Organic LETTERS

Letter

pubs.acs.org/OrgLett

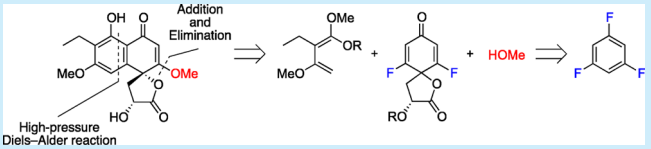
Total Syntheses of Perenniporides

Masao Morita, Ken Ohmori,* and Keisuke Suzuki*

Department of Chemistry, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152-8551, Japan

Supporting Information

ABSTRACT: The total syntheses of perenniporide A (**1**) and related compounds have been achieved. Starting from 1,3,5-trifluorobenzene (**9**), difluorodienone **6** was obtained by oxidative dearomatization, which served as a platform for the high-pressure cycloaddition and for the introduction of the C3-methoxy group. The synthesis allowed access to the natural congeners **2** and **3**, enabling assignment of the absolute structures of these natural products.



Perenniporides A–D (**1**–**4**) (Figure 1) constitute a class of natural products recently isolated from the fungus

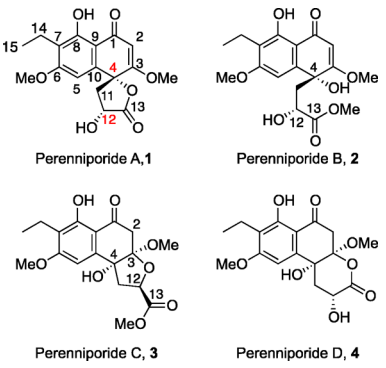


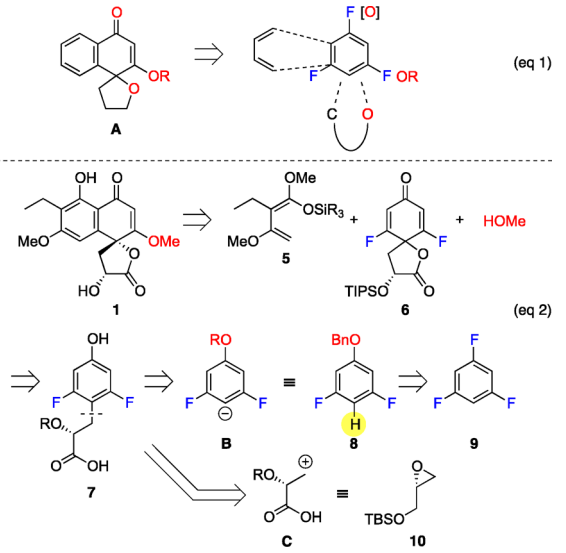
Figure 1. Perenniporides A–D.

Perenniporia sp., inhabiting the larva of a phytophagous weevil, *Euops chinesis*.[1] Since **1** shows a significant inhibitory effect against several plant pathogens, it may serve as a lead for new agrochemicals. Structurally, these compounds share an α-tetralone skeleton possessing a 2-hydroxypropanoic acid appendage. The relative stereochemistry of **1** was assigned as 4*R**,12*R** by X-ray analysis, while the absolute structure has remained unassigned. Aiming at developing a general synthetic route, we undertook the synthetic study of these compounds that would hopefully contribute to the study of the structure–activity relationship.

In this communication, we report the first total synthesis of **1** from 1,3,5-trifluorobenzene (**9**) as well as a viable synthetic access to congeners **2** and **3**, enabling the assignment of the absolute stereochemistry of these natural products.

Scheme 1 shows the retrosynthesis of **1**. The bottom line is the use of 1,3,5-trifluorobenzene (**9**) (Scheme 1, eq 1), which would allow assembly of the basic skeleton **A** by anchoring two rings, a spiro-oxa cycle and a fused aromatic ring, and installing the requisite oxygen functionalities. Scheme 1 shows the specific planning by employing difluorodienone **6** as the immediate precursor to **1**. The hope was that the fluoroenone moiety in **6**

Scheme 1. Retrosynthetic Analysis of Perenniporide A (1)



