11** with 98% ee in 68% overall yield from **13**. Compound **11** was coupled with the known indole derivative **12**, prepared from 4-bromo-3-acetyl-1-methyl-1*H*-indole,[8] in the presence of TMSOTf under the conditions reported by Martin et al.[8,12] to deliver a 93:7 mixture of **15** and **10** in 75% yield. Upon treatment of this mixture with KHMDS followed by aqueous NH_4Cl at −78 °C, the kinetic protonation of the resulting enolate took place to give a 10:90 mixture of **15**[13] and **10**[13] which was chromatographically separated. Lactone **10** thus obtained was then converted to **9** by a four-step sequence involving reaction with lithiated acetonitrile, silylation, selective removal of the TBDPS group under basic conditions,[14] and acetylation in good overall yield. Similarly, compound **16** was also prepared from **15**.

With the desired precursor **9** in hand, we then investigated the crucial tandem cyclization (Table 1). Since the palladium-catalyzed conditions reported by Rawal's group[6] and Martin's group[8] did not promote the desired tandem cyclization, we focused on Verkade's protocol[15] developed for the arylation of ethyl cyanoacetate with aryl bromides. We first examined the reaction employing three palladium sources at 30 mol % loading together with *i*-Bu-PAP (1.2 equiv) and *t*-BuOK (2 equiv) at 90 °C in toluene. As a result, when $Pd_2(dba)_3$ was used as a catalyst, the tandem allylation/arylation took place within 1 h to produce the desired cyclization products **8a** and **8b**[16] in a ratio of 2:1 in 72% yield (entry 3). Both $Pd(Ph_3P)_4$ and $Pd_2(dba)_3{\cdot}CHCl_3$ catalyzed

Table 1. Pd-Catalyzed Tandem Cyclizations



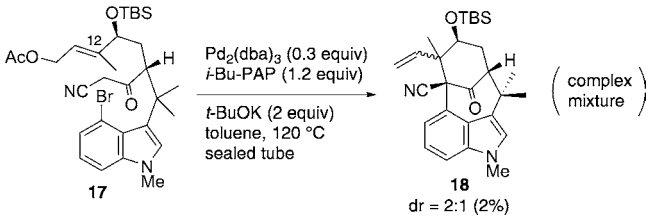
entry	conditions	yield[a] (%) (8a/8b)[b]
1[c]	$Pd(PPh_3)_4$ (0.3 equiv), *i*-Bu-PAP (1.2 equiv), *t*-BuOK (2 equiv), toluene, 90 °C, 3 h	15 (3:1)
2[c]	$Pd_2(dba)_3{\cdot}CHCl_3$ (0.3 equiv), *i*-Bu-PAP (1.2 equiv), *t*-BuOK (2 equiv), toluene, 90 °C, 5 h	62 (2:1)
3[c]	$Pd_2(dba)_3$ (0.3 equiv), *i*-Bu-PAP (1.2 equiv), *t*-BuOK (2 equiv), toluene, 90 °C, 1 h	72 (2:1)
4[c]	$Pd_2(dba)_3$ (0.2 equiv), *i*-Bu-PAP (0.8 equiv), *t*-BuOK (2 equiv), toluene, 90 °C, 2 h	84 (2:1)
5[c]	$Pd_2(dba)_3$ (0.2 equiv), XPhos (0.8 equiv), *t*-BuOK (2 equiv), toluene, 90 °C, 2 h	69 (2:1)
6[d]	$Pd_2(dba)_3$ (0.2 equiv), XPhos (0.8 equiv), *t*-BuOK (2 equiv), toluene, 110 °C, 1 h	100 (2:1)

[a]Total yield of **8a** and **8b**. [b]Determined by ^1H NMR. [c]A mixture of **9** and all reagents in toluene (0.02 M) was heated at 90 °C. [d]A solution of **9** in toluene was added to a mixture of all reagents in boiling toluene (0.05 M) over 20 min and then heated at reflux. *i*-Bu-PAP = 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane, XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

this tandem cyclization less effectively (entries 1 and 2). It was found that decreasing the amounts of $Pd_2(dba)_3$ and *i*-Bu-PAP to 0.2 equiv and 0.8 equiv improved the total yield of **8a** and **8b** to 84%, although the diastereoselectivity did not change. Furthermore, the combination of $Pd_2(dba)_3$ and Xphos was also found to effectively catalyze the tandem process (entry 5). Surprisingly, slow addition of **9** to a mixture of $Pd_2(dba)_3$, Xphos, and *t*-BuOK in boiling toluene provided a 2:1 mixture of **8a** and **8b** in quantitative yield (entry 6). It is important to note that compound **16**, the 15-epimer of **9**, did not produce any cyclization products under the $Pd_2(dba)_3$/*i*-Bu-PAP- or $Pd_2(dba)_3$/XPhos-catalyzed conditions as we expected.[10]

