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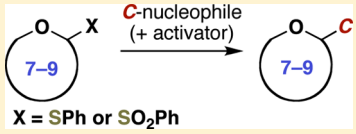
Stereoselective Synthesis of Medium-Sized Cyclic Ethers: Application of *C*-Glycosylation Chemistry to Seven- to Nine-Membered Lactone-Derived Thioacetals and Their Sulfone Counterparts

Yuto Suga, Haruhiko Fuwa,* and Makoto Sasaki

Graduate School of Life Sciences, Tohoku University, 2-1-1 Katahira, Aoba-ku, Sendai 980-8577, Japan

Supporting Information

ABSTRACT: Stereoselective synthesis of α,α'-substituted medium-sized cyclic ethers has been achieved by means of nucleophilic substitution of the corresponding lactone-derived thioacetals and their sulfone counterparts. Nucleophilic substitution of medium-sized lactone-derived thioacetals could be achieved efficiently either by (i) activation with NIS/TMSOTf in the presence of allyltrimethylsilane or TMSCN or by (ii) oxidation to the corresponding sulfones followed by treatment with an appropriate organometallic species such as divinylzinc or dimethyl(2-phenylethynyl)aluminum. Interestingly, the stereochemical consequence was found to be largely dependent on the local structure of substrates. In some cases, the gauche steric interaction developed in the transition state was considered to be responsible for the observed diastereoselectivity. The present method enables an efficient synthesis of a variety of α,α'-substituted seven- to nine-membered cyclic ethers from readily accessible lactone precursors.



INTRODUCTION

A number of marine natural products are known to contain medium-sized cyclic ether(s) within their backbone structures.[1] As shown in Figure 1, the structures of brevetoxin A[2] and gambieric acid A,[3] the representative members of the secondary metabolites of toxic dinoflagellates, are characterized by their ladder-shaped polycyclic ether skeletons containing seven- to nine-membered cyclic ethers. The C15 acetogenin metabolites of the *Laurencia* red algae, such as laurencin,[4] obtusenyne,[5] and rogioloxepane A,[6] are halogenated, medium-sized monocyclic ethers. The construction of medium-sized cyclic ethers poses a formidable challenge to synthetic chemists because their closure inherently accompanies unfavorable entropic penalty and transannular interactions.[7] The vast majority of synthetic methods for medium-sized oxacycles[8] can be categorized into the following three types: (i) intramolecular C–O bond formation of linear alcohols;[9] (ii) intramolecular C–C bond formation of linear ethers;[10] and (iii) functionalization of medium-sized lactones (Scheme 1).[11,12] It is known that direct construction of medium-sized oxacycles via an intramolecular C–O bond formation, i.e., etherification, is difficult

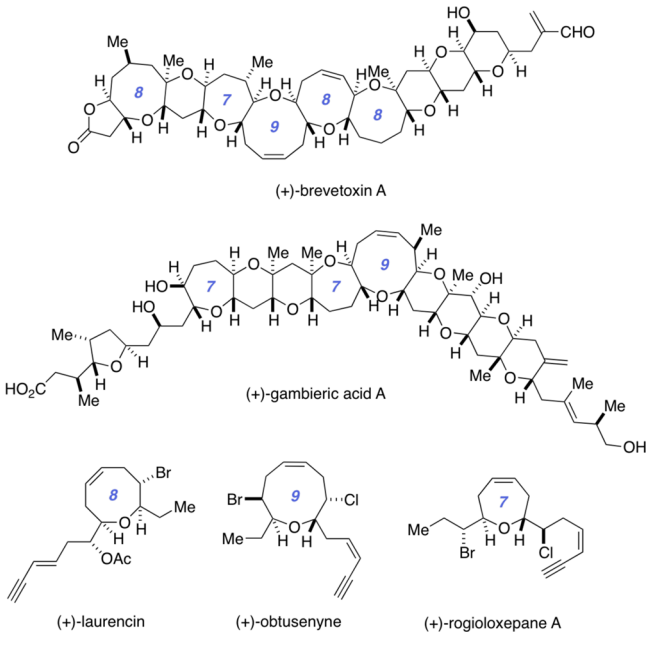
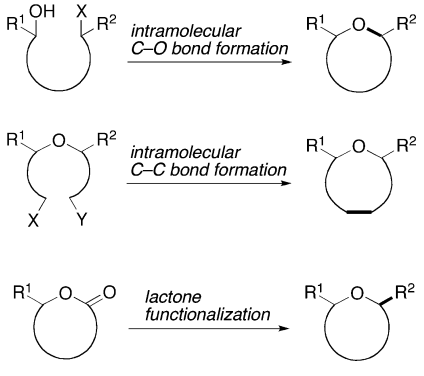


Figure 1. Examples of marine natural products containing medium-sized oxacycles.

Scheme 1. Representative Strategies for the Synthesis of Medium-Sized Oxacycles



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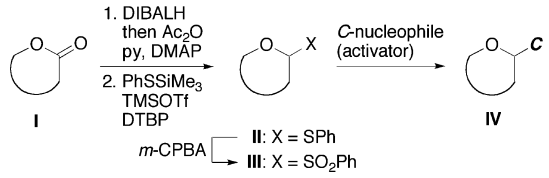
in many cases because of the low nucleophilic character of alcohols. Accordingly, considerable attention has been paid to the development of synthetic methods based on an intramolecular C−C bond formation of linear ethers. In this context, ring-closing metathesis[13] has emerged as a versatile means for the synthesis of medium-sized cyclic ethers.[14] Meanwhile, several groups have exploited the synthetic utility of readily accessible lactones as precursors for medium-sized oxacycles.[11,15] *C*-Glycosylation is a versatile method for the synthesis of five- and six-membered cyclic ethers from appropriate electrophilic precursors.[16] However, its application to the synthesis of medium-sized cyclic ethers has been limited to date. Rychnovsky and Dahanukar have demonstrated the synthesis of five- to eight-membered *α,α′-trans*-substituted cyclic ethers by reacting lactone-derived *α*-acetoxy ethers with diethyl[2-(trimethylsilyl)ethynyl]aluminum in the presence of $BF_3{\cdot}OEt_2$.[17] This study represents a unique and pioneering example of the application of *C*-glycosylation chemistry to the synthesis of medium-sized cyclic ethers. As part of our continuous studies on the synthesis of cyclic ethers, we herein report stereoselective synthesis of *α,α′*-substituted medium-sized cyclic ethers via lactone-derived thioacetals and their sulfone counterparts. We found that nucleophilic substitutions of medium-sized ring thioacetals and sulfones could be performed under mild conditions compatible with a range of functional groups, in a similar manner to *C*-glycosylation of thioglycosides.[16,18] We also found that the stereochemical course of the reactions was largely dependent on the local structure of substrates.

RESULTS AND DISCUSSION

Synthesis Plan. Our strategy for the synthesis of medium-sized cyclic ethers is outlined in Scheme 2. The strategy

Scheme 2. Synthesis Plan



outlined here represents a logical extension of the allylation chemistry uncovered during the course of our total synthesis of gambieric acid A.[15d,e] We planned to convert the lactone **I** to the thioacetal **II** or to the corresponding sulfone **III**. We envisioned that activation of **II** or **III**, followed by trapping of in situ generated oxocarbenium cation with a suitable nucleophile, would be a viable way to synthesize **IV**.[16,18] Although thioglycosides are known to be versatile donors in *O*- and *C*-glycosylation reactions,[16,18,19] their medium-sized ring counterparts have been scarcely used in nucleophilic substitutions.[20] Meanwhile, Rychnovsky and Dahanukar showed that nucleophilic substitution of lactone-derived *α*-acetoxy ethers with diethyl[2-(trimethylsilyl)ethynyl]aluminum and $BF_3{\cdot}OEt_2$ gave the corresponding cyclic ethers in excellent yields.[17] We expected that lactone-derived thioacetals would be superior to the respective *α*-acetoxy ethers in terms of reactivity toward *C*-nucleophiles on the basis of our previous experience.[15d,21]

Preparation of Medium-Sized Lactones. It is known that medium-sized rings exist in solution as ensembles of multiple rapidly interconverting conformers.[22] We anticipated that it would be difficult to discuss the stereoselectivity of nucleophilic substitutions of conformationally flexible medium-sized ring thioacetals and sulfones. Accordingly, in the present study, we favored to use fused 6,*n*-bicyclic ethers as substrates, wherein the fused six-membered ring would reduce the conformational mobility of the medium-sized ring to some extent.

We first prepared a series of medium-sized lactones **1a**−**k** shown in Table 1 as the starting materials. The lactones **1a**,[23] **1h**,[24] and **1k**[25] were prepared from commercially available materials in 5, 11, and 9 steps, respectively, according to the literature precedents.

The C3[26] benzyloxy-substituted seven-membered lactones **1b** and **1c** were prepared from the known olefin **5**,[27] which was available from tri-*O*-acetyl-D-glucal in five steps (Scheme 3). Dihydroxylation of **5** using AD-mix-*α*[28] gave the 1,2-diol **6** in 88% yield and with 1.5:1 diastereoselectivity. Protection of **6** as its benzylidene acetal, DIBALH reduction, and desilylation with TBAF led to the diol **7** (66%, three steps). Selective oxidation[29] of the primary hydroxy group within **7** to the corresponding carboxylic acid **8** (70%, two steps) followed by Yamaguchi lactonization[30] afforded the seven-membered lactones **1b** (55%) and **1c** (38%). These lactones were readily separable by flash column chromatography using silica gel. For each product, the absolute configuration of the C3 stereogenic center was established by an NOE experiment as shown.

The C3 silyloxy-substituted seven-membered lactones **1d** and **1e** were synthesized from the known alcohol **9**,[31] which was prepared from tri-*O*-acetyl-D-glucal in five steps (Scheme 4). The alcohol **9** was converted to the corresponding triflate and then reacted with allylmagnesium chloride/CuI[32] to give the olefin **10** (81%, two steps). Olefin cross-metathesis[33] of **10** with methyl acrylate by the action of the second-generation Hoveyda−Grubbs catalyst (**HG-II** = [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(*o*-isopropoxyphenylmethylene)-ruthenium)[34] afforded the *α,β*-unsaturated ester **11** (85%), which was reduced with DIBALH to give the allylic alcohol **12** (97%). Sharpless asymmetric epoxidation of **12** using (+)-diethyl tartrate (DET) as a chirality source delivered the epoxy alcohol **13** (92%, dr >20:1), which was iodinated and then reduced with zinc to afford the secondary allylic alcohol **14** (98%, two steps). Silylation of **14** followed by removal of the *p*-methoxylphenylmethyl (MPM) group gave the alcohol **15** (95%, two steps). Oxidative cleavage of the double bond[35] and subsequent oxidation of the derived aldehyde provided the seco-acid **16**, whose lactonization under Yamaguchi conditions[30] furnished the seven-membered lactone **1d** (71%, four steps). The seven-membered lactone **1e** was prepared from the allylic alcohol **12** in a similar manner as that described for **1d**.

The C3 methyl-substituted seven-membered lactones **1f** and **1g** were prepared from the alcohol **9**[31] (Scheme 5). Oxidation of **9** followed by Wittig reaction using $Ph_3P{=}CHCO_2Et$ gave the *α,β*-unsaturated ester **21** (87%, two steps). A two-stage reduction of **21** ((i) $NiCl_2$, $NaBH_4$, MeOH;[36] (ii) $LiAlH_4$) led to the alcohol **22** (91%, two steps). Tosylation of **22** (88%) and displacement of the ensuing tosylate with NaCN provided the cyanide **23** (quant). Alkaline hydrolysis of **23** (KOH, EtOH/H_2O, 80 °C) gave the carboxylic acid **24** (98%), which was condensed with (*S*)-4-benzyloxazolidin-2-one via a mixed anhydride[37] to afford the imide **25** (97%). Asymmetric alkylation of **25** according to the Evans conditions (sodium hexamethyldisilazide (NaHMDS), MeI, THF, −78 °C)[38] delivered the methylated product **26** (97%, dr >20:1). Removal of the MPM group gave the alcohol **27** (92%). Hydrolysis of the imide moiety within **27**, followed by lactonization of the resultant seco-acid under Yamaguchi conditions,[30] furnished the seven-membered

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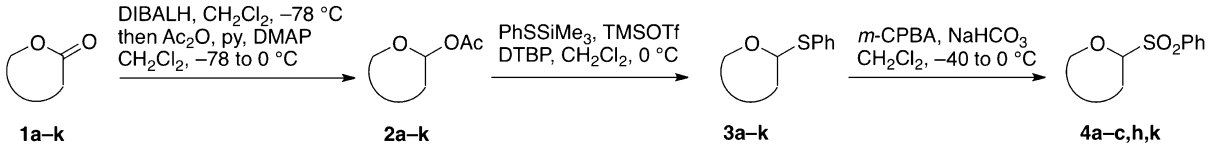
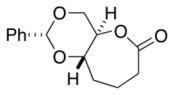
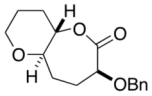
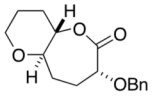
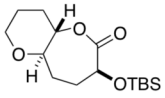
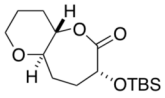
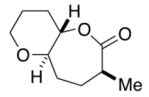
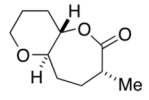
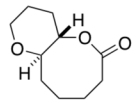
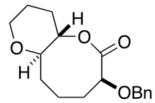
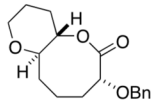
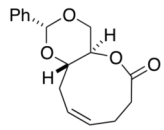
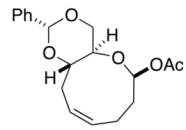
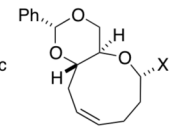
Table 1. Preparation of Lactone-Derived Thioacetals and Their Sulfone Counterparts[a]



Lactone	α-Acetoxy ether	Thioacetal/Sulfone
 **1a**	**2a**: 83%, dr 5:1	**3a**: X = SPh 85%, dr 2.5:1 **4a**: X = SO_2Ph 87%, dr 2.5:1
 **1b**	**2b**: 85%, dr 14:1	**3b**: X = SPh 78%, dr 8:1 **4b**: X = SO_2Ph 80%, dr 8:1
 **1c**	**2c**: 82%, dr >20:1	**3c**: X = SPh 80%, dr 8:1 **4c**: X = SO_2Ph 80%, dr 8:1
 **1d**	**2d**: 77%, dr 15:1	**3d**: X = SPh 83%, dr 8:1
 **1e**	**2e**: 81%, dr >20:1	**3e**: X = SPh 79%, dr 8:1
 **1f**	**2f**: 78%, dr >20:1	**3f**: X = SPh 76%, dr 20:1
 **1g**	**2g**: 72%, dr 10:1	**3g**: X = SPh 76%, dr >20:1
 **1h**	**2h**: 90%, dr >20:1	**3h**: X = SPh 91%, dr 10:1 **4h**: X = SO_2Ph 97%, dr 10:1
 **1i**	**2i**: 78%, dr >20:1	**3i**: X = SPh 85%, dr 9:1
 **1j**	**2j**: 57%, dr 2:1	**3j**: X = SPh 89%, dr 12:1
 **1k**	 **2k**: 71%, dr 7:1	 **3k**: X = SPh 95%, dr 1:1 **4k**: X = SO_2Ph 80%, dr 1:1

[a]DIBALH reduction/in situ acetylation of lactones: DIBALH (1.2 equiv), CH_2Cl_2, −78 °C; then Ac_2O (5 equiv), pyridine (5 equiv), DMAP (1 equiv), −78 to 0 °C. Conversion of lactones into thioacetals: $PhSSiMe_3$ (1.5 equiv), TMSOTf (2 equiv), DTBP (3 equiv), CH_2Cl_2, 0 °C. Oxidation of thioacetals: *m*-CPBA (3 equiv), $NaHCO_3$ (5 equiv), CH_2Cl_2, −40 to 0 °C.

lactone **1f** in good overall yield. The diastereomeric lactone **1g** was prepared from **24** in a similar manner as that described for **1f**.

The C3 benzyloxy-substituted eight-membered lactones **1i** and **1j** were prepared from the triflate **31**,[39] readily available in four steps from tri-*O*-acetyl-D-glucal, in a similar manner as that described for the seven-membered lactone counterparts **1b** and **1c** (Scheme 6).

Preparation of Lactone-Derived Thioacetals and Their Sulfone Counterparts. With the requisite starting materials available, we next prepared lactone-derived thioacetals and their sulfone derivatives according to Scheme 2, and the results are summarized in Table 1. According to the procedure reported by Rychnovsky and co-workers,[40] DIBALH reduction of the lactones **1a**–**k** followed by in situ acetylation provided the corresponding α-acetoxy ethers **2a**–**k**.[41] For the C3-substituted lactones, treatment with DIBALH should be brief as possible. Otherwise, cleavage of the lactone ring was observed as a side reaction. The stereochemical outcome of the DIBALH reduction appears to be controlled simply by steric factor. The α-acetoxy ethers **2a**–**k** were subsequently treated with $PhSSiMe_3$, TMSOTf, and 2,6-di-*t*-butylpyridine (DTBP)[42] to afford the thioacetals **3a**–**k**, respectively.[41] The diastereoselectivity of the transformation of **2a**–**k** to **3a**–**k** is in line with that of the nucleophilic allylation of **3a**–**k** (vide infra), suggesting that the reaction would involve oxocarbenium ion species as a reactive

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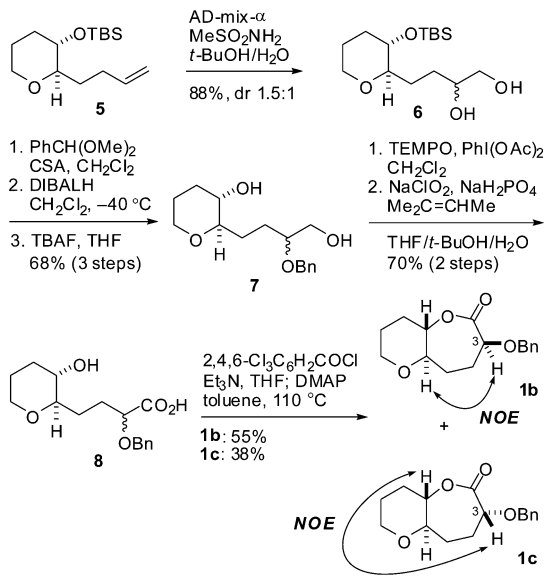
Scheme 3. Synthesis of C3 Benzyloxy-Substituted Lactones 1b and 1c

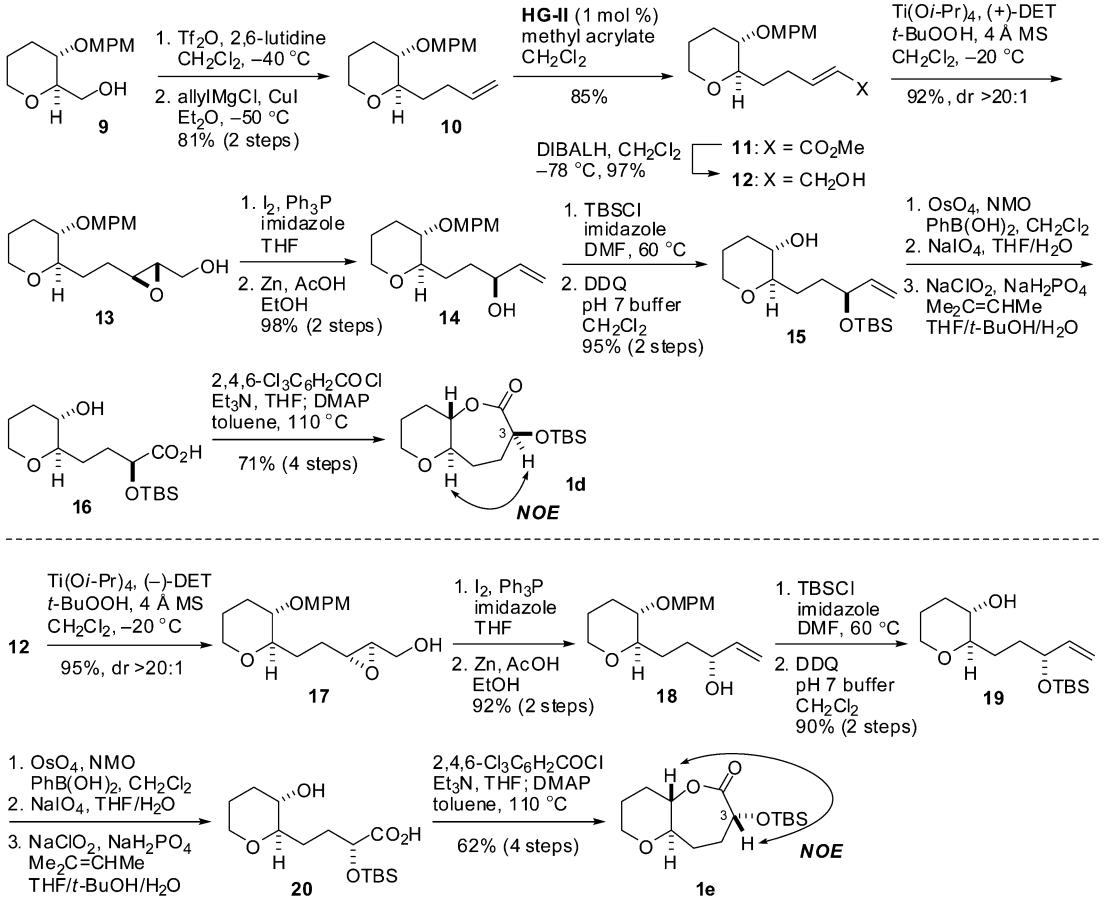


intermediate. Oxidation of **3a–c**, **3h**, and **3k** with *m*-CPBA furnished the corresponding sulfones **4a–c**, **4h**, and **4k**. Notably, all of these products could be chromatographically purified and isolated stably without any special care.