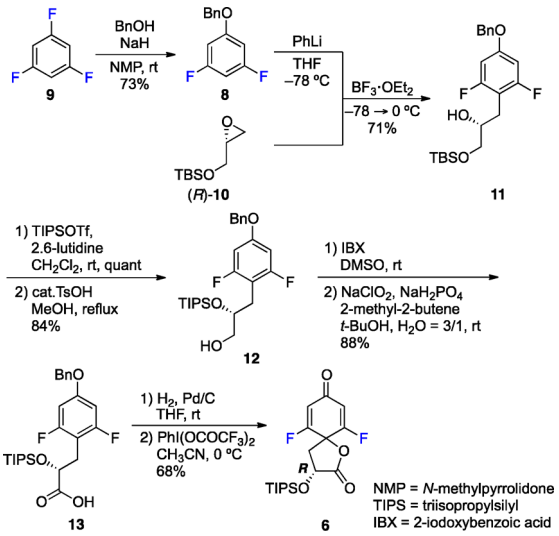
would serve as a dienophile to react with diene **5**,[2] while the other fluorine atom would be replaced by a methoxy group. This key compound **6** would be accessible by the oxidative dearomatization of α-hydroxy acid **7**, which in turn could be dissected into the donor/acceptor synthons **B** and **C**. As the synthetic equivalent to the donor synthon **B**, fluoroarene **8** could be used by exploiting the facile lithiation at the indicated position between two fluorine atoms, while the acceptor **C** could be derived from chiral, nonracemic glycidol **10**.

1,3,5-Trifluorobenzene (**9**) was converted to difluoride **8** via the S_NAr reaction with benzyl alkoxide, which stopped at a single substitution (Scheme 2).[3] Regioselective lithiation of **8** with PhLi[4,5] followed by the addition of (*R*)-**10**[6] in the presence of $BF_3{\cdot}OEt_2$ gave adduct **11**. Protection of the secondary alcohol in **11** (TIPSOTf, 2,6-lutidine, CH_2Cl_2) gave the corresponding TIPS ether, and exposure to catalytic TsOH in MeOH allowed

Received: October 7, 2015

DOI: 10.1021/acs.orglett.5b02906
Org. Lett. XXXX, XXX, XXX–XXX

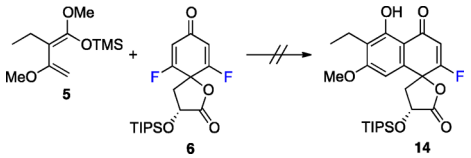
Scheme 2. Preparation of Difluorodienone 6



selective removal of the TBS group under the carefully specified conditions,[7] giving *prim*-alcohol **12** in 84% overall yield from **11**. Oxidation of alcohol **12** with IBX[8] in DMSO followed by Kraus–Pinnick oxidation[9] afforded acid **13** in 88% yield (two steps). Hydrogenolytic removal of the benzyl ether in **13** provided the corresponding labile phenol, which was immediately subjected to the oxidative dearomatization[10] by treatment with PhI-$(OCOCF_3)_2$, giving difluorodienone **6** in 68% yield.

Having the key intermediate **6** in hand, we first examined the Diels–Alder reaction with siloxy diene **5** (Scheme 3).[2,11] In spite

Scheme 3

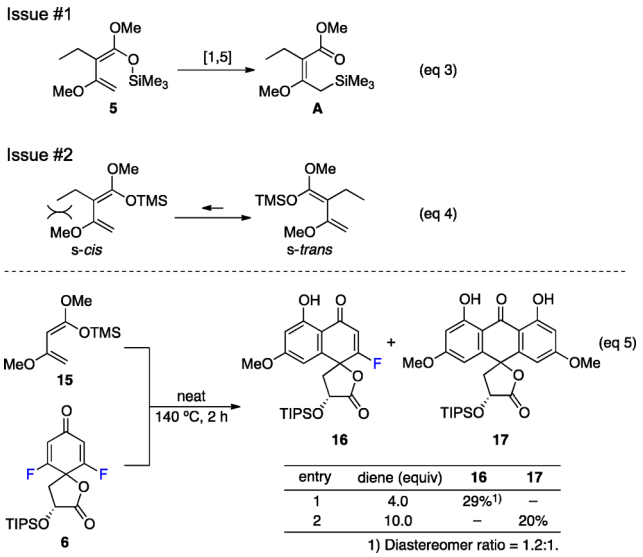


of extensive screening of the reaction conditions, the desired product **14** was not obtained under either thermal conditions (e.g., toluene, reflux, 16 h) or Lewis acidic conditions (e.g., $ZnCl_2$, toluene, rt, 16 h).