We also examined the tandem cyclization of **17** having a 12-methyl group[17] under the $Pd_2(dba)_3$/*i*-Bu-PAP-catalyzed conditions (Scheme 3). However, the reaction afforded a complex

Scheme 3. Cyclization of Compound 17



mixture from which bicyclic compound **18** was isolated as a 2:1 mixture in only 2% yield.

To understand the above-mentioned tandem process, we performed the experiments shown in Scheme 4. The $Pd_2(dba)_3$/*i*-Bu-PAP-catalyzed reaction of **9** at 70 °C for 30 min allowed us to isolate intermediates **19**, a 1.3:1 mixture, and **20**. These intermediates were then exposed to the conditions listed in entry 3 of Table 1. In the reaction of **19**, the major isomer and minor isomer produced **8a** and **8b**, respectively. On the other hand, the

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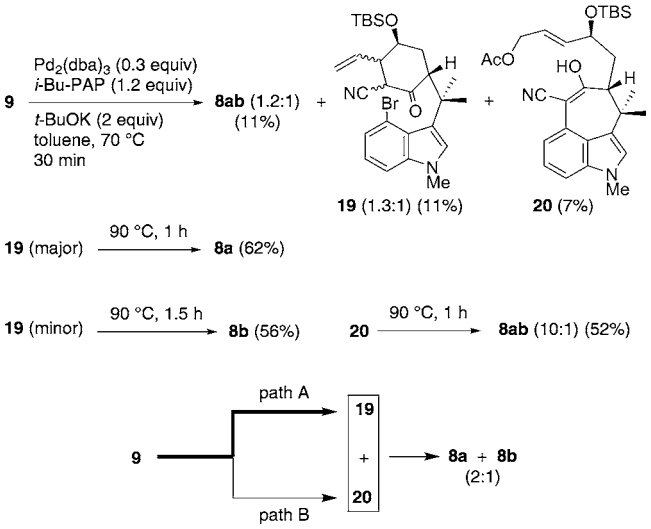
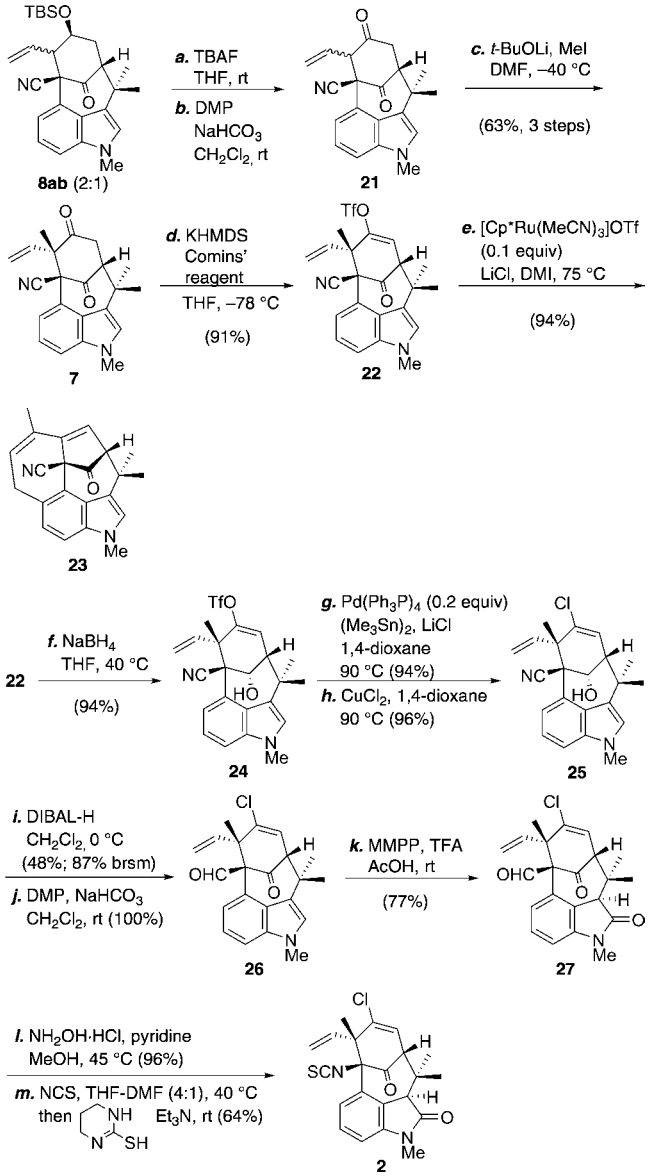
Scheme 4. Reaction Pathways