Nucleophilic Substitutions of Lactone-Derived Thioacetals. Next, we examined NIS/TMSOTf-mediated activation[43] and in situ nucleophilic trapping of the thioacetals **3a–k** (Tables 2 and 3). Thus, **3a–k** were treated with NIS (1.5 equiv), TMSOTf (0.1 equiv), and allyltrimethylsilane (5 equiv) (4 Å molecular sieves, CH_2Cl_2, −40 °C to room temperature) to provide the allylated products **36a–k** in good yields (Table 2).[41] Cyanation of **3a–c**, **3h**, and **3k** was also examined as summarized in Table 3. In all cases, the reaction proceeded smoothly using TMSCN as a nucleophile to give the cyanides **37a–c**, **37h**, and **37k**, respectively, in good yields.[41] In some cases, the diastereoselectivity of the cyanation was obviously different from that of the allylation. For example, allylation of **3a** provided the allylated product **36a** as a single stereoisomer (dr >20:1), whereas cyanation of **3a** delivered the cyanated product **37a** as a 1:1 mixture of diastereomers. These observations can be ascribed to the reactivity difference between allyltrimethylsilane and TMSCN.[44,45]

The thioacetals **3b** and **3c** showed opposite stereoselectivity in their allylation and cyanation. Nucleophilic substitutions of **3b** gave the 2,7-*cis*-substituted oxepanes **36b** and **37b** with excellent stereoselectivity (dr 15–18:1). In contrast, **3c** gave the 2,7-*trans*-substituted oxepanes **36c** and **37c** as single stereoisomers (dr >20:1). The diastereoselectivity of allylation of the thioacetals **3d–g** was in accordance with that of **3b** and **3c**. Thus, allylation of the 3*S*-configured thioacetals **3d** and **3f** led to the 2,7-*cis*-substituted oxepanes **36d** and **36f** as the major diastereomers, while that of the 3*R*-configured thioacetals **3e** and **3g** delivered the 2,7-*trans*-substituted oxepanes **36e** and **36g** with excellent diastereoselectivity. These results indicated that the C3 substituent of **3b–g** has significant influence on the stereochemical course of the nucleophilic substitutions. The stereochemical consequence of nucleophilic substitutions of the

Scheme 4. Synthesis of C3 Silyloxy-Substituted Lactones 1d and 1e



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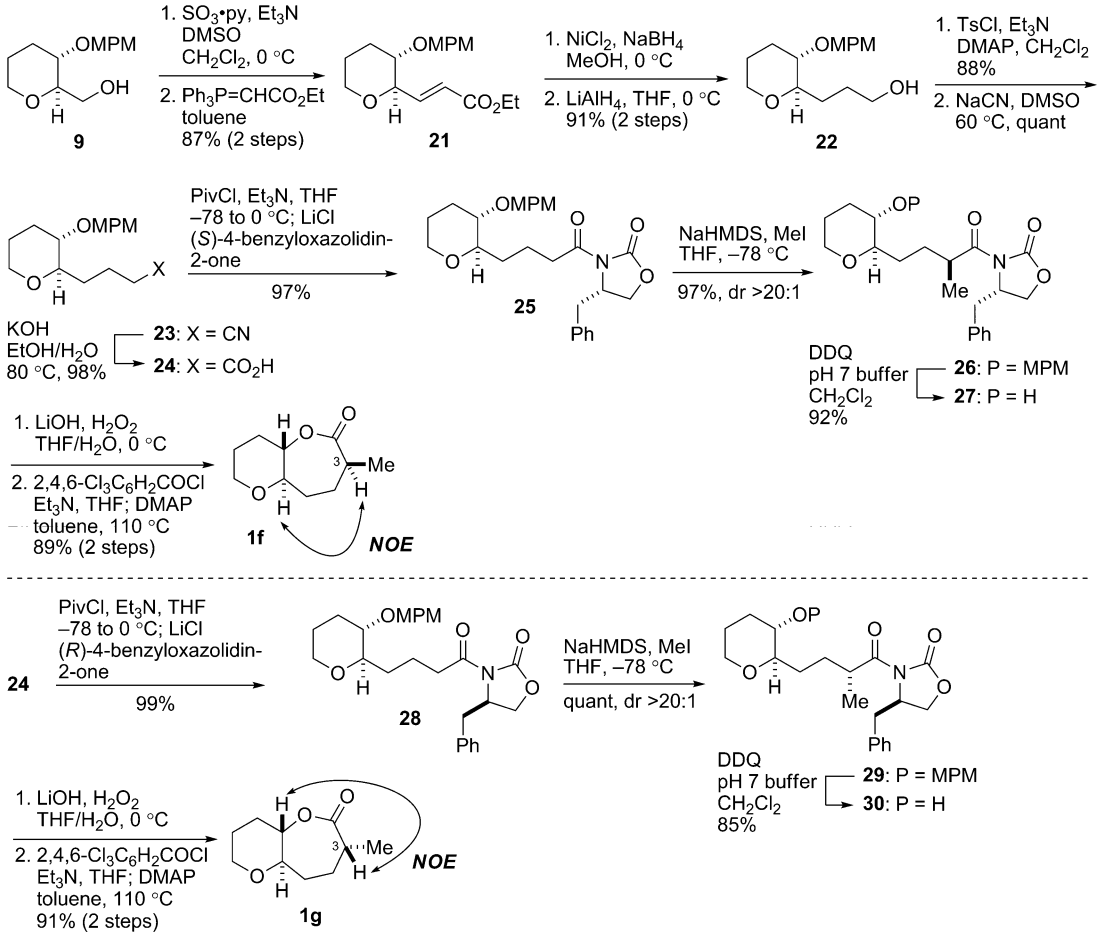
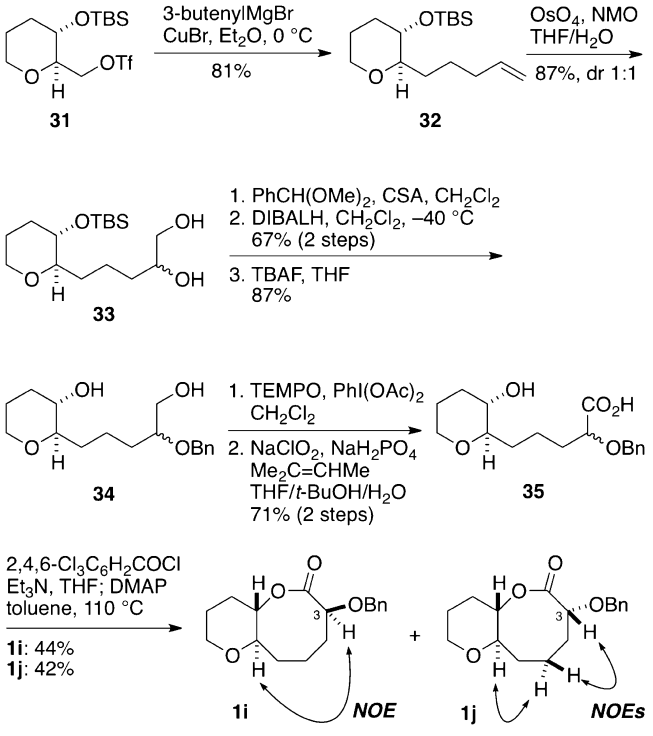
Scheme 5. Synthesis of C3 Methyl-Substituted Lactones 1f and 1g



Scheme 6. Synthesis of C3 Benzyloxy-Substituted Lactones 1i and 1j



eight- and nine-membered thioacetals **3h–k** was similar to that of the seven-membered counterparts **3a–g**.

Notably, individual allylation of 2,7-*cis* and 2,7-*trans* isomers of **3d** delivered the allylated product **36d** with the same diastereoselectivity (Scheme 7). This result suggested that the allylation proceeded through a dissociative S_N1 mechanism involving a solvated oxocarbenium ion.[19,46]

Nucleophilic Substitution of Sulfone Derivatives. Next, we investigated nucleophilic substitution of the sulfones **4a–c**, **4h**, and **4k** (Table 4). Ley and co-workers have demonstrated the utility of alkenylation and alkynylation of 2-(phenylsulfonyl)tetrahydropyran derivatives for the synthesis of *C*-glycosides.[47] By using appropriate organometallic reagents, we found that 2-alkenyl- or 2-alkynyl-substituted medium-sized cyclic ethers could be accessed from **4a–c**, **4h**, and **4k**. Thus, treatment of **4a–c**, **4h**, and **4k** with divinylzinc (1.5 equiv) in THF at room temperature afforded the 2-vinyl-substituted cyclic ethers **38a–c**, **38h**, and **38k** with good to excellent diastereoselectivity.[41] Similarly, treatment of **4a–c**, **4h**, and **4k** with in situ generated dimethyl(2-phenylethynyl)aluminum (1.4 equiv) in toluene/CH_2Cl_2 at room temperature gave the 2-(2′-phenylethynyl)-substituted cyclic ethers **39a–c**, **39h**, and **39k**.[41] Notably, the sulfones **4b** and **4c** having a C3 benzyloxy group showed opposite stereoselectivity, once again suggesting the important role of the C3 benzyloxy group in determining the diastereoselectivity.

Considerations on Stereoselectivity. In contrast to the *O*- and *C*-glycosylations of furanose and pyranose derivatives,

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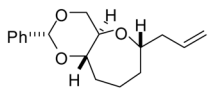
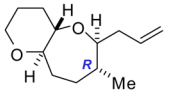
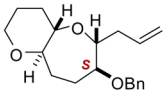
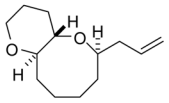
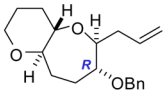
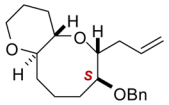
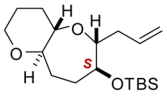
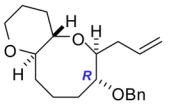
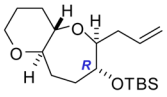
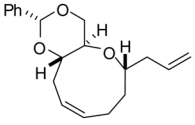
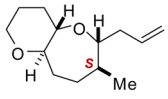
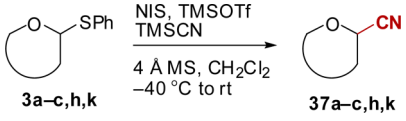
Table 2. Nucleophilic Allylation of Lactone-Derived Thioacetals[a]

3a–k 36a–k

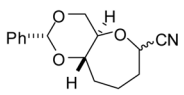
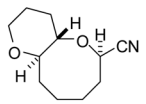
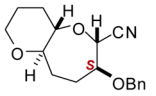
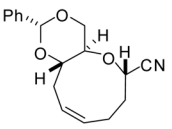
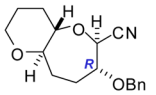
Substrate	Product	Substrate	Product
3a	 **36a**: 80%, dr >20:1[b]	3g	 **36g**: 91%, dr >20:1[b]
3b	 **36b**: 73%, dr 15:1[b]	3h	 **36h**: 66%, dr >20:1[b]
3c	 **36c**: 76%, dr >20:1[b]	3i	 **36i**: 87%, dr 6:1[b]
3d	 **36d**: 87%, dr 3:1[b]	3j	 **36j**: 80%, dr 5:1[b]
3e	 **36e**: 83%, dr 20:1[b]	3k	 **36k**: 63%, dr 2:1[b]
3f	 **36f**: 63%, dr 5:1[b]		

[a]All reactions were performed using NIS (1.5 equiv), TMSOTf (0.1 equiv), allyltrimethylsilane (5 equiv), and 4 Å molecular sieves in CH_2Cl_2 at −40 °C to room temperature. [b]Diastereomer ratio was estimated by 600 MHz ^{1}H NMR spectroscopic analysis of a purified mixture.

Table 3. Nucleophilic Cyanation of Lactone-Derived Thioacetals[a]

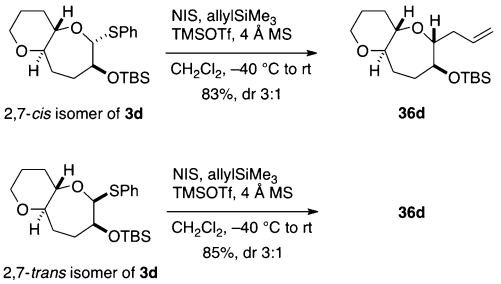


3a–c,h,k 37a–c,h,k

Substrate	Product	Substrate	Product
3a	 **37a**: 77%, dr 1:1[b]	3h	 **37h**: 83%, dr 10:1[b]
3b	 **37b**: 80%, dr 18:1[b]	3k	 **37k**: 71%, dr 4:1[b]
3c	 **37c**: 78%, dr >20:1[b]		

[a]All reactions were performed using NIS (1.5 equiv), TMSOTf (0.1 equiv), TMSCN (5 equiv), and 4 Å molecular sieves in CH_2Cl_2 at −40 °C to room temperature. [b]Diastereomer ratio was estimated by 600 MHz ^{1}H NMR spectroscopic analysis of a purified mixture.

Scheme 7. Individual Allylation of 2,7-*cis* and 2,7-*trans* Isomers of 3d



nucleophilic substitutions involving seven- to nine-membered ring oxocarbenium ions remain largely underexplored.[16−20] One might expect that such reactions would give *α,α′-trans*-substituted cyclic ethers as the products, being similar to what is observed for pyranose-derived oxocarbenium ions. Indeed, we observed pseudoaxial attack of nucleophiles to the oxocarbenium ions generated from seven-, eight-, or nine-membered thioacetals lacking C3 substituent (i.e., **3a**/**4a**, **3h**/**4h**, or **3k**/**4k**, respectively). However, we learned from the results summarized in Tables 2, 3, and 4 that C3 substituent has significant influence on the stereochemical consequence of the reactions.[48,49]

On the basis of the Curtin−Hammett principle,[50] our initial thought was that the diastereoselectivity of the nucleophilic substitutions of medium-sized thioacetals would be influenced both by the conformational preference of the intermediary oxocarbenium ion species and by the energetically unfavorable steric interactions developed in the transition state. Actually, we could not account for the observed diastereoselectivity merely on the basis of the ground-state conformations of the oxocarbenium ions. Possibly because of the conformational flexibility of medium-sized rings,[22] it appears that the transition state does not necessarily reflect the ground-state conformational preference of the oxocarbenium ions. Accordingly, we considered that the developing steric repulsions in the transition state might be the responsible factor for the diastereoselectivity.

As shown in Figure 2, we propose two transition state models **TS-A** and **TS-B** for the nucleophilic substitutions of the 3*S*-substituted thioacetals **3b**, **3d**, **3f**, and **4b**. **TS-B** suffers from the gauche steric interaction between the C3 substituent "R" and the incoming nucleophile "Nu" (the C2/C3 gauche interaction). Accordingly, the reaction would undergo **TS-A**, in which "Nu" is arranged anti to the "R" group, to give the 2,7-*cis*-substituted oxepanes **36b**, **36d**, **36f**, **37b**, **38b**, and **39b**, preferentially. Woerpel and co-workers have described the influence of destabilizing gauche interactions on the diastereoselectivity of reactions involving C3 substituted tetrahydropyran-derived oxocarbenium ions.[48d] In a similar manner, we consider

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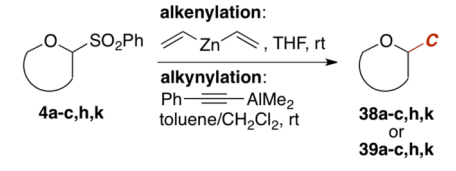
Table 4. Nucleophilic Substitution of Sulfone Derivatives



Substrate	Alkenyl derivative[a]	Alkynyl derivative[b]
4a	**38a**: 80%, dr 18:1[c]	**39a**: 81%, dr 3:1[c]
4b	**38b**: 84%, dr 8:1[c]	**39b**: 74%, dr 7:1[c]
4c	**38c**: 81%, dr >20:1[c]	**39c**: 77%, dr 6:1[c]
4h	**38h**: 80%, dr >20:1[c]	**39h**: 87%, dr >20:1[c]
4k	**38k**: 70%, dr 3:1[c]	**39k**: 70%, dr 1.2:1[c]

[a]Alkenylation: VinylMgBr (3 equiv), $ZnBr_2$ (1.5 equiv), THF, room temperature. [b]Alkynylation: Ethynylbenzene (1.4 equiv), *n*-BuLi (1.4 equiv), Me_2AlCl (1.4 equiv), toluene/CH_2Cl_2, room temperature. [c]Diastereomer ratio was estimated by 600 MHz ^1H NMR spectroscopic analysis of a purified mixture.

that the nucleophilic substitutions of the 3*R*-substituted thioacetals **3c**, **3e**, **3g**, and **4c** would proceed through **TS-D** that avoids unfavorable C2/C3 gauche interaction, leading to the 2,7-*trans*-substituted oxepanes **36c**, **36e**, **36g**, **37c**, **38c**, and **39c**, in a stereoselective manner. However, it should be emphasized that the C2/C3 gauche interaction is not the sole factor that determines the stereochemical outcome of the nucleophilic substitutions of medium-sized ring thioacetals and sulfones; the observed diastereoselectivity for the allylation of **3b**, **3d**, and **3f** did not correlate with the steric bulk of the C3 substituent (Table 2). It is conceivable that the energy of the transition states would be influenced not only by the gauche interaction between the C3 substituent and incoming nucleophile but also by the repulsive interactions between the C3 substituent and hydrogen atoms on the ring periphery.

The diastereoselectivity observed for the nucleophilic allylation of eight-membered thioacetals **3i** and **3j** would also be the result of avoiding the C2/C3 gauche steric interaction in the respective transition state model (Figure 3).[51]

CONCLUSION

In this paper, we described stereoselective synthesis of α,α'-substituted medium-sized cyclic ethers from readily accessible lactone precursors. Seven- to nine-membered lactone-derived

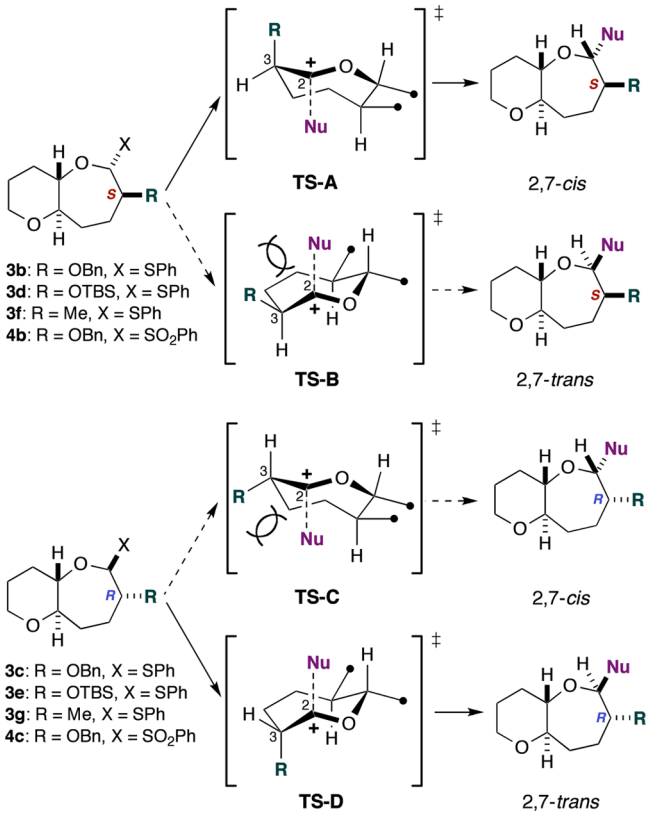


Figure 2. Plausible transition state models of the nucleophilic substitution reactions of seven-membered thioacetals and their sulfone derivatives with a C3 substituent.

thioacetals underwent nucleophilic substitution reactions to afford a series of medium-sized cyclic ethers with good to excellent diastereoselectivity, which appeared to be dependent on the local structure of substrates. Importantly, the steric bulk of a substituent at the C3 position could be exploited to control the stereochemical consequence of the nucleophilic substitutions. The chemistry described herein would enable an efficient synthesis of a variety of α,α'-substituted seven- to nine-membered cyclic ethers.