We noted that two issues are relevant (Scheme 4). First, diene **5** is thermally unstable, undergoing isomerization at ambient temperature, or even at −30 °C, by [1,5]-silatropic shift into the *C*-silyl isomer **A** (Scheme 4, eq 3).[2,12] The second issue in diene **5** is the difficulty in adopting the s-*cis* geometry required for the Diels–Alder reaction (Scheme 4, eq 4). By contrast, the [4 + 2] cycloaddition was possible with siloxydiene **15**[13] without the ethyl group, affording product **16** in 29% yield. Use of the diene in excess resulted in the dual reaction to give **17** in 20% yield.

To cope with the first issue, we examined siloxy diene **18** in which the TMS moiety was replaced by a TBS group, expecting increased thermal stability (Table 1). Although simple thermal reaction was not productive (Table 1, entry 1), use of highly polar media by adding lithium salts,[14] $LiClO_4$ or LiOTf, enabled the reaction to give the product **14**, albeit in low yields (Table 1, entry 2 and 3). Even though the starting material **6** was completely consumed, the reactions were not so clean, and the product **14** was not free from impurities.

Scheme 4. Two Issues in Siloxy Diene 5



entry	diene (equiv)	16	17
1	4.0	29%[1)]	–
2	10.0	–	20%

1) Diastereomer ratio = 1.2:1.

At this stage, we focused on the high-pressure conditions, expecting the pronounced rate-acceleration effect,[15] which, pleasingly, gave a positive result (entry 4). A mixture of **6** and diene **18** (1.5–2.0 equiv) was subjected to the super high-pressure conditions[16] (10 Kbar, CH_2Cl_2, rt, 24 h). The crude mixture was condensed and treated with TsOH in methanol, giving the product **14** in 62–68% reproducible yields.

It is worth noting that the initial cycloadduct **I** persisted under the high-pressure conditions. After we performed the high-pressure reaction in CD_2Cl_2, a part of the mixture was taken to measure ^{1}H NMR, showing *the absence of* ***14*** *and the prevalence of* ***I***.[17] Thus, it was only after acid treatment that HF was eliminated from **I** to give **14**.[18] This must be an important feature to the success of the reaction, as the reaction media remains neutral, where the acid-labile diene **18** is not deteriorated and effectively works for the [4 + 2] cycloaddition. This also indicates that only a slight excess of **18** is necessary, reducing the probability of the double reaction.[19]

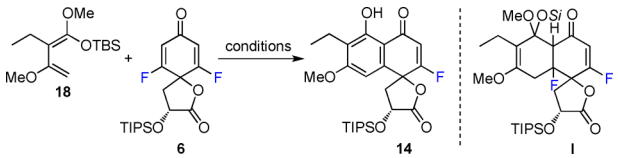
The ^{1}H NMR analysis suggested that **14** is composed of a 3/2 mixture of isomers, inseparable by silica gel chromatography. However, gel-permeation chromatography (YMC-GPC T4000+T2000, AcOEt) enabled a good separation and recovery. In one run (68% combined yield), the separation gave **14a** (40% yield) and **14b** (26% yield), which proved to be a pair of diastereomers arising from the difference in the C4 chiral center. The NOESY analysis assigned the stereochemistry of **14a** as 4*R* on the basis of the correlation between $H_{11\alpha}$ and H_5, while that of **14b** was assigned as 4*S* by the correlation between H_{12} and H_5 as shown in Scheme 5.

Although the selectivity **14a**/**14b** (3/2) was modest, it is worth noting in a formal analysis how this selectivity evolves (Scheme 6). Without regard to the *exo*/*endo* selectivity or the π-facial selectivity on the cyclohexadienone plane, the key is the *group selectivity* on two diastereotopic fluoroenones.[20] By the choice of right or left dienophilic sites, the prochiral C4-center in **6** is converted into the stereogenicity in **14**: 4*R* by the reactions from the left side and 4*S* by those from the right side.[21]

Concerning the drawing of **14b** (Scheme 6), the upper one is more comprehensive for grasping its relationship to the group-selective reaction, while the lower drawing better represents the epimeric relationship of **14a** and **14b** at the C4 spiro center. The