reaction of **20** proceeded with high diastereoselectivity to produce a 10:1 mixture of **8a** and **8b**. These results suggest that the tandem process would occur preferentially via an enolate allylation (path A) rather than an enolate arylation (path B).

Having successfully constructed the bicyclic framework, we then pursued the synthesis of *N*-methylwelwitindolinone C isothiocyanate (**2**) from the diastereoisomeric mixture of **8a** and **8b** (Scheme 5). This mixture **8ab** was first converted to ketone **21** by desilylation followed by Dess–Martin oxidation. The next methylation step turned out to be problematic.[18] After considerable experimentation, we eventually found conditions where the methyl group was introduced stereo- and regioselectively in acceptable yield. Thus, after deprotonation of **21** with *t*-BuOLi in DMF at −40 °C, the resulting dienolate was methylated with methyl iodide to give our envisaged key intermediate **7**[13] as a single diastereoisomer. To assemble the vinyl chloride functionality in **7**, we examined Garg's protocol[7a] involving a triflation, stannylation, and chlorination. However, when triflate **22** was exposed to the stannylation conditions using $(Me_3Sn)_2$, $Pd(Ph_3P)_4$, and LiCl in 1,4-dioxane at 90 °C, none of the desired product was obtained. It is worth noting that, upon heating **22** in the presence of [Cp*Ru(MeCN)$_3$]OTf and LiCl in 1,3-dimethyl-2-imidazolidinone at 75 °C according to Hayashi's procedure,[19] pentacyclic compound **23**[20] was obtained in 94% yield. The production of **23** can be explained by the mechanism proposed by Rawal et al.,[21] which proceeds through a Cope rearrangement followed by C–C bond formation between the resulting α-cyanoketone and dienylruthenium species. We eventually found that triflate **24**,[13] prepared by $NaBH_4$ reduction of **22**, cleanly underwent chlorination under Garg's conditions[7a] to give chloride **25** in good yield. Upon DIBAL-H reduction and Dess–Martin oxidation, **25** afforded keto aldehyde **26**. Finally, following the procedure reported by Rawal et al.,[6c] the total synthesis of (−)-*N*-methylwelwitindolinone C isothiocyanate (**2**) was achieved via selective oxidation of the indole ring with magnesium monoperoxyphthalate (MMPP) giving oxindole **27**[6c,13] and installation of the isothiocyanate functionality by an aldoxime rearrangement. The synthetic **2** exhibited spectral properties identical in all respects to those reported.[1a,6c] Since compound **2** has already been converted to *N*-methylwelwitindolinones **3**–**5**,[6c,7b] the synthesis of **2** constitutes the formal syntheses of these alkaloids.

Scheme 5. Synthesis of (−)-*N*-Methylwelwitindolinone C Isothiocyanate



In summary, we have completed the total synthesis of (−)-*N*-methylwelwitindolinone C isothiocyanate (**2**) in 6% overall yield (24 steps) from commercially available **13**. The present work illustrates the prowess of the palladium-catalyzed tandem cyclization to enable expeditious access to a bicyclic skeleton of welwitindolinone alkaloids. The methodology developed is of general value in approaches to other [4.3.1] bicyclic welwitindolinones.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, ^{1}H and ^{13}C NMR spectra, and X-ray crystallographic data (CIF). The Supporting Information is available free of charge via the Internet at The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01952.

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

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X-ray data of the alcohol derived from **8a** (CIF)
X-ray data of the alcohol derived from **8b** (CIF)
X-ray data of compound **23** (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935−9942. (b) Jimenez, J. I.; Huber, U.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1999**, *62*, 569−572.

(2) (a) Smith, C. D.; Zilfou, J. T.; Stratmann, K.; Patterson, G. M. L.; Moore, R. E. *Mol. Pharmacol.* **1995**, *47*, 241−247. (b) Zhang, X.; Smith, C. D. *Mol. Pharmacol.* **1996**, *49*, 288−294.