EXPERIMENTAL SECTION

General Remarks. All reactions sensitive to moisture and/or air were carried out under an atmosphere of argon in dry, freshly distilled solvents under anhydrous conditions using oven-dried glassware unless otherwise noted. Anhydrous THF, Et_2O, and toluene were purified by a Glass Contour solvent purification system under an atmosphere of argon immediately prior to use. 2,6-Lutidine, pyridine, and triethylamine were distilled from calcium hydride under an atmosphere of argon. DMF and DMSO were distilled from magnesium sulfate under reduced pressure. *m*-CPBA was purified as described elsewhere.[52] TsCl was recrystallized from toluene. All other chemicals were purchased at highest commercial grade and used directly. ^1H and ^{13}C NMR chemical shift values are reported in ppm (δ) downfield from tetramethylsilane with reference to internal residual solvent [^1H NMR, $CHCl_3$ (7.24), C_6HD_5 (7.15), $(CHD_2)(CD_3)CO$ (2.05); ^{13}C NMR, $CDCl_3$ (77.0), C_6D_6 (128.0), $(CD_3)_2CO$ (29.8)]. Coupling constants (J) are reported in Hertz (Hz). The following abbreviations were used to designate the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad. Diastereomer ratio (dr) was estimated by ^1H NMR spectroscopic analysis (600 MHz), unless otherwise noted. HRMS were measured on TOF-MS using ESI probe.

dx.doi.org/10.1021/jo4025545 | J. Org. Chem. 2014, 79, 1656−1682

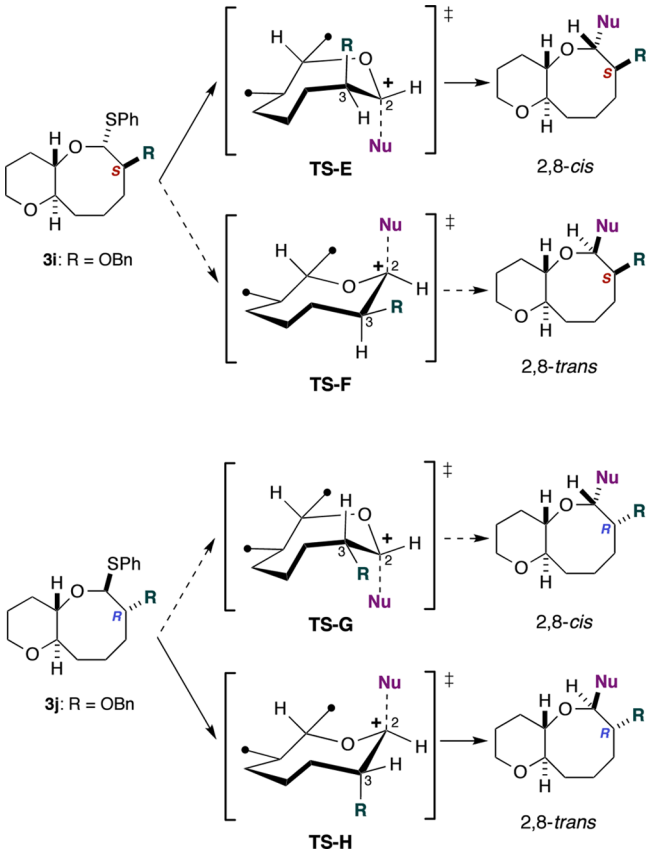
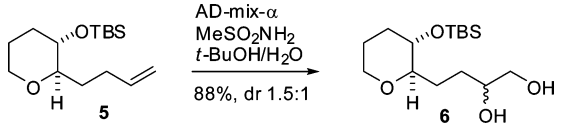
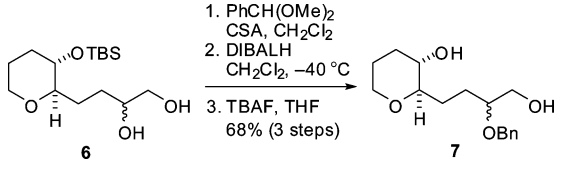


Figure 3. Plausible transition state models of the nucleophilic substitution reactions of eight-membered thioacetals with a C3 substituent.



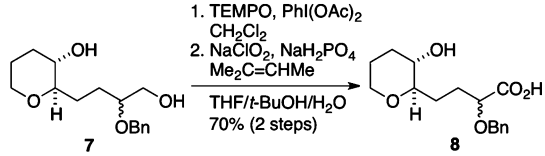
1,2-Diol 6. To a solution of olefin **5** (420 mg, 1.56 mmol) in *t*-BuOH/H_2O (1:1, v/v, 15 mL) at 0 °C were added $MeSO_2NH_2$ (223 mg, 2.34 mmol) and AD-mix-α (2.20 g), and the resultant mixture was stirred at room temperature for 10 h. The reaction mixture was cooled to 0 °C, diluted with saturated aqueous Na_2SO_3 solution, and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 40–70% EtOAc/hexanes) gave 1,2-diol **6** (416 mg, 88%, dr 1.5:1) as a colorless oil. The following data were collected as a 1.5:1 mixture of diastereomers: $[\alpha]_D^{22}$ +13.8 (*c* 1.00, $CHCl_3$); IR (film) 3398, 2931, 2857, 1463, 1253, 1098 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.90–3.84 (m, 6/5H), 3.70 (m, 3/5H), 3.64 (m, 2/5H), 3.59–3.56 (m, 1H), 3.46–3.40 (m, 6/5H), 3.34–3.24 (m, 11/5H), 3.05–2.98 (m, 1H), 2.59 (br s, 7/5H), 2.08 (dddd, *J* = 8.2, 8.2, 5.9, 2.3 Hz, 2/5H), 2.00–1.92 (m, 8/5H), 1.70–1.45 (m, 23/5H), 1.43–1.33 (m, 7/5H), 0.850 (s, 18/5H), 0.848 (s, 27/5H), 0.036 (s, 18/5H), 0.034 (s, 12/5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 83.3 (2/5C), 82.9 (3/5C), 72.4 (2/5C), 71.8 (3/5C), 71.1(2/5C), 70.6 (3/5C), 67.82 (2/5C), 67.77 (3/5C), 67.0 (2/5C), 66.7 (3/5C), 33.48 (3/5C), 33.46 (2/5C), 30.1 (2/5C), 29.3 (3/5C), 28.7 (2/5C), 27.5 (3/5C), 25.7 (3C), 25.54 (3/5C), 25.46 (2/5C), 17.90 (2/5C), 17.89 (3/5C), −3.95 (2/5C), −3.97 (3/5C), −4.740 (2/5C), −4.739 (3/5C); HRMS (ESI) calcd for $C_{15}H_{32}O_4SiNa$ [(M + Na)$^+$] 327.1962, found 327.1966.



Diol 7. To a solution of 1,2-diol **6** (502 mg, 1.65 mmol) in CH_2Cl_2 (16 mL) were added $PhCH(OMe)_2$ (0.37 mL, 2.5 mmol) and CSA (77 mg, 0.33 mmol), and the resultant solution was stirred at room temperature for 12 h. The reaction mixture was neutralized with Et_3N and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, 10–15% EtOAc/hexanes) to give crude benzylidene acetal (596 mg), which was used in the next reaction without further purification.

To a solution of the above benzylidene acetal in CH_2Cl_2 (10 mL) at −40 °C was added DIBALH (1.0 M solution in *n*-hexane, 5.7 mL, 5.7 mmol), and the resultant solution was stirred at −40 °C for 2 h. The reaction was quenched with MeOH. The mixture was diluted with EtOAc and saturated aqueous potassium sodium tartrate solution, and the resultant biphasic mixture was stirred vigorously at room temperature until the layers became clear. The resultant mixture was diluted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, 15–30% EtOAc/hexanes) to give crude alcohol (557 mg), which was used in the next reaction without further purification.

To a solution of the above alcohol in THF (12 mL) was added TBAF (1.0 M solution in THF, 3.2 mL, 3.2 mmol), and the resultant solution was stirred at room temperature for 8 h. The reaction mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 50–80% EtOAc/hexanes) gave diol **7** (315 mg, 68% for the three steps, dr 1.5:1) as a colorless oil. The following data were collected as a 1.5:1 mixture of diastereomers: $[\alpha]_D^{22}$ +8.9 (*c* 1.00, $CHCl_3$); IR (film) 3420, 2934, 2854, 1541, 1456, 1094 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.36–7.25 (m, 5H), 4.61 (d, *J* = 11.5 Hz, 3/5H), 4.60 (d, *J* = 11.5 Hz, 2/5H), 4.52 (d, *J* = 11.5 Hz, 1H), 3.89–3.83 (m, 1H), 3.72–3.66 (m, 1H), 3.56–3.49 (m, 2H), 3.31–3.24 (m, 2H), 2.98–2.92 (m, 1H), 2.08–2.02 (m, 1H), 2.00–1.82 (m, 4H), 1.79–1.56 (m, 3H), 1.51–1.32 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.43 (3/5C), 138.40 (2/5C), 128.5 (2C), 127.88 (6/5C), 127.86 (4/5C), 127.7, 82.3 (3/5C), 82.2 (2/5C), 79.7 (3/5C), 79.4 (2/5C), 71.4, 70.2 (2/5C), 70.1 (3/5C), 67.6, 64.0, 32.89 (3/5C), 32.87 (2/5C), 27.6 (3/5C), 27.2 (2/5C), 26.2 (3/5C), 26.1 (2/5), 25.6; HRMS (ESI) calcd for $C_{16}H_{24}O_4Na$ [(M + Na)$^+$] 303.1567, found 303.1577.



Seco-acid 8. To a solution of diol **7** (1.88 g, 6.39 mmol) in CH_2Cl_2 (60 mL) were added $PhI(OAc)_2$ (2.47 g, 7.67 mmol) and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) (200 mg, 1.28 mmol), and the resultant solution was stirred at room temperature for 4 h. The reaction mixture was cooled to 0 °C, diluted with saturated aqueous Na_2SO_3 solution and extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant crude aldehyde (2.41 g) was used in the next reaction without purification.

To a solution of the above aldehyde in THF/*t*-BuOH/H_2O (2:2:1, v/v/v, 60 mL) were added 2-methyl-2-butene (6.77 mL, 63.9 mmol), NaH_2PO_4 (1.36 g, 9.59 mmol), and $NaClO_2$ (1.73 g, 19.2 mmol). The resultant solution was stirred at room temperature for 8 h, acidified with saturated aqueous NH_4Cl solution, and extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 60–90% EtOAc/hexanes) gave seco-acid **8** (1.41 g, 70%, for the two steps, dr 1.5:1) as a pale yellow oil. The following data were collected as a 1.5:1 mixture of diastereomers: $[\alpha]_D^{22}$ +17.2 (*c* 1.00, $CHCl_3$); IR (film) 2854, 2831, 1701, 1323, 1247, 1063, 1021 cm^{-1};

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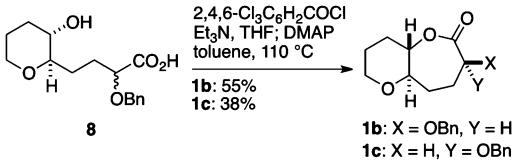
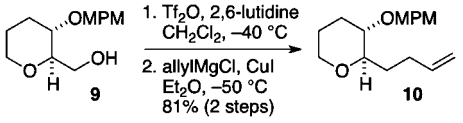
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 4.69 (d, J = 11.5 Hz, 1H), 4.48 (d, J = 11.5 Hz, 1H), 4.04−4.01 (m, 1H), 3.87−3.83 (m, 1H), 3.70 (m, 2/5H), 3.31−3.22 (m, 2H), 2.98−2.94 (m, 1H), 2.50−2.46 (m, 3/5H), 2.07−1.85 (m, 5H), 1.66−1.61 (m, 2H), 1.57−1.50 (m, 1H), 1.38−1.30 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.33 (3/5C), 175.32 (2/5C), 136.95 (3/5C), 136.93 (2/5C), 128.5 (2C), 128.2 (6/5C), 128.14 (4/5C), 128.11, 81.77 (3/5C), 81.75 (2/5C), 77.4 (2/5C), 72.4, 70.0 (3/5C), 69.9 (2/5C), 67.53 (2/5C), 67.51 (3/5C), 61.9 (3/5C), 32.7 (3/5C), 32.6 (2/5C), 28.1 (3/5C), 28.0 (2/5C), 26.87 (2/5C), 26.84 (3/5C), 25.49 (2/5C), 25.48 (3/5C); HRMS (ESI) calcd for $C_{16}H_{21}O_5$ [(M − H)$^-$] 293.1394, found 293.1399.

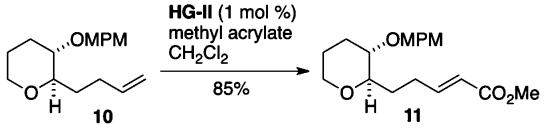


Lactones 1b and 1c. To a solution of seco-acid **8** (651 mg, 2.21 mmol) in THF (15 mL) at 0 °C were added Et_3N (0.62 mL, 4.4 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (0.52 mL, 3.3 mmol), and the resultant solution was stirred at room temperature for 30 min. The mixed anhydride solution thus obtained was diluted with toluene (30 mL) and added dropwise to a solution of DMAP (1.08 g, 8.84 mmol) in toluene (100 mL) at 110 °C over a period of 3 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 15% EtOAc/hexanes) gave lactone **1b** (337 mg, 55%) as pale yellow crystals and lactone **1c** (232 mg, 38%) as pale yellow crystals. Data for **1b**: mp 57−60 °C; $[\alpha]_D^{24}$ +85.2 (c 1.00, $CHCl_3$); IR (film) 2894, 2841, 1716, 1313, 1207, 1075, 943 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37−7.29 (m, 5H), 4.70 (ddd, J = 11.0, 8.7, 5.5 Hz, 1H), 4.63 (d, J = 11.5 Hz, 1H), 4.54 (d, J = 11.5 Hz, 1H), 4.31 (dd, J = 6.9, 0.9 Hz, 1H), 3.85 (dddd, J = 11.0, 6.7, 2.3, 1.8 Hz, 1H), 3.28 (ddd, J = 11.0, 11.0, 3.2 Hz, 1H), 3.20 (ddd, J = 11.0, 9.1, 4.6 Hz, 1H), 2.20−2.04 (m, 3H), 1.89 (dddd, J = 13.7, 4.1, 4.1, 4.1 Hz, 1H), 1.75 (dddd, J = 11.5, 11.5, 3.7, 1.4 Hz, 1H), 1.69−1.53 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.0, 136.7, 128.6 (2C), 128.1, 127.8 (2C), 79.1, 78.1, 76.4, 72.1, 67.0, 30.3, 28.7, 25.4, 24.8; HRMS (ESI) calcd for $C_{16}H_{20}O_4Na$ [(M + Na)$^+$] 299.1254, found 299.1258. Data for **1c**: mp 56−59 °C; $[\alpha]_D^{24}$ +67.9 (c 1.00, $CHCl_3$); IR (film) 2896, 2831, 1725, 1387, 1286, 1103, 915 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37−7.32 (m, 4H), 7.29 (m, 1H), 7.09 (m, 1H), 4.84 (d, J = 11.9 Hz, 1H), 4.43 (d, J = 11.9 Hz, 1H), 4.13 (dd, J = 11.0, 2.3 Hz, 1H), 3.97 (ddd, J = 9.6, 9.2, 5.9 Hz, 1H), 3.84 (m, 1H), 3.29 (m, 1H), 3.21 (ddd, J = 10.5, 9.2, 4.6 Hz, 1H), 2.22−2.15 (m, 2H), 2.09 (dddd, J = 14.6, 4.6, 4.1, 2.3 Hz, 1H), 1.94 (dddd, J = 14.6, 14.2, 11.0, 3.2 Hz, 1H), 1.72−1.61 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.6, 137.3, 128.5 (2C), 127.95, 127.93 (2C), 77.3, 76.3, 76.1, 71.9, 67.0, 33.0, 30.1, 28.7, 24.8; HRMS (ESI) calcd for $C_{16}H_{20}O_4Na$ [(M + Na)$^+$] 299.1254, found 299.1248.

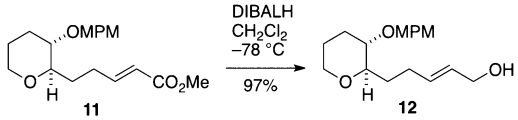


Olefin 10. To a mixture of alcohol **9** (670 mg, 2.66 mmol) and 2,6-lutidine (0.46 mL, 4.0 mmol) in CH_2Cl_2 (25 mL) at −40 °C was added Tf_2O (0.58 mL, 3.5 mmol), and the resultant mixture was stirred at −40 °C for 30 min. The reaction mixture was warmed to 0 °C, diluted with saturated aqueous $NaHCO_3$ solution, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, 5−10% EtOAc/hexanes) to give crude triflate (875 mg), which was used in the next reaction without further purification.

To a suspension of CuI (556 mg, 2.93 mmol) in Et_2O (20 mL) at −50 °C was added a solution of the above triflate in Et_2O (5 mL), and the resultant mixture was stirred at −50 °C for 10 min. To the suspension was added allylmagnesium chloride (2.0 M solution in THF, 2.93 mL, 5.85 mmol) dropwise at −50 °C, and the resultant mixture was stirred at −50 °C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The mixture was diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5% EtOAc/hexanes) gave olefin **10** (595 mg, 81% for the two steps) as a colorless oil: $[\alpha]_D^{24}$ +10.5 (c 1.00, $CHCl_3$); IR (film) 2936, 2849, 1613, 1514, 1248, 1098 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24−7.21 (m, 2H), 6.87−6.84 (m, 2H), 5.81 (dddd, J = 17.0, 10.1, 6.8, 6.8 Hz, 1H), 4.99 (dddd, J = 17.0, 1.9, 1.9, 1.9 Hz, 1H), 4.92 (dddd, J = 10.1, 1.9, 1.4, 1.4 Hz, 1H), 4.54 (d, J = 11.0 Hz, 1H), 4.37 (d, J = 11.0 Hz, 1H), 3.86 (m, 1H), 3.78 (s, 3H), 3.29 (ddd, J = 11.5, 11.5, 2.8 Hz, 1H), 3.11 (ddd, J = 8.7, 8.7, 2.3 Hz, 1H), 3.06 (ddd, J = 10.5, 8.7, 4.6 Hz, 1H), 2.24−2.17 (m, 2H), 2.07 (m, 1H), 1.96 (m, 1H), 1.66 (m, 1H), 1.59 (m, 1H), 1.43 (dddd, J = 9.7, 9.7, 8.8, 5.0 Hz, 1H), 1.35 (dddd, J = 12.8, 12.8, 10.6, 4.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 138.9, 130.6, 129.3 (2C), 114.3, 113.8 (2C), 80.4, 76.8, 70.5, 67.6, 55.3, 31.5, 29.6, 29.3, 25.5; HRMS (ESI) calcd for $C_{17}H_{24}O_3Na$ [(M + Na)$^+$] 299.1618, found 299.1624.



α,β-Unsaturated Ester 11. To a solution of olefin **10** (4.86 g, 17.6 mmol) and methyl acrylate (15.8 mL, 176 mmol) in CH_2Cl_2 (100 mL) was added the Hoveyda−Grubbs second-generation catalyst (110 mg, 0.176 mmol), and the resultant solution was stirred at room temperature overnight. The resultant solution was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 15% EtOAc/hexanes) gave α,β-unsaturated ester **11** (5.01 g, 85%) as a colorless oil: $[\alpha]_D^{22}$ −8.7 (c 1.00, $CHCl_3$); IR (film) 2948, 2850, 1722, 1514, 1248, 1098 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23−7.20 (m, 2H), 6.96 (ddd, J = 15.6, 6.9, 6.9 Hz, 1H), 6.87−6.84 (m, 2H), 5.79 (ddd, J = 15.6, 1.9, 1.4 Hz, 1H), 4.54 (d, J = 11.5 Hz, 1H), 4.35 (d, J = 11.5 Hz, 1H), 3.85 (m, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.28 (ddd, J = 11.9, 11.9, 2.8 Hz, 1H), 3.09 (ddd, J = 9.2, 9.2, 2.8 Hz, 1H), 3.04 (ddd, J = 10.5, 9.1, 4.1 Hz, 1H), 2.33 (m, 1H), 2.26−2.17 (m, 2H), 2.01 (m, 1H), 1.66 (m, 1H), 1.59 (m, 1H), 1.47 (m, 1H), 1.34 (dddd, J = 12.8, 12.8, 10.6, 4.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.2, 159.2, 149.6, 130.4, 129.4 (2C), 120.8, 113.8 (2C), 80.1, 76.8, 70.4, 67.7, 55.3, 51.3, 30.6, 29.2, 28.2, 25.4; HRMS (ESI) calcd for $C_{19}H_{26}O_5Na$ [(M + Na)$^+$] 357.1672, found 357.1677.