DOI: 10.1021/acs.orglett.5b02906
Org. Lett. XXXX, XXX, XXX–XXX

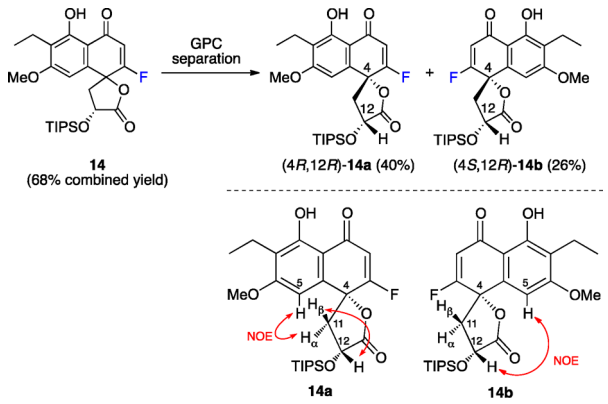
Table 1. [4 + 2]-Cycloaddition of 6



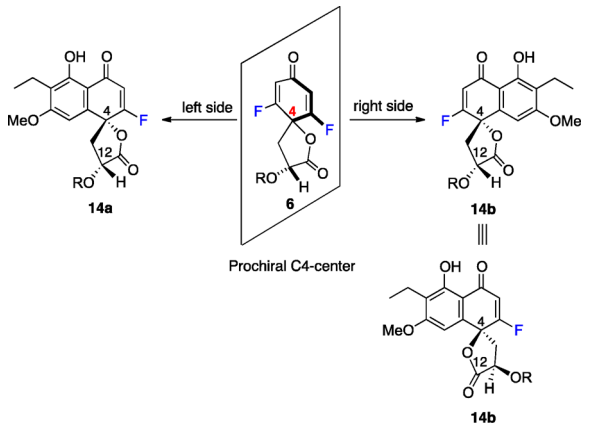
entry	diene (equiv)	conditions				additive	yield of **14** (%)
1	4.0	neat	100 °C	1 h			0
2[a]	4.0	Et_2O	100 °C	1 h		$LiClO_4$ (1 M)	ca. 16
3[a]	4.0	THF	100 °C	1 h		LiOTf (5 M)	ca. 26
4[b]	1.5−2.0	CH_2Cl_2	rt	24 h	10 Kbar		62−68

[a]In a sealed tube. [b]RIKEN apparatus.

Scheme 5. Separation and Stereochemical Assignment of Isomers 14a and 14b



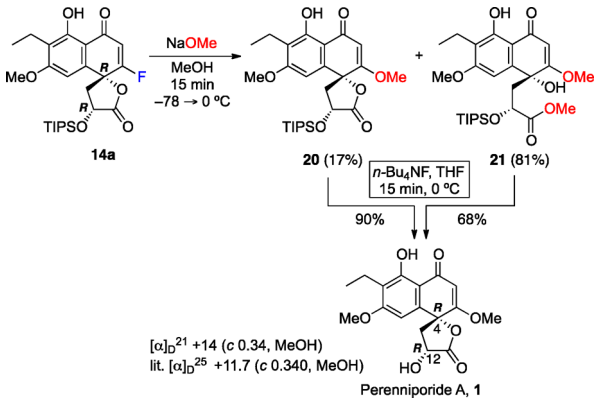
Scheme 6. Group-Selectivity Diverging into 14a and 14b



latter will be used in the synthetic transformation of **14b** into 4-*epi*-perenniporide A (**23**) (vide infra, Scheme 8).

Having identified **14a** as the (4*R*,12*R*) isomer, i.e., the same relative configuration of the natural product (4*R**,12*R**), we converted it to the final product for comparing the $[\alpha]_D$ values to assign the absolute stereochemistry (Scheme 7). The fluorine atom in **14a** was replaced by a methoxy group by treatment with sodium methoxide (MeOH, − 78 → 0 °C, 15 min), where lactone **20** was obtained in 17% yield and ester **21** in 81% yield. Although these compounds were separated by silica gel chromatography (**20**: R_f 0.70, **21**: R_f 0.29, toluene/AcOEt = 95:5), both converged into perenniporide A (**1**) upon treatment with *n*-Bu_4NF for removal of the TIPS group (**20** → **1**: 90% yield, **21** → **1**: 68% yield). After purification on the silica gel preparative

Scheme 7. Total Synthesis of Perenniporide A (1)