(3) For reviews, see: (a) Avendaño, C.; Menéndez, J. C. *Curr. Org. Synth.* **2004**, *1*, 65−82. (b) Brown, L. E.; Konopelski, J. P. *Org. Prep. Proced. Int.* **2008**, *40*, 411−445. (c) Huters, A. D.; Styduhar, E. D.; Garg, N. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 3758−3765. (d) Wood, J. L. *Nat. Chem.* **2012**, *4*, 341−343.

(4) Total syntheses of welwitindolinone A isonitrile, a cyclobutane-containing alkaloid: (a) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394−15396. (b) Reisman, S. E.; Ready, J. M.; Hasuoka, A.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 1448−1449.

(5) Cleary, L.; Pitzen, J.; Brailsford, J. A.; Shea, K. J. *Org. Lett.* **2014**, *16*, 4460−4463 and references therein.

(6) (a) Bhat, V.; Allan, K. M.; Rawal, V. H. *J. Am. Chem. Soc.* **2011**, *133*, 5798−5801. (b) Bhat, V.; Rawal, V. H. *Chem. Commun.* **2011**, *47*, 9705−9707. (c) Allan, K. M.; Kobayashi, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2012**, *134*, 1392−1395.

(7) (a) Huters, A. D.; Quasdorf, K. W.; Styduhar, E. D.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 15797−15799. (b) Quasdorf, K. W.; Huters, A. D.; Lodewyk, M. W.; Tantillo, D. J.; Garg, N. K. *J. Am. Chem. Soc.* **2012**, *134*, 1396−1399. (c) Styduhar, E. D.; Huters, A. D.; Weires, N. A.; Garg, N. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 12422−12425. (d) Weires, N. A.; Styduhar, E. D.; Baker, E. L.; Garg, N. K. *J. Am. Chem. Soc.* **2014**, *136*, 14710−14713.

(8) (a) Fu, T.-h.; McElroy, W. T.; Shamszad, M.; Martin, S. F. *Org. Lett.* **2012**, *14*, 3834−3837. (b) Fu, T.-h.; McElroy, W. T.; Shamszad, M.; Heidebrecht, R. W., Jr.; Gulledge, B.; Martin, S. F. *Tetrahedron* **2013**, *69*, 5588−5603.

(9) It was assumed that a *β*-keto ester functionality would cause severe steric interactions during the tandem cyclization process due to the bulky bent ester structure.

(10) It was assumed that the 13*R*-isomer of **9** would experience severe steric interactions between the TBSO group and indole residue in any transition state, unlike 13*S*-isomer **9**.

(11) Cooke, R. C.; van Leeuwen, K. A.; Capone, D. L.; Gawel, R.; Elsey, G. M.; Sefton, M. A. *J. Agric. Food Chem.* **2009**, *57*, 2462−2467.

(12) Fu, T.-h.; Bonaparte, A.; Martin, S. F. *Tetrahedron Lett.* **2009**, *50*, 3253−3257.

(13) The stereostructure was determined by the NOESY spectra.

(14) Hatakeyama, S.; Irie, H.; Shintani, T.; Noguchi, Y.; Yamada, H.; Nishizawa, M. *Tetrahedron* **1994**, *50*, 13369−13376.

(15) You, J.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8003−8007.

(16) The stereostructures were determined by X-ray crystallographic analysis of the corresponding alcohols derived from **8a** and **8b**. The crystallographic data (CCDC 1403797 and CCDC 1403798) can be obtained free of charge from the Cambridge Crystallographic Data centre via www.ccdc.cam.ac.uk/data_request/cif.

(17) See the Supporting Information for the preparation of **17**.

(18) For example, methylation of **21** under Martin's conditions (NaHDMS, MeI, DMF, −40 °C) produced **7** (22%) and the corresponding *α*,*α*′-dimethylated compound (12%).

(19) Imazaki, Y.; Shirakawa, E.; Ueno, R.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 14760−14763.

(20) The stereostructure was determined by X-ray crystallographic analysis. The crystallographic data (CCDC 1403796) can be obtained free of charge from the Cambridge Crystallographic Data centre via www.ccdc.cam.ac.uk/data_request/cif.

(21) Bhat, V.; MacKay, J. A.; Rawal, V. H. *Tetrahedron* **2011**, *67*, 10097−10104.

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Org. Lett. 2015, 17, 3918−3921