Allylic Alcohol 12. To a solution of α,β-unsaturated ester **11** (5.01 g, 15.0 mmol) in CH_2Cl_2 (100 mL) at −78 °C was added DIBALH (1.0 M solution in n-hexane, 32 mL, 32 mmol), and the resultant solution was stirred at −78 °C for 1 h. The reaction was quenched with MeOH. The mixture was diluted with EtOAc and saturated aqueous potassium sodium tartrate solution, and the resultant biphasic mixture was stirred vigorously at room temperature until the layers became clear. The resultant mixture was diluted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 20−30% EtOAc/hexanes) gave allylic alcohol **12** (4.46 g, 97%) as a colorless oil: $[\alpha]_D^{22}$ +14.2 (c 1.00, $CHCl_3$); IR (film) 3420, 2935 2851, 1516, 1247, 1097, 1035 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24−7.21 (m, 2H), 6.87−6.84 (m, 2H), 5.68 (ddd, J = 15.1, 6.4, 6.4 Hz, 1H), 5.62 (ddd, J = 15.1, 5.5, 5.5 Hz, 1H), 4.53 (d, J = 11.5 Hz, 1H), 4.36 (d, J = 11.5 Hz, 1H), 4.07−4.05 (m, 2H), 3.86 (m, 1H), 3.79 (s, 3H), 3.29 (ddd, J = 11.5, 11.5, 2.3 Hz, 1H), 3.10 (ddd, J = 8.7, 8.7, 2.3 Hz, 1H), 3.05 (ddd, J = 10.6, 9.2,

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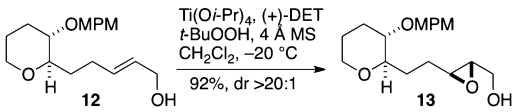
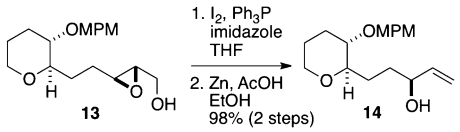
4.6 Hz, 1H), 2.25−2.16 (m, 2H), 2.06 (m, 1H), 1.94 (m, 1H), 1.66 (m, 1H), 1.59 (m, 1H), 1.48 (br s, 1H), 1.42 (m, 1H), 1.35 (dddd, J = 12.8, 12.8, 10.5, 4.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 133.2, 130.5, 129.4 (2C), 129.0 (2C), 113.8 (2C), 80.3, 77.1, 70.5, 67.7, 63.9, 55.3, 31.7, 29.3, 28.1, 25.5; HRMS (ESI) calcd for $C_{18}H_{26}O_4Na$ [(M + Na)$^+$] 329.1723, found 329.1726.

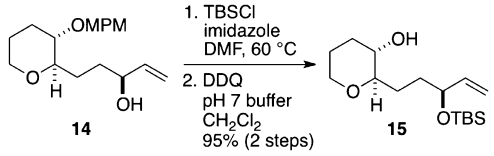


Epoxy Alcohol 13. To a mixture of allylic alcohol **12** (2.23 g, 7.29 mmol), freshly activated 4 Å molecular sieves (2.50 g), and (+)-diethyl tartrate (0.37 mL, 2.2 mmol) in CH_2Cl_2 (60 mL) at −20 °C was added Ti(Oi-Pr)$_4$ (0.43 mL, 1.5 mmol), and the resultant mixture was stirred at −20 °C for 30 min. To this mixture was added t-BuOOH (4.4 M solution in isooctane, 3.3 mL, 15 mmol), and the resultant mixture was stirred at −20 °C for 16 h. The reaction mixture was treated with wet Na_2SO_4, stirred at room temperature for 0.5 h, and then filtered through a pad of Celite. The filtrate was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was taken up in Et_2O (100 mL) and treated with 1 M aqueous NaOH solution (30 mL) at 0 °C. The resultant biphasic mixture was stirred vigorously at 0 °C for 1 h. The resultant mixture was diluted with EtOAc and washed successively with H_2O, saturated aqueous NH_4Cl solution, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 50% EtOAc/hexanes) gave epoxy alcohol **13** (2.15 g, 92%, dr >20:1) as a colorless oil: $[\alpha]_D^{22}$ +13.4 (c 1.00, $CHCl_3$); IR (film) 3418, 2934, 2853, 1516, 1247, 1097 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24−7.21 (m, 2H), 6.87−6.84 (m, 2H), 4.54 (d, J = 11.5 Hz, 1H), 4.36 (d, J = 11.5 Hz, 1H), 3.85 (m, 1H), 3.78 (s, 3H), 3.60 (ddd, J = 11.9, 7.3, 4.1 Hz, 1H), 3.29 (ddd, J = 11.5, 11.5, 2.8 Hz, 1H), 3.11 (ddd, J = 8.7, 8.7, 2.8 Hz, 1H), 3.05 (ddd, J = 10.6, 8.7, 4.1 Hz, 1H), 2.94 (ddd, J = 5.5, 5.5, 2.3 Hz, 1H), 2.88 (ddd, J = 4.1, 2.3, 2.3 Hz, 1H), 2.24 (m, 1H), 2.05 (m, 1H), 1.71−1.57 (m, 6H), 1.44 (dddd, J = 13.7, 8.7, 8.7, 5.9 Hz, 1H), 1.35 (dddd, J = 12.8, 12.8, 10.6, 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 130.5, 129.4 (2C), 113.8 (2C), 80.7, 76.9, 70.4, 67.9, 61.8, 58.4, 56.2, 55.3, 29.2, 28.5, 27.9, 25.4; HRMS (ESI) calcd for $C_{18}H_{26}O_5Na$ [(M + Na)$^+$] 345.1672, found 345.1671.



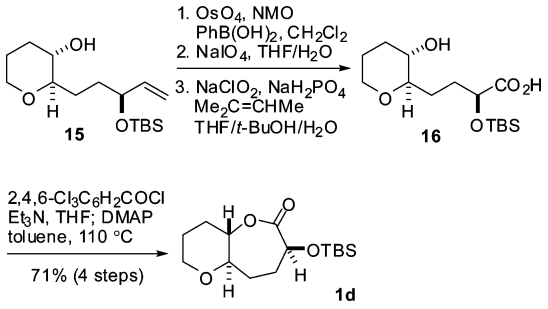
Allylic Alcohol 14. To a solution of epoxy alcohol **13** (1.38 g, 4.29 mmol) in THF (30 mL) were added imidazole (584 mg, 8.57 mmol), PPh_3 (1.91 g, 6.44 mmol), and I_2 (1.63 g, 6.44 mmol), and the resultant solution was stirred at room temperature for 15 min. The reaction mixture was diluted with saturated aqueous Na_2SO_3 solution at 0 °C and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant crude iodide (4.41 g) was used in the next reaction without further purification.

To a solution of the above iodide in EtOH (35 mL) were added zinc powder (2.81 g, 42.9 mmol) and AcOH (0.49 mL, 8.6 mmol), and the resultant mixture was stirred at room temperature for 20 min. The reaction mixture was passed through a pad of Celite. The filtrate was diluted with saturated aqueous $NaHCO_3$ solution at 0 °C and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10−30% EtOAc/hexanes) gave secondary allylic alcohol **14** (1.29 g, 98% for the two steps) as a colorless oil: $[\alpha]_D^{22}$ +13.1 (c 1.00, $CHCl_3$); IR (film) 3420, 2934, 2852, 1514, 1248, 1096 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24−7.21 (m, 2H), 6.87−6.84 (m, 2H), 5.83 (ddd, J = 17.0, 10.6, 5.5 Hz, 1H), 5.21 (ddd, J = 17.0, 1.9, 1.4 Hz, 1H), 5.07 (ddd, J = 10.6, 1.8, 1.4 Hz, 1H), 4.54 (d, J = 11.5 Hz, 1H), 4.36 (d, J = 11.5 Hz, 1H), 4.11 (m, 1H), 3.88 (m, 1H), 3.78 (s, 3H), 3.32 (ddd, J = 11.5, 11.5, 2.8 Hz, 1H), 3.14 (ddd, J = 8.7, 8.7, 2.3 Hz, 1H), 3.09 (ddd, J = 10.5, 9.1, 4.6 Hz, 1H), 2.23 (m, 1H), 2.00 (m, 1H), 1.72−1.56 (m, 5H), 1.49 (m, 1H), 1.36 (dddd, J = 12.8, 12.8, 10.5, 4.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 141.1, 130.5, 129.4 (2C), 114.1, 113.8 (2C), 81.2, 76.5, 72.5, 70.5, 67.7, 55.3, 33.2, 29.2, 27.5, 25.3; HRMS (ESI) calcd for $C_{18}H_{26}O_4Na$ [(M + Na)$^+$] 329.1723, found 329.1722.



Alcohol 15. To a solution of allylic alcohol **14** (1.29 g, 4.22 mmol) in DMF (30 mL) were added imidazole (575 mg, 8.44 mmol) and TBSCl (950 mg, 6.33 mmol), and the resultant solution was stirred at 60 °C for 3 h. The reaction mixture was cooled to room temperature, diluted with t-BuOMe, and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant crude silyl ether (2.14 g) was used in the next reaction without further purification.

To a solution of the above silyl ether in CH_2Cl_2/pH 7 buffer (4:1, v/v, 50 mL) was added DDQ (1.15 g, 5.06 mmol) at 0 °C, and the resultant mixture was stirred at room temperature for 45 min. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution at 0 °C and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10−20% EtOAc/hexanes) gave alcohol **15** (1.21 g, 95% for the two steps) as a colorless oil: $[\alpha]_D^{23}$ +19.5 (c 1.00, $CHCl_3$); IR (film) 3420, 2932, 2854, 1508, 1247, 1096 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.78 (ddd, J = 16.9, 10.6, 6.4 Hz, 1H), 5.12 (ddd, J = 16.9, 1.8, 1.4 Hz, 1H), 5.01 (ddd, J = 10.6, 1.8, 1.4 Hz, 1H), 4.09 (ddd, J = 6.0, 6.0, 6.0 Hz, 1H), 3.86 (dddd, J = 11.5, 4.1, 2.3, 1.8 Hz, 1H), 3.32−3.26 (m, 2H), 2.96 (ddd, J = 8.7, 8.7, 3.2 Hz, 1H), 2.06 (m, 1H), 1.89 (m, 1H), 1.72 (m, 1H), 1.67−1.63 (m, 2H), 1.56−1.49 (m, 2H), 1.41−1.34 (m, 2H), 0.87 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.6, 113.8, 82.4, 74.0, 70.5, 67.5, 33.5, 32.8, 27.7, 25.9 (3C), 25.6, 18.3, −4.4, −4.8; HRMS (ESI) calcd for $C_{16}H_{32}O_3SiNa$ [(M + Na)$^+$] 323.2013, found 323.2012.



Lactone 1d. To a solution of alcohol **15** (480 mg, 1.59 mmol), in CH_2Cl_2 (15 mL) were added $PhB(OH)_2$ (580 mg, 4.78 mmol), NMO (560 mg, 4.78 mmol), and OsO_4 (10 mg/mL solution in t-BuOH, 4.1 mL, 0.16 mmol), and the resultant mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with saturated aqueous Na_2SO_3 solution at 0 °C and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant crude boronate (877 mg) was used in the next reaction without further purification.

To a solution of the above boronate in THF/H_2O (1:1, v/v, 15 mL) was added $NaIO_4$ (1.70 g, 7.95 mmol), and the resultant

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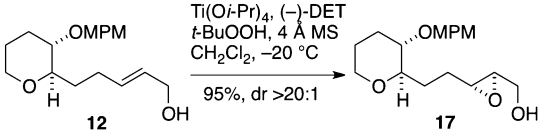
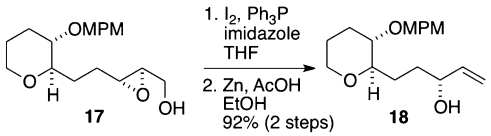
solution was stirred at room temperature for 45 min. The reaction mixture was diluted with saturated aqueous Na_2SO_3 solution at 0 °C and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant crude aldehyde (983 mg) was used in the next reaction without further purification.

To a solution of the above aldehyde in THF/*t*-BuOH/H_2O (2:2:1, v/v/v, 15 mL) were added 2-methyl-2-butene (1.68 mL, 15.9 mmol), NaH_2PO_4 (340 mg, 2.39 mmol), and $NaClO_2$ (430 mg, 4.77 mmol). The resultant solution was stirred at room temperature for 8 h, acidified with saturated aqueous NH_4Cl solution, and extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, 40−70% EtOAc/hexanes) to give crude seco-acid **16** (559 mg), which was used in the next reaction without further purification.

To a solution of the above seco-acid **16** in THF (15 mL) at 0 °C were added Et_3N (0.67 mL, 4.8 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (0.56 mL, 3.6 mmol), and the resultant solution was stirred at room temperature for 30 min. The mixed anhydride solution thus obtained was diluted with toluene (20 mL) and added dropwise to a solution of DMAP (976 mg, 8.00 mmol) in toluene (80 mL) at 110 °C over a period of 3 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 3−10% EtOAc/hexanes) gave lactone **1d** (337 mg, 71% for the four steps) as colorless crystals: mp 48−52 °C; $[\alpha]_D^{22}$ +33.9 (*c* 1.00, $CHCl_3$); IR (film) 2931, 2857, 1763, 1255, 1129, 1089 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.96 (m, 1H), 4.30 (m, 1H), 3.86 (dddd, *J* = 11.5, 4.1, 1.8, 1.8 Hz, 1H), 3.33 (m, 1H), 3.09 (ddd, *J* = 7.8, 6.8, 2.3 Hz, 1H), 2.23 (m, 1H), 2.03−1.92 (m, 2H), 1.81−1.68 (m, 3H), 1.61 (m, 1H), 1.47 (m, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.5, 83.2, 72.9, 68.0, 64.0, 39.1, 29.8, 25.72, 25.65 (3C), 25.5, 18.1, −5.1, −5.2; HRMS (ESI) calcd for $C_{15}H_{28}O_4SiNa$ [(M + Na)$^+$] 323.1649, found 323.1655.

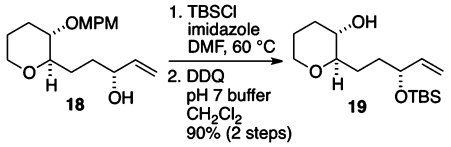


Epoxy Alcohol 17. To a mixture of allylic alcohol **12** (2.50 g, 8.17 mmol), freshly activated 4 Å molecular sieves (2.50 g), and (−)-diethyl tartrate (0.42 mL, 2.5 mmol) in CH_2Cl_2 (70 mL) at −20 °C was added Ti(O*i*-Pr)$_4$ (0.48 mL, 1.6 mmol), and the resultant mixture was stirred at −20 °C for 30 min. To this mixture was added *t*-BuOOH (4.4 M solution in isooctane, 3.7 mL, 16 mmol), and the resultant mixture was stirred at −20 °C for 8 h. The reaction mixture was treated with wet Na_2SO_4, stirred at room temperature for 0.5 h, and then filtered through a pad of Celite. The filtrate was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was taken up in Et_2O (70 mL) and treated with 1 M aqueous NaOH solution (50 mL) at 0 °C. The resultant biphasic mixture was stirred vigorously at 0 °C for 1 h. The resultant mixture was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 30−50% EtOAc/hexanes) gave epoxy alcohol **17** (2.51 g, 95%, dr >20:1) as a colorless oil: $[\alpha]_D^{26}$ +9.1 (*c* 1.00, $CHCl_3$); IR (film) 3421, 2936, 2855, 1513, 1248, 1097, 1034 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.24−7.21 (m, 2H), 6.87−6.84 (m, 2H), 4.54 (d, *J* = 11.0 Hz, 1H), 4.36 (d, *J* = 11.0 Hz, 1H), 3.85 (m, 1H), 3.80 (m, 1H), 3.78 (s, 3H), 3.60 (m, 1H), 3.28 (ddd, *J* = 11.5, 11.5, 2.3 Hz, 1H), 3.12 (ddd, *J* = 8.8, 8.8, 2.8 Hz, 1H), 3.05 (ddd, *J* = 10.5, 8.7, 4.2 Hz, 1H), 2.92 (ddd, *J* = 6.0, 6.0, 2.3 Hz, 1H), 2.88 (ddd, *J* = 4.1, 2.8, 1.9 Hz, 1H), 2.24 (m, 1H), 1.99 (m, 1H), 1.89 (br s, 1H), 1.74 (m, 1H), 1.66 (m, 1H), 1.63−1.47 (m, 3H), 1.35 (dddd, *J* = 12.8, 12.8, 10.6, 4.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 130.4, 129.4 (2C), 113.8 (2C), 80.2, 76.9, 70.4, 67.7, 61.9, 58.4, 56.0, 55.3, 29.2, 28.2, 27.4, 25.4; HRMS (ESI) calcd for $C_{18}H_{26}O_5Na$ [(M + Na)$^+$] 345.1672, found 345.1677.



Allylic Alcohol 18. To a solution of epoxy alcohol **17** (2.51 g, 7.80 mmol) in THF (60 mL) were added imidazole (1.06 g, 15.6 mmol), PPh_3 (3.47 g, 13.3 mmol), and I_2 (2.97 g, 11.7 mmol), and the resultant solution was stirred at room temperature for 15 min. The reaction mixture was diluted with saturated aqueous Na_2SO_3 solution at 0 °C and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant crude iodide was used in the next reaction without further purification.

To a solution of the above iodide in EtOH (70 mL) were added zinc powder (5.1 g, 78 mmol) and AcOH (0.90 mL, 16 mmol), and the resultant mixture was stirred at room temperature for 30 min. The reaction mixture was passed through a pad of Celite. The filtrate was diluted with saturated aqueous $NaHCO_3$ solution at 0 °C and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5−30% EtOAc/hexanes) gave secondary allylic alcohol **18** (2.20 g, 92% for the two steps) as a colorless oil: $[\alpha]_D^{24}$ +8.3 (*c* 1.00, $CHCl_3$); IR (film) 2931, 2857, 1472, 1255, 1129, 1089 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.24−7.21 (m, 2H), 6.87−6.84 (m, 2H), 5.84 (ddd, *J* = 17.0, 10.5, 5.5 Hz, 1H), 5.21 (ddd, *J* = 17.0, 1.8, 1.4 Hz, 1H), 5.05 (ddd, *J* = 10.5, 1.4, 1.4 Hz, 1H), 4.54 (d, *J* = 11.0 Hz, 1H), 4.37 (d, *J* = 11.0 Hz, 1H), 4.06 (m, 1H), 3.88 (m, 1H), 3.78 (s, 3H), 3.30 (ddd, *J* = 11.5, 11.5, 2.8 Hz, 1H), 3.14 (ddd, *J* = 8.7, 8.7, 2.8 Hz, 1H), 3.08 (ddd, *J* = 10.5, 9.2, 4.1 Hz, 1H), 2.24 (m, 1H), 2.07 (dddd, *J* = 14.2, 7.3, 7.3, 2.3 Hz, 1H), 1.72−1.53 (m, 5H), 1.46 (m, 1H), 1.36 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 141.3, 130.4, 129.4 (2C), 113.9, 113.8 (2C), 81.3, 76.6, 73.0, 70.5, 67.8, 55.3, 33.8, 29.2, 28.5, 25.3; HRMS (ESI) calcd for $C_{18}H_{26}O_4Na$ [(M + Na)$^+$] 329.1723, found 329.1730.



Alcohol 19. To a solution of allylic alcohol **18** (2.20 g, 7.19 mmol) in DMF (60 mL) were added imidazole (1.47 g, 21.6 mmol) and TBSCl (2.16 g, 14.4 mmol), and the resultant solution was stirred at 60 °C for 4.5 h. The reaction mixture was cooled to room temperature. The resultant solution was diluted with *t*-BuOMe and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant crude silyl ether (3.31 g) was used in the next reaction without further purification.