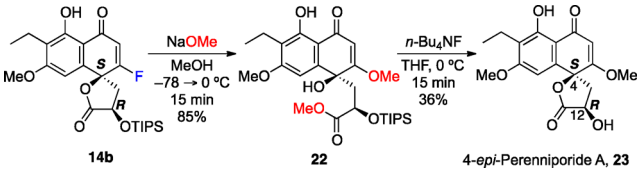


TLC (**1**: R_f 0.37, toluene/AcOEt = 1:1), the material was recrystallized from acetone to give a pale yellow needles (mp 197 °C, dec). The physical data (^1H, ^{13}C NMR and high-resolution MS) of **1** fully coincided with those reported for the natural product.[1]

Conformity of the sign and magnitude of the $[\alpha]_D$ values of synthetic and natural materials[1] of **1** identified its absolute structure as 4*R*,12*R*. Furthermore, the rigorous enantiomeric purtiy (>99% ee) of synthetic **1** was proven by HPLC analysis with a chiral stationary phase by comparison with *ent*-**1** that was prepared from the enantiomeric epoxide (*S*)-**10**.[22]

Furthermore, the same conversion was applied to the epimer **14b**, giving 4-*epi*-perenniporide A (**23**) (Scheme 8). Upon

Scheme 8. Synthesis of 4-*epi*-Perenniporide A (23)

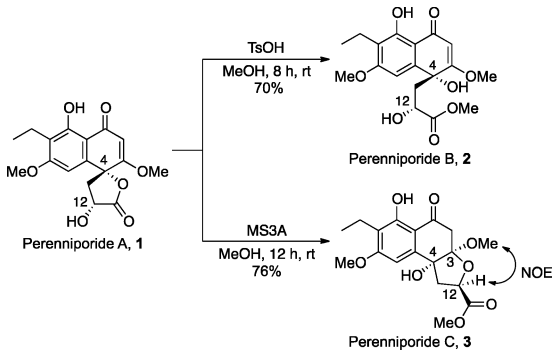


treatment of **14b** with sodium methoxide (MeOH, − 78 → 0 °C, 15 min), ester **22** was obtained as the sole product in 85% yield. Removal of the TIPS group in **22** gave the C4-epimer **23**, which was clearly discernible from **1** by ^1H NMR analysis.

Having confirmed the identity of **1**, the conversion into other congeners was examined (Scheme 9). It turned out that acidic methanolysis of **1** (TsOH, MeOH, rt, 8 h) followed by purification on the preparative TLC (diol silica gel) afforded perenniporide B (**2**) as a colorless oil. On the other hand, treatment of **1** with MS3A in MeOH allowed methanolysis and

DOI: 10.1021/acs.orglett.5b02906
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 9. Conversion of 1 into Congeners 2 and 3



an oxa-Michael addition to give perenniporide C (**3**) as a colorless oil. The physical data of the synthetic materials **2** and **3** also coincided with the reported data, respectively.[1]

In summary, we have achieved the first total syntheses of perenniporide A (**1**) and the congeners **2** and **3** and their epimers using difluorodienone **6** derived from 1,3,5-trifluorobenzene (**9**). The absolute structure of these natural products was assigned.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02906.

Full experimental procedure, characterization data, and NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: kohmori@chem.titech.ac.jp.
*E-mail: ksuzuki@chem.titech.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Specially Promoted Research (No. 23000006) from JSPS. We thank Prof. Oliver Reiser, Mr. Martin Hofmann (Regensburg), Prof. Mikiko Sodeoka, and Dr. Go Hirai (RIKEN) for helpful discussions and generous offers to use the high-pressure reactors. A generous donation of (*S*)- and (*R*)-3-chloro-1,2-propanediol from Sanyo Fine Co. Ltd. is gratefully acknowledged.

■ DEDICATION

Dedicated to Prof. Dieter Seebach on occasion of his 78th birthday.

■ REFERENCES

(1) Feng, Y.; Wang, L.; Niu, S.; Li, L.; Si, Y.; Liu, X.; Che, Y. *J. Nat. Prod.* **2012**, *75*, 1339.

(2) Caron, B.; Brassard, P. *Tetrahedron* **1991**, *47*, 4287.