To a solution of the above silyl ether in CH_2Cl_2/pH 7 buffer (4:1, v/v, 60 mL) was added DDQ (1.96 g, 8.63 mmol) at 0 °C, and the resultant mixture was stirred at room temperature for 45 min. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution at 0 °C and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5−15% EtOAc/hexanes) gave alcohol **19** (1.95 g, 90% for the two steps) as a colorless oil: $[\alpha]_D^{24}$ +10.3 (*c* 0.65, $CHCl_3$); IR (film) 2929, 2856, 1541, 1507, 1094 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.78 (ddd, *J* = 17.0, 10.5, 5.9 Hz, 1H), 5.13 (ddd, *J* = 17.0, 1.8, 1.4 Hz, 1H), 5.05 (ddd, *J* = 10.5, 1.8, 1.4 Hz, 1H), 4.12 (m, 1H), 3.86 (m, 1H), 3.31−3.26 (m, 2H), 2.98 (ddd, *J* = 8.7, 8.7, 2.8 Hz, 1H), 2.06 (m, 1H),

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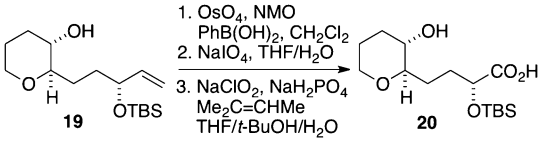
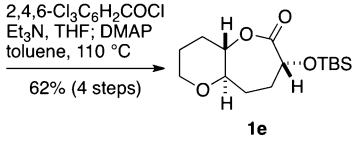
1.82 (m, 1H), 1.73 (m, 1H), 1.67−1.62 (m, 2H), 1.54−1.34 (m, 4H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.6, 113.8, 82.4, 73.7, 70.4, 67.5, 33.5, 32.8, 27.2, 25.9 (3C), 25.6, 18.2, −4.4, −4.8; HRMS (ESI) calcd for $C_{16}H_{32}O_3SiNa$ $[(M + Na)^+]$ 323.2013, found 323.2011.





Lactone 1e. To a solution of alcohol **19** (225 mg, 0.748 mmol) in CH_2Cl_2 (8 mL) were added $PhB(OH)_2$ (274 mg, 2.24 mmol), NMO (262 mg, 2.24 mmol), and OsO_4 (10 mg/mL solution in *t*-BuOH, 0.95 mL, 0.037 mmol), and the resultant mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with saturated aqueous Na_2SO_3 solution at 0 °C and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant crude boronate (459 mg) was used in the next reaction without further purification.

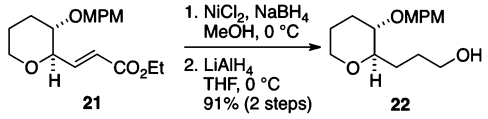
To a solution of the above boronate in THF/H_2O (1:1, v/v, 8 mL) was added $NaIO_4$ (640 mg, 2.99 mmol), and the resultant solution was stirred at room temperature for 30 min. The reaction mixture was diluted with saturated aqueous Na_2SO_3 solution at 0 °C and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant crude aldehyde (505 mg) was used in the next reaction without further purification.

To a solution of the above aldehyde in THF/*t*-BuOH/H_2O (2:2:1, v/v/v, 10 mL) were added 2-methyl-2-butene (0.80 mL, 7.5 mmol), NaH_2PO_4 (180 mg, 1.50 mmol), and $NaClO_2$ (203 mg, 2.24 mmol). The resultant solution was stirred at room temperature for 3 h, acidified with saturated aqueous NH_4Cl solution, and extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, 40−90% EtOAc/hexanes) to give crude seco-acid **20** (257 mg), which was used in the next reaction without further purification.

To a solution of the above seco-acid **20** in THF (8 mL) at 0 °C were added Et_3N (0.31 mL, 2.2 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (0.28 mL, 1.5 mmol), and the resultant solution was stirred at room temperature for 30 min. The mixed anhydride solution thus obtained was diluted with toluene (10 mL) and added dropwise to a solution of DMAP (456 mg, 3.74 mmol) in toluene (50 mL) at 110 °C over a period of 2.5 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 3−15% EtOAc/hexanes) gave lactone **1e** (139 mg, 62% for the four steps) as colorless crystals: mp 47−50 °C; $[\alpha]_D^{24}$ +21.2 (*c* 0.80, $CHCl_3$); IR (film) 2929, 2856, 1768, 1255, 1129, 1089 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.39 (dd, *J* = 10.6, 3.2 Hz, 1H), 3.95 (ddd, *J* = 9.6, 9.6, 5.5 Hz, 1H), 3.85 (dd, *J* = 11.5, 4.1 Hz, 1H), 3.29 (ddd, *J* = 11.5, 11.5, 2.3 Hz, 1H), 3.18 (ddd, *J* = 10.6, 9.2, 4.6 Hz, 1H), 2.21 (m, 1H), 2.16 (dddd, *J* = 13.8, 4.6, 4.6, 3.2 Hz, 1H), 2.00−1.90 (m, 2H), 1.73−1.62 (m, 4H), 0.89 (s, 9H), 0.13 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0, 77.6, 75.9, 72.0, 66.5, 33.4, 31.9, 30.5, 26.0 (3C), 25.1, 18.7, −4.0, −5.1; HRMS (ESI) calcd for $C_{15}H_{28}O_4SiNa$ $[(M + Na)^+]$ 323.1649, found 323.1644.

***α,β*-Unsaturated Ester 21.** To a solution of alcohol **9** (6.55 g, 26.0 mmol) and Et_3N (18.1 mL, 130 mmol) in CH_2Cl_2/DMSO (5:1, v/v, 120 mL) at 0 °C was added SO_3·pyridine complex (14.5 g, 91.2 mmol), and the resultant mixture was stirred at 0 °C for 20 min. The reaction mixture was diluted with Et_2O and washed with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant crude aldehyde (6.78 g) was used in the next reaction without further purification.

To a solution of the above aldehyde was added $Ph_3P{=}CHCO_2Et$ (13.6 g, 39.1 mmol), and the resultant mixture was stirred at room temperature for 43 h. The reaction mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5−10% EtOAc/hexanes) gave *α,β*-unsaturated ester **21** (7.24 g, 87% for the two steps) as pale yellow crystals: mp 58−61 °C; $[\alpha]_D^{24}$ −18.4 (*c* 1.00, $CHCl_3$); IR (film) 2956, 2851, 1751, 1390, 1242, 1090 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24−7.21 (m, 2H), 7.15 (dd, *J* = 16.1, 4.1 Hz, 1H), 6.87−6.83 (m, 2H), 6.07 (dd, *J* = 15.6, 1.8 Hz, 1H), 4.51 (d, *J* = 11.0 Hz, 1H), 4.39 (d, *J* = 11.0 Hz, 1H), 4.19 (q, *J* = 6.9 Hz, 2H), 3.93 (m, 1H), 3.79−3.76 (m, 4H), 3.38 (ddd, *J* = 11.9, 11.9, 2.3 Hz, 1H), 3.11 (ddd, *J* = 11.0, 9.6, 4.1 Hz, 1H), 2.23 (m, 1H), 1.69 (m, 1H), 1.61 (m, 1H), 1.45 (dddd, *J* = 12.4, 12.4, 10.5, 4.1 Hz, 1H), 1.28 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.6, 159.2, 145.7, 130.1, 129.4 (2C), 121.2, 113.8 (2C), 79.2, 77.6, 71.0, 67.5, 60.3, 55.3, 29.8, 25.0, 14.3; HRMS (ESI) calcd for $C_{18}H_{24}O_5Na$ $[(M + Na)^+]$ 343.1516, found 343.1519.



Alcohol 22. To a suspension of $NiCl_2$ (2.18 g, 16.8 mmol) in MeOH (80 mL) at 0 °C were added a solution of *α,β*-unsaturated ester **21** (4.47 g, 16.8 mmol) in MeOH (20 mL) and $NaBH_4$ (1.59 g, 42.1 mmol), and the resultant mixture was stirred at 0 °C for 100 min. The reaction mixture was filtered through a pad of Celite and diluted with saturated aqueous $NaHCO_3$ solution. The solution was concentrated under reduced pressure to remove MeOH, and the resultant solution was diluted with EtOAc. The resultant mixture was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant crude ester (4.81 g) was used in the next reaction without further purification.

To a solution of the above ester in THF (120 mL) at 0 °C was added $LiAlH_4$ (638 mg, 16.8 mmol) portionwise, and the resultant mixture was stirred at 0 °C for 30 min. The reaction was quenched with H_2O. To the resultant mixture were added 3 M aqueous NaOH (10 mL) and H_2O (10 mL), and the resultant suspension was stirred at room temperature for 20 min. The reaction mixture was treated with $MgSO_4$ (20 g) and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 40−70% EtOAc/hexanes) gave alcohol **22** (3.56 g, 91% for the two steps) as a colorless oil: $[\alpha]_D^{24}$ −9.6 (*c* 1.50, $CHCl_3$); IR (film) 3422, 2949, 2853, 1477, 1412, 1093 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24−7.21 (m, 2H), 6.87−6.84 (m, 2H), 4.54 (d, *J* = 11.0 Hz, 1H), 4.37 (d, *J* = 11.0 Hz, 1H), 3.88 (m, 1H), 3.78 (m, 3H), 3.64−3.55 (m, 2H), 3.33 (ddd, *J* = 11.9, 11.9, 2.7 Hz, 1H), 3.14 (ddd, *J* = 8.3, 8.3, 2.3 Hz, 1H), 3.09 (ddd, *J* = 10.6, 9.2, 4.6 Hz, 1H), 2.24 (m, 1H), 2.21−2.02 (m, 3H), 1.72−1.57 (m, 3H), 1.46 (dddd, *J* = 15.1, 8.3, 6.9, 6.9 Hz, 1H), 1.34 (dddd, *J* = 12.8, 12.8, 10.6, 4.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 130.4, 129.4 (2C), 113.8 (2C), 81.2, 76.6, 70.5, 67.8, 63.1, 55.3, 29.23, 29.16, 29.13, 25.3; HRMS (ESI) calcd for $C_{16}H_{24}O_4Na$ $[(M + Na)^+]$ 303.1567, found 303.1567.

Cyanide 23. To a solution of alcohol **22** (4.42 g, 15.8 mmol) in CH_2Cl_2 (120 mL) were added Et_3N (8.79 mL, 63.1 mmol), DMAP (578 mg, 4.74 mmol), and TsCl (7.54 g, 39.5 mmol), and the resultant solution was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc and washed successively with 1 M aqueous

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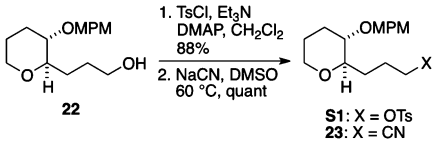
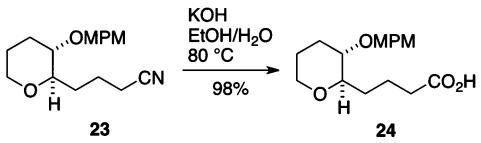


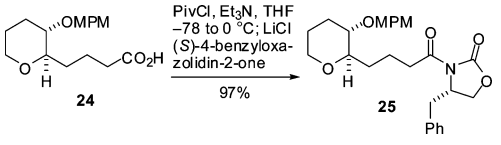
HCl solution, saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 40−70% EtOAc/hexanes) gave tosylate **S1** (6.03 g, 88%) as a colorless oil: $[\alpha]_D^{24}$ +10.0 (*c* 0.90, $CHCl_3$); IR (film) 2961, 2847, 1556, 1387, 1221, 1097 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.77−7.74 (m, 2H), 7.30−7.27 (m, 2H), 7.22−7.19 (m, 2H), 6.87−6.84 (m, 2H), 4.51 (d, *J* = 11.0 Hz, 1H), 4.32 (d, *J* = 11.0 Hz, 1H), 4.01 (ddd, *J* = 6.9, 6.9, 0.9 Hz, 1H), 3.81−3.77 (m, 4H), 3.22 (ddd, *J* = 11.5, 11.5, 2.3 Hz, 1H), 3.02−2.96 (m, 2H), 2.41 (s, 3H), 2.21 (m, 1H), 2.25 (m, 1H), 1.77 (m, 1H), 1.70−1.61 (m, 2H), 1.59−1.50 (m, 2H), 1.37−1.27 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 144.5, 133.2, 130.4, 129.7 (2C), 129.4 (2C), 127.9 (2C), 113.8 (2C), 80.2, 76.7, 70.9, 70.4, 67.6, 55.3, 29.2, 28.0, 25.4, 25.0, 21.6; HRMS (ESI) calcd for $C_{23}H_{30}O_6SNa$ $[(M + Na)^+]$ 457.1655, found 457.1651.

To a solution of tosylate **S1** (6.02 g, 13.9 mmol) in DMSO (100 mL) was added NaCN (3.40 g, 69.4 mmol), and the resultant solution was heated to 60 °C. After being stirred at 60 °C for 2.5 h, the reaction mixture was cooled to room temperature and diluted with Et_2O. The resultant mixture was washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 25% EtOAc/hexanes) gave cyanide **23** (4.20 g, quant) as a colorless oil: $[\alpha]_D^{24}$ +14.1 (*c* 1.20, $CHCl_3$); IR (film) 2948, 2851, 2281, 1387, 1257, 1092 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.24−7.21 (m, 2H), 6.88−6.85 (m, 2H), 4.54 (d, *J* = 11.0 Hz, 1H), 4.35 (d, *J* = 11.0 Hz, 1H), 3.84 (m, 1H), 3.79 (s, 3H), 3.28 (ddd, *J* = 11.5, 11.5, 2.3 Hz, 1H), 3.09 (ddd, *J* = 8.8, 8.8, 2.3 Hz, 1H), 3.04 (ddd, *J* = 10.5, 9.1, 4.6 Hz, 1H), 2.34−2.30 (m, 2H), 2.25 (m, 1H), 1.98 (m, 1H), 1.77 (m, 1H), 1.72−1.64 (m, 2H), 1.59 (m, 1H), 1.46 (dddd, *J* = 13.7, 9.2, 9.2, 2.3 Hz, 1H), 1.34 (dddd, *J* = 12.8, 12.8, 10.5, 4.1 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3, 130.3, 129.5 (2C), 119.9, 113.8 (2C), 80.2, 76.5, 70.3, 67.7, 55.3, 31.1, 29.2, 25.3, 21.7, 17.3; HRMS (ESI) calcd for $C_{17}H_{23}NO_3Na$ $[(M + Na)^+]$ 312.1570, found 312.1563.

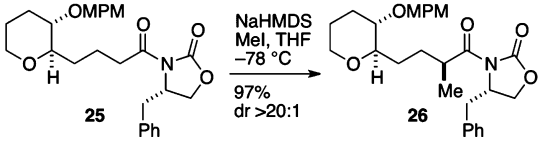


Carboxylic Acid 24. To a solution of cyanide **23** (1.53 g, 5.29 mmol) in EtOH/H_2O (1:1, v/v, 40 mL) was added KOH (2.97 g, 52.9 mmol), and the resultant solution was heated to 80 °C. After being stirred at 80 °C for 18 h, the reaction mixture was cooled to room temperature and acidified with 1 M aqueous HCl solution. The reaction mixture was extracted five times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% MeOH/$CHCl_3$) gave carboxylic acid **24** (1.59 g, 98%) as a colorless oil: $[\alpha]_D^{24}$ +2.6 (*c* 1.30, $CHCl_3$); IR (film) 2937, 2855, 1707, 1514, 1248, 1097 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.23−7.21 (m, 2H), 6.87−6.84 (m, 2H), 4.53 (d, *J* = 11.0 Hz, 1H), 4.36 (d, *J* = 11.0 Hz, 1H), 3.85 (m, 1H), 3.78 (s, 3H), 3.28 (ddd, *J* = 11.5, 11.5, 2.8 Hz, 1H), 3.11 (ddd, *J* = 8.7, 8.7, 2.7 Hz, 1H), 3.06 (ddd, *J* = 10.5, 8.7, 4.6 Hz, 1H), 2.40−2.30 (m, 2H), 2.23 (m, 1H), 1.91 (m, 1H), 1.79 (m, 1H), 1.70−1.55 (m, 4H), 1.45−1.31 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.4, 159.2, 130.5, 129.4 (2C), 113.8 (2C), 80.7, 76.7, 70.4, 67.6, 55.3, 33.9, 31.3, 29.3, 25.4, 20.8; HRMS (ESI) calcd for $C_{17}H_{23}O_5$ $[(M - H)^-]$ 307.1551, found 307.1555.

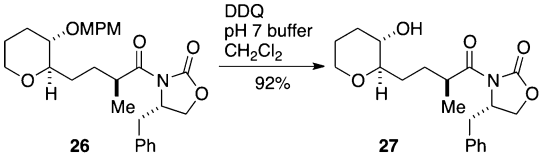
Imide 25. To a solution of carboxylic acid **24** (278 mg, 0.903 mmol) in THF (10 mL) at −78 °C were added Et_3N (0.25 mL, 1.8 mmol) and PivCl (0.13 mL, 1.1 mmol), and the resultant solution was



allowed to warm to 0 °C over a period of 3 h. To the reaction mixture were added (*S*)-4-benzyloxazolidin-2-one (160 mg, 0.903 mmol) and LiCl (115 mg, 2.71 mmol), and the resultant solution was stirred at room temperature for 33 h. The reaction mixture was diluted with EtOAc, and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 25% EtOAc/hexanes) gave imide **25** (410 mg, 97%) as a pale yellow oil: $[\alpha]_D^{24}$ +13.8 (*c* 1.00, $CHCl_3$); IR (film) 2917, 2849, 1780, 1699, 1386, 1249, 1098 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33−7.29 (m, 2H), 7.27−7.22 (m, 3H), 7.19−7.17 (m, 2H), 6.85−6.83 (m, 2H), 4.63 (m, 1H), 4.54 (d, *J* = 11.0 Hz, 1H), 4.37 (d, *J* = 11.0 Hz, 1H), 4.15 (dd, *J* = 9.2, 7.3 Hz, 1H), 4.12 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.86 (m, 1H), 3.76 (s, 3H), 3.71 (m, 1H), 3.30 (ddd, *J* = 11.9, 11.9, 2.8 Hz, 1H), 3.27 (dd, *J* = 12.8, 3.2 Hz, 1H), 3.14 (ddd, *J* = 8.7, 8.7, 2.8 Hz, 1H), 3.07 (ddd, *J* = 10.1, 8.7, 4.1 Hz, 1H), 2.96 (ddd, *J* = 17.0, 8.7, 6.0 Hz, 1H), 2.72 (dd, *J* = 13.3, 9.6 Hz, 1H), 2.23 (m, 1H), 1.95 (m, 1H), 1.86 (m, 1H), 1.75−1.55 (m, 3H), 1.46 (m, 1H), 1.36 (dddd, *J* = 12.4, 12.4, 10.6, 4.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.2, 159.2, 153.5, 135.4, 130.6, 129.41 (2C), 129.38 (2C), 128.9 (2C), 127.3, 113.8 (2C), 80.7, 76.9, 70.5, 67.6, 66.1, 55.24, 55.16, 37.9, 35.4, 31.3, 29.3, 25.5, 20.2; HRMS (ESI) calcd for $C_{27}H_{33}NO_6Na$ $[(M + Na)^+]$ 490.2200, found 490.2197.



Imide 26. To a solution of imide **25** (405 mg, 0.865 mmol) in THF (10 mL) at −78 °C was added NaHMDS (1.0 M solution in THF, 1.1 mL, 1.1 mmol), and the resultant solution was stirred at −78 °C for 1 h. To the reaction mixture was added MeI (0.11 mL, 1.7 mmol), and the resultant solution was stirred at −78 °C for 4 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resultant mixture was diluted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 20−40% EtOAc/hexanes) gave imide **26** (403 mg, 97%, dr >20:1) as a pale yellow oil: $[\alpha]_D^{24}$ +9.8 (*c* 1.00, $CHCl_3$); IR (film) 2930, 2861, 1779, 1698, 1514, 1247, 1098 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.32−7.29 (m, 2H), 7.27−7.21 (m, 3H), 7.19−7.17 (m, 2H), 6.84−6.81 (m, 2H), 4.56 (m, 1H), 4.52 (d, *J* = 11.0 Hz, 1H), 4.35 (d, *J* = 11.0 Hz, 1H), 4.07 (dd, *J* = 8.7, 2.3 Hz, 1H), 4.03 (dd, *J* = 8.7, 8.3 Hz, 1H), 3.83 (m, 1H), 3.74 (s, 3H), 3.71 (m, 1H), 3.27 (ddd, *J* = 11.5, 11.5, 2.8 Hz, 1H), 3.23 (dd, *J* = 13.3, 3.2 Hz, 1H), 3.09−3.03 (m, 2H), 2.72 (dd, *J* = 13.3, 9.7 Hz, 1H), 2.22 (m, 1H), 1.96−1.83 (m, 2H), 1.66−1.57 (m, 2H), 1.47 (m, 1H), 1.41−1.30 (m, 2H), 1.20 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.1, 159.2, 153.1, 135.5, 130.6, 129.43 (2C), 129.41 (2C), 128.9 (2C), 127.3, 113.7 (2C), 80.7, 77.2, 70.5, 67.6, 65.9, 55.4, 55.3, 37.9, 37.4, 29.4, 29.3, 29.1, 25.4, 17.7; HRMS (ESI) calcd for $C_{28}H_{35}NO_6Na$ $[(M + Na)^+]$ 504.2357, found 504.2351.



Alcohol 27. To a solution of imide **26** (403 mg, 0.836 mmol) in CH_2Cl_2/pH 7 buffer (4:1, v/v, 10 mL) was added DDQ (227 mg, 1.00 mmol) at 0 °C, and the resultant mixture was stirred at room

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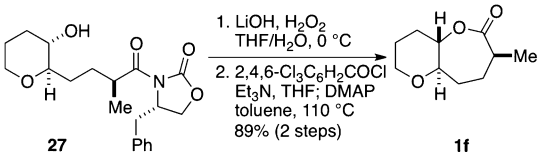
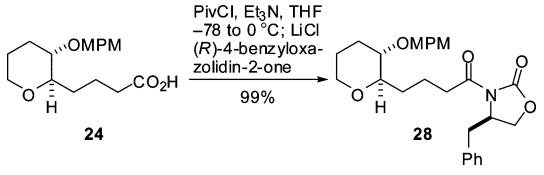
temperature for 90 min. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution at 0 °C and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 30−50% EtOAc/hexanes) gave alcohol **27** (276 mg, 92%) as colorless crystals: mp 61−64 °C; $[\alpha]_D^{24}$ +33.8 (*c* 0.84, $CHCl_3$); IR (film) 3420, 2932, 2855, 1778, 1697, 1387, 1212, 1095 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.32−7.29 (m, 2H), 7.27−7.24 (m, 2H), 7.19 (m, 1H), 4.17 (dddd, *J* = 9.7, 7.8, 3.2, 3.2 Hz, 1H), 4.18 (dd, *J* = 8.7, 7.8 Hz, 1H), 4.14 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.85 (m, 1H), 3.71 (m, 1H), 3.34 (ddd, *J* = 10.6, 8.7, 4.6 Hz, 1H), 3.28 (ddd, *J* = 11.5, 11.5, 3.2 Hz, 1H), 3.24 (dd, *J* = 13.3, 3.2 Hz, 1H), 2.99 (m, 1H), 2.74 (dd, *J* = 13.3, 9.7 Hz, 1H), 2.07 (m, 1H), 1.98 (m, 1H), 1.83 (m, 1H), 1.68−1.60 (m, 4H), 1.52−1.34 (m, 2H), 1.23 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.2, 153.1, 135.3, 129.4 (2C), 128.9 (2C), 127.3, 82.0, 69.8, 67.5, 66.0, 55.3, 37.9, 37.7, 32.8, 29.3, 28.6, 25.6, 17.8; HRMS (ESI) calcd for $C_{20}H_{27}NO_5Na$ [(M + Na)$^+$] 384.1781, found 384.1788.

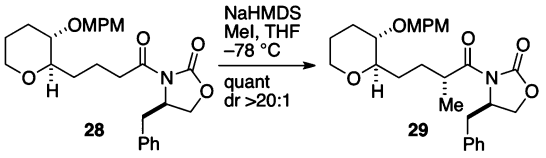


Lactone 1f. To a solution of alcohol **27** (273 mg, 0.756 mmol) in THF/H_2O (3:1, v/v, 8 mL) at 0 °C were added 30% aqueous H_2O_2 solution (0.25 mL, 3.0 mmol) and LiOH·H_2O (64 mg, 1.5 mmol), and the resultant mixture was stirred at 0 °C for 45 min. The reaction mixture was diluted with saturated aqueous Na_2SO_3 solution and extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, 1−20% MeOH/$CHCl_3$) to give crude seco-acid (187 mg), which was used in the next reaction without further purification.

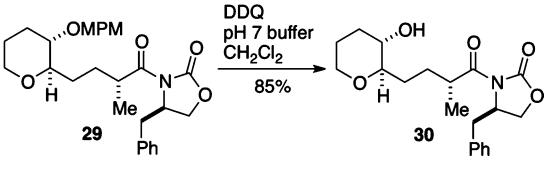
To a solution of the above seco-acid in THF (7 mL) at 0 °C were added Et_3N (0.16 mL, 1.1 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (0.15 mL, 0.98 mmol), and the resultant solution was stirred at room temperature for 30 min. The mixed anhydride solution thus obtained was diluted with toluene (10 mL) and added dropwise to a solution of DMAP (369 mg, 3.02 mmol) in toluene (30 mL) at 110 °C over a period of 1 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 3−15% EtOAc/hexanes) gave lactone **1f** (124 mg, 89% for the two steps) as colorless crystals: mp 89−91 °C; $[\alpha]_D^{24}$ +65.1 (*c* 0.70, $CHCl_3$); IR (film) 2938, 2856, 1778, 1728, 1386, 1262, 1082 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.17 (ddd, *J* = 10.6, 9.2, 5.0 Hz, 1H), 3.88 (dddd, *J* = 11.5, 4.1, 1.9, 1.9 Hz, 1H), 3.32 (ddd, *J* = 11.5, 11.5, 2.8 Hz, 1H), 3.26 (ddd, *J* = 8.7, 8.3, 4.6 Hz, 1H), 3.08 (m, 1H), 2.20 (m, 1H), 1.97 (m, 1H), 1.91−1.80 (m, 2H), 1.73−1.56 (m, 4H), 1.36 (d, *J* = 7.7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.3, 78.8, 75.8, 67.3, 41.0, 30.5, 29.4, 25.4, 25.1, 15.2; HRMS (ESI) calcd for $C_{10}H_{16}O_3Na$ [(M + Na)$^+$] 207.0992, found 207.0996.



Imide 28. To a solution of carboxylic acid **24** (920 mg, 2.99 mmol) in THF (30 mL) at −78 °C were added Et_3N (0.83 mL, 6.0 mmol) and PivCl (0.44 mL, 3.6 mmol), and the resultant solution was allowed to warm to 0 °C over a period of 3 h. To the reaction mixture were added (*R*)-4-benzyloxazolidin-2-one (582 mg, 3.29 mmol) and LiCl (380 mg, 8.97 mmol), and the resultant solution was stirred at room temperature for 12 h. The reaction mixture was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 25% EtOAc/hexanes) gave imide **28** (1.39 g, 99%) as a pale yellow oil: $[\alpha]_D^{24}$ +23.6 (*c* 1.00, $CHCl_3$); IR (film) 2935, 2854, 1780, 1698, 1514, 1249, 1098 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33−7.29 (m, 2H), 7.27−7.22 (m, 3H), 7.19−7.17 (m, 2H), 6.85−6.82 (m, 2H), 4.63 (m, 1H), 4.54 (d, *J* = 11.0 Hz, 1H), 4.37 (d, *J* = 11.0 Hz, 1H), 4.17−4.11 (m, 2H), 3.86 (m, 1H), 3.75 (s, 3H), 3.33−3.25 (m, 2H), 3.14 (ddd, *J* = 8.7, 8.7, 2.8 Hz, 1H), 3.07 (ddd, *J* = 10.1, 8.7, 4.1 Hz, 1H), 2.99−2.87 (m, 2H), 2.72 (dd, *J* = 13.3, 9.7 Hz, 1H), 2.23 (m, 1H), 1.95 (m, 1H), 1.88 (m, 1H), 1.74−1.56 (m, 3H), 1.47 (m, 1H), 1.36 (dddd, *J* = 12.4, 12.4, 10.6, 4.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.2, 159.1, 153.4, 135.4, 130.6, 129.4 (2C), 129.3 (2C), 128.9 (2C), 127.3, 113.8 (2C), 80.7, 76.9, 70.5, 67.6, 66.1, 55.2, 55.1, 37.9, 35.5, 31.3, 29.3, 25.5, 20.2; HRMS (ESI) calcd for $C_{27}H_{33}NO_6Na$ [(M + Na)$^+$] 490.2200, found 490.2195.



Imide 29. To a solution of imide **28** (1.39 g, 2.97 mmol) in THF (30 mL) at −78 °C was added NaHMDS (1.0 M solution in THF, 3.9 mL, 3.9 mmol), and the resultant solution was stirred at −78 °C for 30 min. To the reaction mixture was added MeI (0.37 mL, 5.9 mmol), and the resultant solution was stirred at −78 °C for 7 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was diluted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 25% EtOAc/hexanes) gave imide **29** (1.53 g, quant, dr >20:1) as a pale yellow oil: $[\alpha]_D^{24}$ +19.1 (*c* 1.00, $CHCl_3$); IR (film) 2934, 2857, 1780, 1698, 1389, 1213, 1094 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.32−7.29 (m, 2H), 7.27−7.22 (m, 3H), 7.19−7.17 (m, 2H), 6.85−6.82 (m, 2H), 4.64 (m, 1H), 4.54 (d, *J* = 11.0 Hz, 1H), 4.38 (d, *J* = 11.0 Hz, 1H), 4.16 (dd, *J* = 8.7, 8.7 Hz, 1H), 4.12 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.86 (m, 1H), 3.75 (s, 3H), 3.33−3.25 (m, 2H), 3.14 (ddd, *J* = 8.7, 8.7, 2.8 Hz, 1H), 3.07 (ddd, *J* = 10.5, 9.1, 4.1 Hz, 1H), 2.98−2.88 (m, 2H), 2.72 (dd, *J* = 13.3, 9.7 Hz, 1H), 2.23 (m, 1H), 1.95 (m, 1H), 1.88 (m, 1H), 1.74−1.56 (m, 5H), 1.47 (m, 1H), 1.36 (dddd, *J* = 12.8, 12.8, 10.6, 4.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.2, 159.1, 153.4, 135.4, 130.6, 129.4 (2C), 129.3 (2C), 128.9 (2C), 127.3, 113.8 (2C), 80.7, 76.9, 70.5, 67.7, 66.1, 55.2, 55.1, 37.9, 35.5, 31.3, 29.33, 29.31, 25.5, 20.2; HRMS (ESI) calcd for $C_{28}H_{35}NO_6Na$ [(M + Na)$^+$] 504.2357, found 504.2357.



Alcohol 30. To a solution of imide **29** (1.53 g, 2.97 mmol) in CH_2Cl_2/pH 7 buffer (4:1, v/v, 25 mL) at 0 °C was added DDQ (809 mg, 3.56 mmol), and the resultant mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 30−50% EtOAc/hexanes) gave alcohol **30** (910 mg, 85%) as a pale yellow oil: $[\alpha]_D^{24}$ +17.9 (*c* 1.00, $CHCl_3$); IR (film) 3419, 2933, 2851, 1487, 1157, 1096 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.32−7.29 (m, 2H), 7.26 (m, 1H), 7.20−7.18 (m, 2H), 4.66 (m, 1H), 4.18 (dd, *J* = 7.8, 7.8 Hz, 1H), 4.14 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.83 (m, 1H), 3.71 (m, 1H), 3.31−3.22 (m, 3H), 2.96 (ddd, *J* = 8.7, 8.7, 2.8 Hz, 1H), 2.74 (dd, *J* = 13.3, 9.6 Hz, 1H), 2.07 (m, 1H), 1.87−1.76 (m, 2H), 1.70−1.62 (m, 3H), 1.55 (br s,

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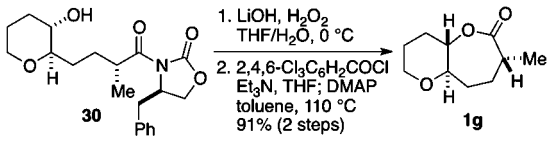
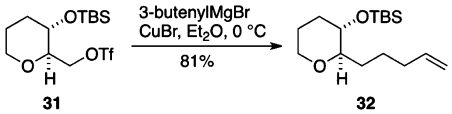
1H), 1.46−1.33 (m, 2H), 1.22 (d, J = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.2, 161.6, 135.3, 129.4 (2C), 128.9 (2C), 127.3, 82.3, 70.6, 67.5, 66.0, 55.3, 37.9, 37.6, 33.0, 29.6, 29.4, 25.6, 17.5; HRMS (ESI) calcd for $C_{20}H_{27}NO_5Na$ [(M + Na)$^+$] 384.1781, found 384.1777.

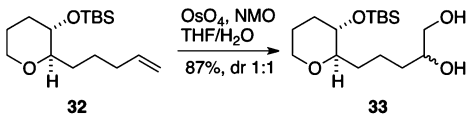


Lactone 1g. To a solution of alcohol **30** (910 mg, 2.52 mmol) in THF/H_2O (3:1, v/v, 32 mL) at 0 °C were added 30% aqueous H_2O_2 solution (1.14 mL, 10.1 mmol) and $LiOH·H_2O$ (212 mg, 5.04 mmol), and the resultant mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with saturated aqueous Na_2SO_3 solution and extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, 5% $MeOH/CHCl_3$) to give crude seco-acid (453 mg), which was used in the next reaction without further purification.

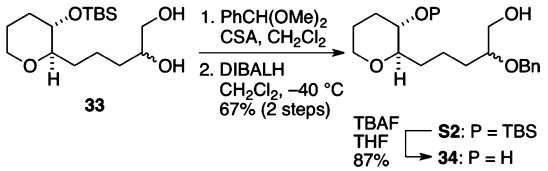
To a solution of the above seco-acid in THF (20 mL) at 0 °C were added Et_3N (0.52 mL, 3.7 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (0.50 mL, 3.2 mmol), and the resultant solution was stirred at room temperature for 30 min. The mixed anhydride solution thus obtained was diluted with toluene (30 mL) and added dropwise to a solution of DMAP (1.21 g, 9.88 mmol) in toluene (70 mL) at 110 °C over a period of 1.5 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 3−15% EtOAc/hexanes) gave lactone **1g** (429 mg, 91% for the two steps) as colorless crystals: mp 92−94 °C; $[\alpha]_D^{24}$ +57.3 (c 0.80, $CHCl_3$); IR (film) 2935, 2861, 1734, 1457, 1179, 1098 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.06 (ddd, J = 10.1, 9.2, 6.0 Hz, 1H), 3.85 (dddd, J = 12.8, 4.1, 1.9, 1.8 Hz, 1H), 3.30 (m, 1H), 3.22 (m, 1H), 2.65 (m, 1H), 2.22−2.13 (m, 2H), 1.72−1.61 (m, 6H), 1.18 (d, J = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.0, 77.7, 76.3, 66.9, 38.0, 35.7, 30.1, 29.3, 24.8, 18.0; HRMS (ESI) calcd for $C_{10}H_{16}O_3Na$ [(M + Na)$^+$] 207.0992, found 207.0997.



Olefin 32. To a mixture of CuBr (2.49 g, 17.4 mmol) and triflate **31** (5.97 g, 15.8 mmol) in Et_2O (110 mL) at 0 °C was added 3-butenylmagnesium bromide (0.60 M solution in THF, 58 mL, 35 mmol), and the resultant mixture was stirred at 0 °C for 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 2% EtOAc/hexanes) gave olefin **32** (3.65 g, 81%) as a colorless oil: $[\alpha]_D^{22}$ +21.2 (c 1.00, $CHCl_3$); IR (film) 2928, 1507, 1413, 1036, 980 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.79 (dddd, J = 16.9, 10.1, 6.9, 6.4 Hz, 1H), 4.98 (dddd, J = 16.9, 1.9, 1.9, 1.9 Hz, 1H), 4.91 (dddd, J = 10.1, 1.9, 1.4, 1.4 Hz, 1H), 3.85 (m, 1H), 3.30−3.21 (m, 2H), 2.96 (ddd, J = 8.7, 8.7, 2.3 Hz, 1H), 2.08−1.99 (m, 2H), 1.96 (m, 1H), 1.81 (m, 1H), 1.65−1.53 (m, 3H), 1.43−1.35 (m, 2H), 1.27 (dddd, J = 14.2, 9.6, 9.6, 5.0 Hz, 1H), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.9, 114.4, 82.6, 71.4, 67.8, 33.9, 33.68, 33.67, 31.7, 25.8 (3C), 24.7, 18.0, −4.0, −4.7; HRMS (ESI) calcd for $C_{16}H_{32}O_2SiNa$ [(M + Na)$^+$] 307.2064, found 307.2059.



1,2-Diol 33. To a solution of olefin **32** (3.65 g, 12.8 mmol) in THF/H_2O (1:1, v/v, 80 mL) were added NMO (4.49 g, 38.4 mmol) and OsO_4 (10 mg/mL solution in t-BuOH, 16 mL, 0.64 mmol), and the resultant mixture was stirred at room temperature for 7 h. The reaction was quenched with saturated aqueous Na_2SO_3 solution at 0 °C. The resultant mixture was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 20−60% EtOAc/hexanes) gave 1,2-diol **33** (3.55 g, 87%, dr 1:1) as a colorless oil. The following data were collected as a 1:1 mixture of diastereomers: $[\alpha]_D^{22}$ +15.2 (c 1.00, $CHCl_3$); IR (film) 3397, 2933, 2857, 1461, 1251, 1099 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.84 (m, 1H), 3.69 (m, 1H), 3.61 (m, 1H), 3.41 (m, 1H), 3.30−3.20 (m, 2H), 2.97 (m, 1H), 2.30−2.23 (m, 2H), 1.96 (m, 1H), 1.81 (m, 1H), 1.66−1.58 (m, 2H), 1.54−1.28 (m, 4H), 0.85 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 82.6 (1/2C), 82.5 (1/2C), 72.2 (1/2C), 72.1 (1/2C), 71.3 (1/2C), 71.2 (1/2C), 67.8, 66.8 (1/2C), 66.7 (1/2C), 33.6, 33.2 (1/2C), 33.1 (1/2C), 31.9 (1/2C), 31.7 (1/2C), 25.8 (3C), 25.7, 21.5 (1/2C), 21.2 (1/2C), 17.9, −4.0, −4.7; HRMS (ESI) calcd for $C_{16}H_{34}O_4SiNa$ [(M + Na)$^+$] 341.2119, found 341.2111.



Diol 34. To a solution of 1,2-diol **33** (3.54 g, 11.1 mmol) in CH_2Cl_2 (70 mL) were added $PhCH(OMe)_2$ (2.51 mL, 16.7 mmol) and CSA (515 mg, 2.22 mmol), and the resultant solution was stirred at room temperature for 8 h. The reaction mixture was neutralized with Et_3N and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, 2−5% EtOAc/hexanes) to give crude benzylidene acetal (4.97 g), which was used in the next reaction without further purification.

To a solution of the above benzylidene acetal in CH_2Cl_2 (70 mL) at −40 °C was added DIBALH (1.0 M solution in n-hexane, 38 mL, 38 mmol), and the resultant solution was stirred at −40 °C for 2 h. The reaction was quenched with MeOH. The mixture was diluted with EtOAc and saturated aqueous potassium sodium tartrate solution, and the resultant biphasic mixture was stirred vigorously at room temperature until the layers became clear. The resultant mixture was diluted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5−30% EtOAc/hexanes) gave alcohol **S2** (3.04 g, 67% for the two steps, dr 1:1) as a colorless oil. The following data were collected as a 1:1 mixture of diastereomers: $[\alpha]_D^{22}$ +7.1 (c 1.00, $CHCl_3$); IR (film) 3411, 2929, 2856, 1541, 1252, 1098 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34−7.32 (m, 4H), 7.27 (m, 1H), 4.62 (d, J = 11.5 Hz, 1/2H), 4.61 (d, J = 11.5 Hz, 1/2H), 4.51 (d, J = 11.5 Hz, 1/2H), 4.50 (d, J = 11.5 Hz, 1/2H), 3.84 (m, 1H), 3.68 (m, 1H), 3.54−3.48 (m, 2H), 3.30−3.21 (m, 2H), 2.96 (m, 1H), 1.97 (m, 1H), 1.83−1.70 (m, 2H), 1.68−1.57 (m, 3H), 1.56−1.44 (m, 2H), 1.43−1.27 (m, 3H), 0.859 (s, 9/2H), 0.857 (s, 9/2H), 0.04 (s, 3H), 0.03 (s, 3/2H), 0.02 (s, 1.5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.5, 128.5 (2C), 127.8 (2C), 127.7, 82.5 (1/2C), 82.4 (1/2C), 80.0 (1/2C), 79.9 (1/2C), 71.54 (1/2C), 71.48 (1/2C), 71.4, 67.8, 64.33 (1/2C), 64.28 (1/2C), 33.7, 32.4 (1/2C), 32.3 (1/2C), 31.0 (1/2C), 30.8 (1/2C), 25.80 (3C), 25.77, 21.4 (1/2C), 21.2 (1/2C), 17.8, −4.0, −4.7; HRMS (ESI) calcd for $C_{23}H_{40}O_4SiNa$ [(M + Na)$^+$] 431.2588, found 431.2591.