(3) (a) Rodriguez, J. R.; Agejas, J.; Bueno, A. B. *Tetrahedron Lett.* **2006**, *47*, 5661. (b) Seo, H.; Ohmori, K.; Suzuki, K. *Chem. Lett.* **2011**, *40*, 744. (c) Stadlbauer, S.; Ohmori, K.; Hattori, F.; Suzuki, K. *Chem. Commun.* **2012**, *48*, 8425.

(4) (a) Bridges, A. J.; Lee, A.; Maduakor, E. C.; Schwartz, C. E. *Tetrahedron Lett.* **1992**, *33*, 7495. (b) Bridges, A. J.; Lee, A.; Maduakor, E. C.; Schwartz, C. E. *Tetrahedron Lett.* **1992**, *33*, 7499. (c) Schlosser, M. *Eur. J. Org. Chem.* **2001**, *2001*, 3975. (d) Han, Y. H.; Zhou, T.; Sui, Y.; Hua, R. *Org. Process Res. Dev.* **2014**, *18*, 1229.

(5) Use of *n*-BuLi as the base led to a nonregioselective lithiation, while PhLi allowed the lithiation at the desired position (see the Supporting Information).

(6) For the preparation of (*R*)-**10** by the silylation of (*S*)-glycidol, see: Donohoe, T. J.; Ironmonger, A.; Kershaw, N. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7314. For the preparation of (*S*)-glycidol by the base-promoted cyclization of (*S*)-3-chloro-1,2-propanediol, see: Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 6776.

(7) The concentration of TsOH (0.5 mg/mL in methanol) was important to achieve the selective removal of the TBS-group.

(8) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.

(9) (a) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825. (b) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(10) (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. For contributions from our laboratory, see: (b) Yasui, Y.; Koga, Y.; Suzuki, K.; Matsumoto, T. *Synlett* **2004**, 615. (c) Yasui, Y.; Suzuki, K.; Matsumoto, T. *Synlett* **2004**, 619. For reviews, see: (d) Pouysegu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (e) Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068.

(11) Patrick, T. B.; Neumann, J.; Tatro, A. *J. Fluorine Chem.* **2011**, *132*, 779.

(12) (a) Casey, C. P.; Jones, C. R.; Tukada, H. *J. Org. Chem.* **1981**, *46*, 2089. (b) Anderson, G.; Cameron, G. W.; Feutrill, G. I.; Read, R. W. *Tetrahedron Lett.* **1981**, *22*, 4347.

(13) Savard, J.; Brassard, P. *Tetrahedron* **1984**, *40*, 3455.

(14) (a) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595. (b) Grieco, P. A. *Aldrichimica Acta* **1991**, *24*, 59.

(15) Dauben, W. G.; Kessel, C. R.; Takamura, K. H. *J. Am. Chem. Soc.* **1980**, *102*, 6893. For a review, see: Matsumoto, K.; Hamana, H.; Iida, H. *Helv. Chim. Acta* **2005**, *88*, 2033.

(16) The high-pressure reaction was conducted by the super high-pressure apparatus (PVS-1400R, TERAMECS Co., Ltd., Japan) at RIKEN with the generous support of Prof. Sodeoka and Dr. Hirai.

(17) For comparison of the ^{1}H NMR charts of the crude material and the pure sample of **14**, see the Supporting Information.

(18) The acid sensitivity of the cycloadduct **I** was extremely high: it quickly underwent decomposition upon attempted silica gel chromatographic purification, giving the aromatized product **14** and other unidentified products.

(19) The double reaction did not occur, even with diene **18** (3.0 equiv); only the product **14** was obtained in 65% yield.

(20) For the general reactivity of diastereotopic enones, see: (a) Takagi, R.; Nishi, T. *Org. Biomol. Chem.* **2015**, DOI: 10.1039/C5OB01760B. (b) Sparling, B. A.; Tucker, J. K.; Moebius, D. C.; Shair, M. D. *Org. Lett.* **2015**, *17*, 3398. (c) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106.

(21) If the steric bulkiness of the siloxy group in **6** is considered, the left-side approach appears to be unfavorable. Nonetheless, however, the major product **14a** is formally arising from the left-side approach, although the details are not clear at this moment. See also ref 20.

(22) DAICEL CHIRALPAK IF, *n*-hexane/AcOEt = 7/3, see the Supporting Information.

DOI: 10.1021/acs.orglett.5b02906
Org. Lett. XXXX, XXX, XXX−XXX