To a solution of alcohol **S2** (3.03 g, 7.41 mmol) in THF (60 mL) was added TBAF (1.0 M solution in THF, 15 mL, 15 mmol), and the resultant solution was stirred at room temperature for 10 h. The reaction mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 30−80% EtOAc/hexanes) gave diol **34** (1.89 g, 87%, dr 1:1) as a pale yellow oil. The following data were collected as a 1:1 mixture of

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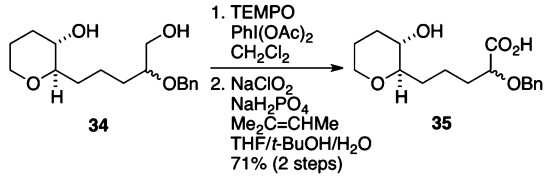
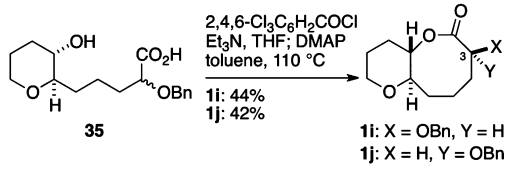
diastereomers: $[\alpha]_D^{22}$ +10.2 (*c* 1.00, $CHCl_3$); IR (film) 3397, 2937, 2860, 1455, 1348, 1095 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33–7.31 (m, 4H), 7.26 (m, 1H), 4.589 (d, *J* = 11.5 Hz, 1/2H), 4.586 (d, *J* = 11.5 Hz, 1/2H), 4.51 (d, *J* = 11.5 Hz, 1/2H), 4.50 (d, *J* = 11.5 Hz, 1/2H), 3.85 (m, 1H), 3.66 (m, 1H), 3.53–3.47 (m, 2H), 3.29–3.20 (m, 2H), 2.94 (m, 1H), 2.46–2.20 (br m, 2H), 2.02 (m, 1H), 1.80 (m, 1H), 1.66–1.46 (m, 5H), 1.44–1.29 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.4, 128.4 (2C), 127.8 (2C), 127.7, 82.1, 79.8 (1/2C), 79.7 (1/2C), 71.44 (1/2C), 71.36 (1/2C), 70.22 (1/2C), 70.16 (1/2C), 67.5, 64.1 (1/2C), 64.0 (1/2C), 32.9, 32.0, 30.8 (1/2C), 30.6 (1/2C), 25.6, 21.1 (1/2C), 21.0 (1/2C); HRMS (ESI) calcd for $C_{17}H_{26}O_4Na$ [(M + Na)$^+$] 317.1723, found 317.1723.

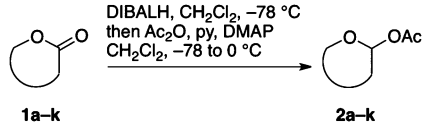


Seco-acid 35. To a solution of diol **34** (1.88 g, 6.39 mmol) in CH_2Cl_2 (60 mL) were added $PhI(OAc)_2$ (2.47 g, 7.67 mmol) and TEMPO (200 mg, 1.28 mmol), and the resultant solution was stirred at room temperature for 4 h. The reaction mixture was cooled to 0 °C, diluted with saturated aqueous Na_2SO_3 solution, and extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant crude aldehyde (3.15 g) was used in the next reaction without purification.

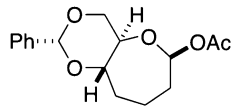
To a solution of the above aldehyde in THF/*t*-BuOH/H_2O (2:2:1, v/v/v, 60 mL) were added 2-methyl-2-butene (6.77 mL, 63.9 mmol), NaH_2PO_4 (1.36 g, 9.59 mmol), and $NaClO_2$ (1.73 g, 19.2 mmol). The resultant solution was stirred at room temperature overnight, acidified with saturated aqueous NH_4Cl solution, and extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 60–90% EtOAc/hexanes) gave seco-acid **35** (1.40 g, 71% for the two steps) as a pale yellow oil. The following data were collected as a 1:1 mixture of diastereomers: $[\alpha]_D^{22}$ +14.1 (*c* 1.00, $CHCl_3$); IR (film) 3328, 2851, 2831, 1699, 1335, 1247, 1063, 1021 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34–7.27 (m, 5H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.02 (br s, 1H), 3.99 (m, 1H), 3.86 (m, 1H), 3.30–3.24 (m, 2H), 2.96 (m, 1H), 2.06 (m, 1H), 1.88–1.76 (m, 3H), 1.70–1.61 (m, 3H), 1.52–1.32 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.81 (1/2C), 175.80 (1/2C), 137.02 (1/2C), 137.01 (1/2C), 128.5 (2C), 128.11, 128.08 (2C), 82.0 (1/2C), 81.9 (1/2C), 77.5, 72.5, 70.3 (1/2C), 70.2 (1/2C), 67.5 (1/2C), 67.4 (1/2C), 32.80 (1/2C), 32.78 (1/2C), 32.39 (1/2C), 32.38 (1/2C), 31.4, 25.6 (1/2C), 25.5 (1/2C), 20.75 (1/2C), 20.74 (1/2C); HRMS (ESI) calcd for $C_{17}H_{23}O_5$ [(M − H)$^-$] 307.1551, found 307.1557.



Lactones 1i and 1j. To a solution of seco-acid **35** (1.39 g, 4.51 mmol) in THF (30 mL) at 0 °C were added Et_3N (0.94 mL, 6.8 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (1.2 mL, 6.3 mmol), and the resultant solution was stirred at room temperature for 30 min. The mixed anhydride solution thus obtained was diluted with toluene (30 mL) and added dropwise to a solution of DMAP (2.20 g, 18.0 mmol) in toluene (120 mL) at 110 °C over a period of 1.5 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10–15% EtOAc/hexanes) gave lactone **1i** (575 mg, 44%) as colorless crystals and lactone **1j** (546 mg, 42%) as colorless crystals. Data for **1i**: mp 54–57 °C; $[\alpha]_D^{24}$ +77.6 (*c* 1.00, $CHCl_3$); IR (film) 2888, 2831, 1721, 1343, 1227, 1080, 760 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34–7.31 (m, 4H), 7.27 (m, 1H), 4.82 (m, 1H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.38 (d, *J* = 11.5 Hz, 1H), 3.98 (dd, *J* = 10.1, 6.0 Hz, 1H), 3.87 (dddd, *J* = 11.5, 4.1, 1.9, 1.4 Hz, 1H), 3.34 (ddd, *J* = 11.5, 11.5, 3.7 Hz, 1H), 3.04 (ddd, *J* = 9.2, 9.2, 1.9 Hz, 1H), 2.20–2.12 (m, 2H), 2.02 (m, 1H), 1.90 (dd, *J* = 13.3, 12.4 Hz, 1H), 1.77–1.69 (m, 3H), 1.63 (dddd, *J* = 11.5, 11.5, 11.5, 5.0 Hz, 1H), 1.47–1.36 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.2, 137.2, 128.4 (2C), 127.92 (2C), 127.89, 83.9, 78.9, 78.2, 71.7, 68.1, 36.7, 33.4, 29.8, 25.7, 21.3; HRMS (ESI) calcd for $C_{17}H_{22}O_4Na$ [(M + Na)$^+$] 313.1410, found 313.1412. Data for **1j**: mp 51–54 °C; $[\alpha]_D^{24}$ +69.2 (*c* 1.00, $CHCl_3$); IR (film) 2881, 2821, 1720, 1303, 1210, 1121, 779 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35–7.32 (m, 4H), 7.29 (m, 1H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.38 (d, *J* = 11.5 Hz, 1H), 4.36 (m, 1H), 4.21 (dd, *J* = 6.4, 5.5 Hz, 1H), 3.86 (m, 1H), 3.34 (ddd, *J* = 11.5, 11.5, 3.2 Hz, 1H), 3.20 (ddd, *J* = 8.7, 8.7, 2.8 Hz, 1H), 2.12 (m, 1H), 1.99–1.90 (m, 2H), 1.86 (ddd, *J* = 14.2, 11.0, 2.8 Hz, 1H), 1.82–1.63 (m, 5H), 1.49 (ddd, *J* = 15.1, 8.3, 8.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.8, 137.2, 128.5 (2C), 128.1 (2C), 128.0, 82.3, 77.2, 75.1, 71.8, 67.9, 35.8, 32.4, 30.2, 25.7, 18.5; HRMS (ESI) calcd for $C_{17}H_{22}O_4Na$ [(M + Na)$^+$] 313.1410, found 313.1417.



General Procedure for Preparation of α-Acetoxy Ethers 2a–k.

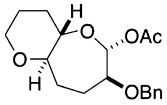


2a

To a solution of lactone **1a** (2.04 g, 8.22 mmol) in CH_2Cl_2 (60 mL) at −78 °C was added DIBALH (1.0 M solution in *n*-hexane, 9.7 mL, 9.7 mmol), and the resultant solution was stirred at −78 °C for 30 min. To the reaction mixture were added pyridine (3.3 mL, 41 mmol), Ac_2O (3.9 mL, 41 mmol), and DMAP (1.0 g, 8.2 mmol), and the resultant solution was stirred at −78 °C for 4 h. The mixture was allowed to warm to 0 °C over a period of 1 h, and the reaction was quenched with saturated aqueous NH_4Cl solution. The mixture was diluted with EtOAc and saturated aqueous potassium sodium tartrate solution, and the resultant biphasic mixture was stirred vigorously at room temperature until the layers became clear. The resultant mixture was diluted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 30% EtOAc/hexanes) gave α-acetoxy ether **2a** (2.00 g, 83%, dr 5:1) as a pale yellow oil. The following data were collected as a 5:1 mixture of diastereomers: $[\alpha]_D^{22}$ +15.7 (*c* 1.00, $CHCl_3$); IR (film) 2939, 2864, 1751, 1373, 1220, 1080 cm^{-1}; H NMR (600 MHz, $CDCl_3$) δ 7.47–7.45 (m, 2H), 7.36–7.30 (m, 3H), 6.00 (dd, *J* = 4.1, 4.1 Hz, 1H), 5.43 (s, 1H), 4.28 (dd, *J* = 10.1, 4.6 Hz, 5/6H), 4.15 (dd, *J* = 11.0, 6.0 Hz, 1/6H), 3.94 (ddd, *J* = 9.6, 9.6, 5.9 Hz, 1/6H), 3.66 (ddd, *J* = 10.1, 8.7, 4.6 Hz, 5/6H), 3.61 (dd, *J* = 10.1, 10.1 Hz, 1H), 3.58 (m, 1H), 2.24 (m, 1/6H), 2.16 (m, 5/6H), 2.08 (s, 5/2H), 2.05 (s, 1/2H), 2.00–1.91 (m, 2H), 1.78–1.72 (m, 2H), 1.59 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9 (1/6C), 169.3 (5/6C), 137.5, 128.9, 129.1, 128.3 (2C), 126.1 (2C), 100.9 (5/6C), 100.7 (1/6C), 81.6 (5/6C), 81.2 (1/6C), 70.5 (5/6C), 69.4 (1/6C), 69.3 (5/6C), 65.8 (1/6C), 35.6 (1/6C), 33.8 (5/6C), 33.1 (5/6C), 32.7 (1/6C), 21.3 (1/6C), 21.2 (5/6C), 18.2 (1/6C), 17.2 (5/6C); HRMS (ESI) calcd for $C_{16}H_{20}O_5Na$ [(M + Na)$^+$] 315.1203, found 315.1209.

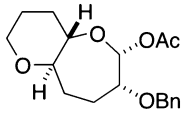
2b (isolated and characterized as a 14:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{22}$ +22.6 (*c* 1.00, $CHCl_3$); IR (film) 2935, 2858, 1746, 1363, 1231, 1091 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 7.33–7.24 (m, 5H), 5.64 (d, *J* = 6.4 Hz, 1H), 4.58

dx.doi.org/10.1021/jo4025545 | J. Org. Chem. 2014, 79, 1656–1682



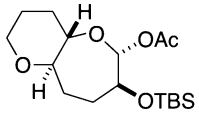
2b

(d, J = 11.9 Hz, 1H), 4.47 (d, J = 11.9 Hz, 1H), 3.86 (dddd, J = 11.5, 4.6, 1.9, 1.4 Hz, 1H), 3.73 (ddd, J = 6.8, 4.6, 2.7 Hz, 1H), 3.40 (ddd, J = 11.0, 9.2, 4.1 Hz, 1H), 3.30 (ddd, J = 11.5, 11.5, 3.2 Hz, 1H), 2.93 (ddd, J = 10.1, 10.1, 3.7 Hz, 1H), 2.07 (m, 1H), 2.05 (s, 3H), 2.02 (m, 1H), 1.82−1.74 (m, 3H), 1.73−1.62 (m, 2H), 1.42 (dddd, J = 11.5, 11.5, 11.5, 5.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 169.8, 138.2, 128.3 (2C), 127.6, 127.5 (2C), 100.5, 83.1, 80.8, 79.4, 71.5, 67.9, 30.6, 27.4, 26.1, 25.6, 21.2; HRMS (ESI) calcd for $C_{18}H_{24}O_5Na$ [(M + Na)$^+$] 343.1516, found 343.1519.



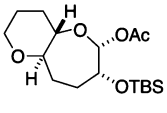
2c

2c (dr >20:1): colorless oil; $[\alpha]_D^{22}$ +31.3 (c 1.00, $CHCl_3$); IR (film) 2941, 2867, 1748, 1230, 1089, 1035 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34−7.29 (m, 4H), 7.26 (m, 1H), 5.75 (d, J = 2.3 Hz, 1H), 4.68 (d, J = 12.4 Hz, 1H), 4.61 (d, J = 12.4 Hz, 1H), 3.84 (m, 1H), 3.68 (ddd, J = 7.7, 6.4, 2.3 Hz, 1H), 3.32−3.27 (m, 2H), 3.07 (ddd, J = 9.7, 9.7, 3.7 Hz, 1H), 2.12 (s, 3H), 2.11−2.06 (m, 2H), 1.95 (m, 1H), 1.74 (dddd, J = 14.7, 12.4, 7.8, 2.3 Hz, 1H), 1.67−1.62 (m, 2H), 1.52−1.45 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 138.4, 128.3 (2C), 127.8 (2C), 127.6, 97.3, 82.6, 79.8, 79.2, 72.5, 67.8, 30.6, 29.4, 26.9, 25.6, 21.2; HRMS (ESI) calcd for $C_{18}H_{24}O_5Na$ [(M + Na)$^+$] 343.1516, found 343.1525.



2d

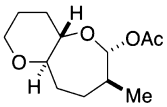
2d (isolated and characterized as a 15:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{22}$ +13.9 (c 1.00, $CHCl_3$); IR (film) 2947, 2853, 1751, 1367, 1101, 1096 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 5.64 (d, J = 6.4 Hz, 1H), 3.86 (dddd, J = 11.5, 4.6, 1.9, 1.4 Hz, 1H), 3.73 (ddd, J = 6.8, 4.6, 2.7 Hz, 1H), 3.40 (ddd, J = 11.0, 9.2, 4.1 Hz, 1H), 3.30 (ddd, J = 11.5, 11.5, 3.2 Hz, 1H), 2.93 (ddd, J = 10.1, 10.1, 3.7 Hz, 1H), 2.07 (m, 1H), 2.05 (s, 3H), 2.02 (m, 1H), 1.82−1.74 (m, 3H), 1.73−1.62 (m, 2H), 1.42 (dddd, J = 11.5, 11.5, 11.5, 5.0 Hz, 1H), 0.86 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 169.8, 100.5, 80.8, 79.4, 71.5, 67.9, 30.6, 27.4, 26.1, 25.6, 25.2 (3C), 21.2, 17.9, −4.1, −4.7; HRMS (ESI) calcd for $C_{17}H_{32}O_5SiNa$ [(M + Na)$^+$] 367.1911, found 367.1909.



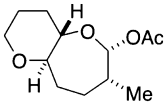
2e

2e (dr >20:1): colorless oil; $[\alpha]_D^{22}$ +19.0 (c 0.60, $CHCl_3$); IR (film) 2950, 2856, 1750, 1449, 1170, 1095 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.74 (d, J = 2.5 Hz, 1H), 3.85 (m, 1H), 3.67 (ddd, J = 7.8, 6.6, 2.5 Hz, 1H), 3.34−3.28 (m, 2H), 3.07 (ddd, J = 9.5, 9.5, 3.6 Hz, 1H), 2.12 (s, 3H), 2.10−2.05 (m, 2H), 1.94 (m, 1H), 1.74 (dddd, J = 14.6, 12.2, 7.2, 2.5 Hz, 1H), 1.68−1.61 (m, 2H), 1.53−1.45 (m, 2H), 0.84 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 97.3, 82.6, 79.8, 72.5, 67.8, 30.6, 29.4, 26.9, 25.6, 25.3 (3C), 21.2, 17.9, −4.1, −4.7; HRMS (ESI) calcd for $C_{17}H_{32}O_5SiNa$ [(M + Na)$^+$] 367.1911, found 367.1907.

2f (dr >20:1): colorless oil; $[\alpha]_D^{22}$ +34.7 (c 0.50, $CHCl_3$); IR (film) 2937, 2869, 1748, 1230, 1091, 1021 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.30 (d, J = 9.2 Hz, 1H), 3.85 (m, 1H), 3.33−3.26 (m, 2H), 2.94 (ddd, J = 9.6, 9.6, 3.7 Hz, 1H), 2.09−2.03 (m, 5H), 1.85−1.77 (m, 2H), 1.72−1.58 (m, 3H), 1.51 (m, 1H), 1.43 (m, 1H), 0.92 (d, J = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 103.0, 83.7, 80.6, 68.0, 36.1, 30.6, 28.6, 27.9, 25.8, 21.2, 17.6; HRMS (ESI) calcd for $C_{12}H_{20}O_4Na$ [(M + Na)$^+$] 251.1254, found 251.1261.

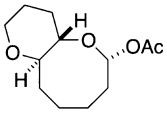


2f



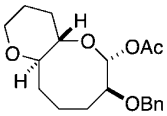
2g

2g (isolated and characterized as a 10:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{22}$ +27.8 (c 0.80, $CHCl_3$); IR (film) 2933, 2860, 1745, 1235, 1147, 1096 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 5.53 (d, J = 8.7 Hz, 1H), 3.81 (m, 1H), 3.60 (ddd, J = 10.6, 9.2, 5.0 Hz, 1H), 3.26 (m, 1H), 3.04 (ddd, J = 10.1, 10.1, 5.5 Hz, 1H), 2.07 (m, 1H), 2.05 (s, 3H), 1.96−1.83 (m, 2H), 1.66−1.49 (m, 3H), 1.47−1.35 (m, 3H), 0.92 (d, J = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 173.5, 102.1, 83.2, 81.2, 67.2, 40.2, 36.9, 35.8, 31.6, 29.8, 25.6, 20.9; HRMS (ESI) calcd for $C_{12}H_{20}O_4Na$ [(M + Na)$^+$] 251.1254, found 251.1255.



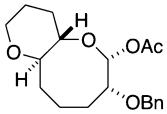
2h

2h (dr >20:1): colorless oil; $[\alpha]_D^{22}$ −14.2 (c 1.00, $CHCl_3$); IR (film) 2939, 2850, 1541, 1438, 1093 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.71 (dd, J = 8.7, 3.2 Hz, 1H), 3.82 (dddd, J = 11.5, 4.6, 1.8, 1.4 Hz, 1H), 3.51 (ddd, J = 11.0, 9.2, 4.6 Hz, 1H), 3.26 (ddd, J = 11.9, 11.9, 2.8 Hz, 1H), 3.00 (ddd, J = 9.6, 9.6, 1.9 Hz, 1H), 2.07−1.99 (m, 3H), 2.04 (s, 3H), 1.93−1.85 (m, 2H), 1.78−1.54 (m, 4H), 1.50−1.34 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 101.6, 84.0, 82.9, 67.8, 36.0, 34.6, 31.1, 27.1, 26.0, 24.2, 21.3; HRMS (ESI) calcd for $C_{12}H_{20}O_4Na$ [(M + Na)$^+$] 251.1254, found 251.1251.



2i

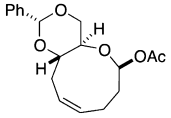
2i (dr >20:1): pale yellow oil; $[\alpha]_D^{22}$ +7.2 (c 1.00, $CHCl_3$); IR (film) 2935, 2854, 1746, 1463, 1331, 1091 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32−7.23 (m, 5H), 5.69 (d, J = 11.5 Hz, 1H), 4.59 (d, J = 11.9 Hz, 1H), 4.54 (d, J = 11.9 Hz, 1H), 3.83 (m, 1H), 3.60−3.53 (m, 2H), 3.24 (ddd, J = 12.4, 12.4, 2.8 Hz, 1H), 3.00 (ddd, J = 10.1, 8.7, 1.4 Hz, 1H), 2.09−1.87 (m, 4H), 2.05 (s, 3H), 1.72−1.58 (m, 4H), 1.51 (m, 1H), 1.36 (dddd, J = 12.8, 12.8, 11.0, 4.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 138.4, 128.3 (2C), 127.54, 127.49 (2C), 101.5, 83.8, 81.5, 79.5, 72.2, 67.8, 35.0, 30.8, 30.1, 25.7, 21.2, 19.9; HRMS (ESI) calcd for $C_{19}H_{26}O_5Na$ [(M + Na)$^+$] 357.1672, found 357.1668.



2j

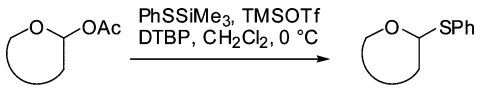
dx.doi.org/10.1021/jo4025545 | J. Org. Chem. 2014, 79, 1656−1682

2j (isolated and characterized as a 2:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{22}$ −10.4 (*c* 1.00, $CHCl_3$); IR (film) 2935, 2858, 1751, 1737, 1463, 1234, 1088 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.37 (m, 1H), 7.34−7.23 (m, 4H), 5.84 (d, *J* = 8.7 Hz, 1/3H), 5.84 (s, 2/3H), 4.69 (d, *J* = 12.8 Hz, 2/3H), 4.61 (d, *J* = 12.8 Hz, 2/3H), 4.60 (d, *J* = 11.5 Hz, 1/3H), 4.56 (d, *J* = 11.5 Hz, 1/3H), 3.84−3.72 (m, 4/3H), 3.55 (ddd, *J* = 10.6, 10.6, 4.6 Hz, 1/3H), 3.49 (ddd, *J* = 10.6, 9.4, 4.6 Hz, 2/3H), 3.47 (m, 2/3H), 3.29 (m, 1/3H), 3.27 (ddd, *J* = 11.5, 11.5, 3.2 Hz, 2/3H), 3.09 (m, 1H), 2.14 (m, 2/3H), 2.09−2.03 (m, 4/3H), 2.05 (s, 2H), 2.04 (s, 1H), 1.92 (m, 1H), 1.82−1.58 (m, 5H), 1.56−1.33 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5 (2/3C), 169.8 (1/3C), 138.5 (2/3C), 138.3 (1/3C), 128.3 (2/3C), 128.2 (4/3C), 128.0 (4/3C), 127.6 (1/3C), 127.54 (2/3C), 127.48 (2/3C), 101.0 (2/3C), 96.5 (1/3C), 85.4 (1/3C), 82.5 (2/3C), 81.1 (1/3C), 80.4 (2/3C), 76.6 (1/3C), 75.6 (2/3C), 72.6 (1/3C), 71.4 (2/3C), 67.8 (1/3C), 67.7 (2/3C), 36.5 (1/3C), 36.4 (2/3C), 32.4 (2/3C), 32.3 (1/3C), 31.2 (1/3C), 30.9 (2/3C), 26.0 (2/3C), 25.9 (1/3C), 21.3, 19.0 (1/3C), 17.2 (2/3C); HRMS (ESI) calcd for $C_{19}H_{26}O_5Na$ $[(M + Na)^+]$ 357.1672, found 357.1668.



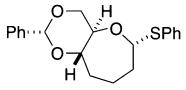
2k

2k (isolated and characterized as a 7:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{22}$ +19.3 (*c* 1.00, $CHCl_3$); IR (film) 2925, 2854, 1738, 1240, 1088, 1031 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 7.46−7.43 (m, 2H), 7.37−7.30 (m, 3H), 6.02 (dd, *J* = 10.6, 5.0 Hz, 1H), 5.83 (ddd, *J* = 9.6, 9.6, 6.4 Hz, 1H), 5.64 (ddd, *J* = 9.6, 9.6, 6.9 Hz, 1H), 5.45 (s, 1H), 4.23 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.93 (ddd, *J* = 9.7, 9.7, 5.0 Hz, 1H), 3.79 (ddd, *J* = 9.7, 3.7, 3.2 Hz, 1H), 3.67 (dd, *J* = 10.1, 10.1 Hz, 1H), 2.84 (m, 1H), 2.30 (m, 1H), 2.03 (s, 3H), 2.09−1.85 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 171.2, 137.6, 131.2, 128.3 (2C), 126.2 (2C), 125.5, 125.1, 100.4, 100.3, 78.9, 68.1, 66.7, 29.9, 28.5, 23.8, 21.0; HRMS (ESI) calcd for $C_{18}H_{22}O_5Na$ $[(M + Na)^+]$ 341.1359, found 341.1357.



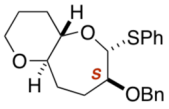
2a–k **3a–k**

General Procedure for Preparation of Thioacetals 3a–k.



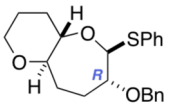
3a

To a solution of α-acetoxy ether **2a** (1.98 g, 6.79 mmol) in CH_2Cl_2 (30 mL) at 0 °C were added Me_3SiSPh (1.9 mL, 10 mmol), di-*tert*-butylpyridine (4.6 mL, 20 mmol), and TMSOTf (2.5 mL, 14 mmol), and the resultant mixture was stirred at 0 °C for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resultant mixture was diluted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 2−10% EtOAc/hexanes) gave thioacetal **3a** (1.97 g, 85%, dr 2.5:1) as colorless crystals. The following data were collected as a 2.5:1 mixture of diastereomers: mp 78−80 °C; $[\alpha]_D^{22}$ +48.2 (*c* 1.00, $CHCl_3$); IR (film) 2933, 2859, 1455, 1122, 1092 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.48−7.43 (m, 4H), 7.36−7.21 (m, 6H), 5.43 (s, 1H), 5.35 (dd, *J* = 11.5, 5.9 Hz, 5/7H), 5.15 (dd, *J* = 6.9, 5.5 Hz, 2/7H), 4.15 (dd, *J* = 10.6, 5.5 Hz, 2/7H), 4.13 (dd, *J* = 11.0, 5.5 Hz, 5/7H), 3.98 (ddd, *J* = 9.7, 9.7, 5.9 Hz, 5/7H), 3.67−3.61 (m, 9/7H), 3.51 (dd, *J* = 10.6, 10.5 Hz, 5/7H), 3.39 (ddd, *J* = 10.1, 10.1, 5.5 Hz, 2/7H), 2.39 (ddd, *J* = 14.6, 7.3, 6.4 Hz, 5/7H), 2.26−2.14 (m, 9/7H), 2.06 (m 2/7H), 1.87 (m, 2/7H), 1.83−1.70 (m, 12/7H), 1.67−1.47 (m, 12/7H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.8 (5/7C), 137.6 (2/7C), 135.1 (5/7C), 134.5 (2/7C), 131.4 (4/7C), 131.1 (10/7C), 128.9 (4/7C), 128.84 (10/7C), 128.82 (4/7C), 128.3 (15/7C), 127.3 (2/7C), 127.0, 126.14 (10/7C), 126.08 (4/7C), 101.0 (2/7C), 100.8 (5/7C), 87.7 (2/7C), 87.1 (5/7C), 82.1 (2/7C), 80.5 (5/7C), 75.1 (2/7C), 69.6 (5/7C), 69.3 (2/7C), 64.7 (5/7C), 35.5 (5/7C), 35.3 (5/7C), 34.8 (2/7C), 33.1 (2/7), 20.5 (5/7C), 20.1 (2/7C); HRMS (ESI) calcd for $C_{20}H_{22}O_3SNa$ $[(M + Na)^+]$ 365.1182, found 365.1188.



3b

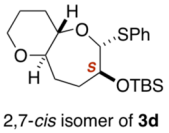
3b (isolated and characterized as a 8:1 mixture of diastereomers): colorless crystals; mp 48−51 °C; $[\alpha]_D^{22}$ +18.6 (*c* 1.00, $CHCl_3$); IR (film) 2938, 2859, 1421, 1354, 1157, 1086 cm^{-1}; ^1H NMR (600 MHz, C_6D_6, major diastereomer) δ 7.84−7.82 (m, 2H), 7.30−7.27 (m, 2H), 7.17−7.14 (m, 2H), 7.09 (m, 1H), 6.89 (m, 1H), 6.85−6.81 (m, 2H), 4.65 (d, *J* = 8.7 Hz, 1H), 4.52 (d, *J* = 10.6 Hz, 1H), 4.26 (d, *J* = 10.6 Hz, 1H), 4.25 (ddd, *J* = 10.6, 8.7, 1.8 Hz, 1H), 4.08 (ddd, *J* = 10.6, 9.2, 5.0 Hz, 1H), 3.60 (dddd, *J* = 11.0, 4.6, 1.8, 1.4 Hz, 1H), 2.90 (ddd, *J* = 12.4, 11.5, 2.3 Hz, 1H), 2.84 (ddd, *J* = 10.5, 9.6, 5.0 Hz, 1H), 2.33 (m, 1H), 1.97 (m, 1H), 1.69 (dddd, *J* = 13.7, 5.9, 2.3, 2.3 Hz, 1H), 1.59 (dddd, *J* = 13.3, 13.3, 10.6, 1.8 Hz, 1H), 1.49−1.39 (m, 2H), 1.23 (m, 1H), 1.14 (m, 1H); ^{13}C NMR (150 MHz, C_6D_6, major diastereomer) δ 140.8, 138.6, 132.9, 128.8 (2C), 128.7 (2C), 128.4 (2C), 128.2 (2C), 127.8, 96.7, 80.2, 78.8, 76.7, 72.0, 67.0, 32.4, 31.0, 27.7, 25.7; HRMS (ESI) calcd for $C_{22}H_{26}O_3SNa$ $[(M + Na)^+]$ 393.1495, found 393.1498.



3c

3c (isolated and characterized as a 8:1 mixture of diastereomers): colorless crystals; mp 46−49 °C; $[\alpha]_D^{22}$ +33.0 (*c* 1.00, $CHCl_3$); IR (film) 2939, 2862, 1456, 1070, 1038 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 7.90−7.87 (m, 2H), 7.56 (m, 1H), 7.47−7.44 (m, 2H), 7.32−7.26 (m, 5H), 4.622 (d, *J* = 11.5 Hz, 1H), 4.620 (d, *J* = 8.3 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.28 (ddd, *J* = 10.6, 8.7, 1.8 Hz, 1H), 3.86 (ddd, *J* = 10.1, 9.1, 5.0 Hz, 1H), 3.81 (m, 1H), 3.24 (ddd, *J* = 11.5, 11.5, 2.8 Hz, 1H), 2.99 (ddd, *J* = 10.6, 9.7, 5.0 Hz, 1H), 2.17 (m, 1H), 2.10 (m, 1H), 2.02 (m, 1H), 1.79 (dddd, *J* = 14.2, 13.3, 11.0, 1.9 Hz, 1H), 1.71−1.59 (m, 2H), 1.44 (dddd, *J* = 13.3, 13.3, 10.6, 2.3 Hz, 1H), 1.30 (dddd, *J* = 12.8, 12.8, 11.0, 5.1 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 139.6, 137.6, 133.6, 129.1 (2C), 128.5 (2C), 128.4 (2C), 128.2 (2C), 127.9, 96.4, 79.8, 78.5, 76.4, 72.2, 67.3, 32.1, 30.6, 27.5, 25.4; HRMS (ESI) calcd for $C_{22}H_{26}O_3SNa$ $[(M + Na)^+]$ 393.1495, found 393.1491.

3d: A 8:1 mixture of 2,7-*cis* and 2,7-*trans* isomers of **3d** was separated by flash column chromatography using silica gel (3% EtOAc/hexanes) and characterized individually.



2,7-*cis* isomer of **3d**

2,7-*cis* isomer of **3d**: colorless oil; $[\alpha]_D^{22}$ +15.6 (*c* 1.00, $CHCl_3$); IR (film) 2944, 2847, 1521, 1467, 1246, 1090 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.52−7.49 (m, 2H), 7.18−7.11 (m, 3H), 4.81 (d, *J* = 3.2 Hz, 1H), 4.02 (ddd, *J* = 8.8, 6.4, 3.7 Hz, 1H), 3.68 (m, 1H), 3.10 (m, 1H), 2.91 (ddd, *J* = 9.7, 9.7, 3.7 Hz, 1H), 2.69 (ddd, *J* = 11.5, 9.2, 4.6 Hz, 1H), 1.96 (m, 1H), 1.88−1.82 (m, 2H), 1.64 (m, 1H), 1.48 (m, 1H), 1.38−1.25 (m, 3H), 0.96 (s, 9H), 0.17 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.8, 132.7 (2C), 128.5 (2C), 127.3, 96.6, 84.2, 83.2, 74.3, 67.7, 31.4, 30.6, 28.1, 26.0 (3C), 25.8, 18.3, −4.4, −5.0;

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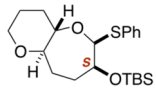
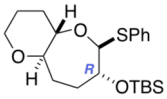
HRMS (ESI) calcd for $C_{21}H_{34}O_3SSiNa$ [(M + Na)$^+$] 417.1890, found 417.1896.



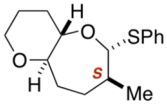
2,7-*trans* isomer of **3d**

2,7-*trans* isomer of **3d**: colorless oil; $[\alpha]_D^{22}$ +19.7 (*c* 1.00, $CHCl_3$); IR (film) 2942, 2845, 1413, 1347, 1245, 1096 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54−7.50 (m, 2H), 7.37 (m, 1H), 7.25−7.17 (m, 2H), 4.91 (d, *J* = 7.6 Hz, 1H), 4.04 (ddd, *J* = 7.6, 3.7, 3.7 Hz, 1H), 3.74 (dddd, *J* = 11.5, 4.6, 1.9, 1.4 Hz, 1H), 3.14 (ddd, *J* = 10.5, 9.1, 4.6 Hz, 1H), 3.04 (ddd, *J* = 12.4, 11.5, 2.3 Hz, 1H), 2.92 (ddd, *J* = 8.7, 8.7, 2.8 Hz, 1H), 2.57 (m, 1H), 2.34−2.23 (m, 2H), 1.83 (m, 1H), 1.61 (m, 1H), 1.49 (ddddd, *J* = 12.8, 12.8, 12.8, 4.6, 4.1 Hz, 1H), 1.26 (m, 1H), 1.16 (dddd, *J* = 12.8, 12.8, 11.0, 4.1 Hz, 1H), 0.96 (s, 9H), 0.17 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 134.9, 132.6 (2C), 128.2 (2C), 127.6, 82.4, 80.9, 72.7, 70.5, 67.4, 32.8, 28.5, 27.7, 25.6, 24.0 (3C), 16.0, −6.4, −7.0; HRMS (ESI) calcd for $C_{21}H_{34}O_3SSiNa$ [(M + Na)$^+$] 417.1890, found 417.1895.



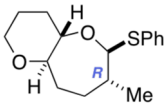
3e

3e (isolated and characterized as a 8:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{22}$ +21.0 (*c* 1.00, $CHCl_3$); IR (film) 2956, 2851, 1415, 1157, 1093 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 7.53−7.51 (m, 2H), 7.29−7.23 (m, 3H), 4.92 (d, *J* = 3.7 Hz, 1H), 4.15 (ddd, *J* = 8.7, 6.4, 3.2 Hz, 1H), 3.80 (m, 1H), 3.28 (ddd, *J* = 11.5, 11.5, 2.3 Hz, 1H), 3.02 (ddd, *J* = 9.6, 9.6, 3.7 Hz, 1H), 2.78 (ddd, *J* = 10.1, 9.2, 3.7 Hz, 1H), 2.19 (m, 1H), 1.95−1.88 (m, 2H), 1.71 (m, 1H), 1.62−1.49 (m, 3H), 1.38 (m, 1H), 0.93 (s, 9H), 0.16 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 135.8, 132.7 (2C), 128.6 (2C), 127.4, 96.8, 84.3, 83.2, 74.4, 67.9, 31.4, 30.6, 28.2, 26.0, 25.9 (3C), 18.4, −4.4, −4.9; HRMS (ESI) calcd for $C_{21}H_{34}O_3SSiNa$ [(M + Na)$^+$] 417.1890, found 417.1891.



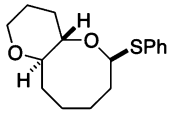
3f

3f (isolated and characterized as a 20:1 mixture of diastereomers): colorless crystals; mp 68−71 °C; $[\alpha]_D^{22}$ +50.2 (*c* 1.00, $CHCl_3$); IR (film) 2926, 2850, 1438, 1096, 1081 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 7.50−7.47 (m, 2H), 7.27−7.24 (m, 2H), 7.18 (m, 1H), 4.85 (d, *J* = 10.1 Hz, 1H), 3.83 (dddd, *J* = 11.5, 4.6, 1.9, 1.4 Hz, 1H), 3.73 (ddd, *J* = 11.0, 9.7, 5.0 Hz, 1H), 3.28 (ddd, *J* = 11.5, 11.5, 2.3 Hz, 1H), 3.11 (ddd, *J* = 10.5, 9.6, 5.5 Hz, 1H), 2.09 (dddd, *J* = 13.3, 5.5, 5.5, 1.9 Hz, 1H), 1.90 (m, 1H), 1.79 (m, 1H), 1.69−1.54 (m, 3H), 1.49 (m, 1H), 1.40−1.28 (m, 2H), 1.14 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 136.5, 130.3 (2C), 128.7 (2C), 126.4, 94.3, 80.3, 70.7, 67.3, 41.5, 35.7, 31.3, 29.4, 25.3, 20.9; HRMS (ESI) calcd for $C_{16}H_{22}O_2SNa$ [(M + Na)$^+$] 301.1233, found 301.1237.



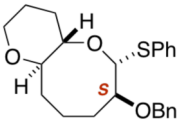
3g

3g (dr >20:1): colorless crystals; mp 73−75 °C; $[\alpha]_D^{22}$ +28.2 (*c* 1.00, $CHCl_3$); IR (film) 2956, 2854, 1471, 1257, 1098 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47−7.45 (m, 2H), 7.26−7.22 (m, 2H), 7.17 (m, 1H), 4.82 (d, *J* = 10.1 Hz, 1H), 3.78 (m, 1H), 3.69 (ddd, *J* = 10.8, 9.6, 5.0 Hz, 1H), 3.24 (ddd, *J* = 11.5, 11.5, 2.4 Hz, 1H), 3.07 (ddd, *J* = 10.5, 10.5, 5.0 Hz, 1H), 2.05 (m, 1H), 1.87 (m, 1H), 1.77 (m, 1H), 1.64−1.54 (m, 3H), 1.46 (m, 1H), 1.37−1.26 (m, 2H), 1.11 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.3, 130.3 (2C), 128.6 (2C), 126.3, 94.2, 80.1, 70.6, 67.0, 41.3, 35.5, 31.1, 29.3, 25.2, 20.6; HRMS (ESI) calcd for $C_{16}H_{22}O_2SNa$ [(M + Na)$^+$] 301.1233, found 301.1231.



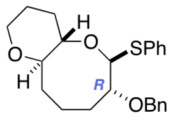
3h

3h (isolated and characterized as a 10:1 mixture of diastereomers): colorless crystals; mp 71−74 °C; $[\alpha]_D^{22}$ −23.3 (*c* 1.00, $CHCl_3$); IR (film) 2948, 2845, 1382, 1227, 1095 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 7.45−7.43 (m, 2H), 7.27−7.24 (m, 2H), 7.16 (m, 1H), 5.32 (dd, *J* = 11.9, 2.3 Hz, 1H), 3.84 (dddd, *J* = 11.5, 5.0, 1.8, 1.4 Hz, 1H), 3.70 (ddd, *J* = 10.5, 10.5, 4.6 Hz, 1H), 3.27 (ddd, *J* = 12.4, 11.5, 2.3 Hz, 1H), 3.05 (ddd, *J* = 10.1, 10.1, 4.1 Hz, 1H), 2.19 (dddd, *J* = 15.1, 11.9, 11.9, 5.0 Hz, 1H), 1.94−1.83 (m, 3H), 1.78−1.62 (m, 5H), 1.55 (m, 1H), 1.46 (m, 1H), 1.32 (dddd, *J* = 12.8, 12.8, 11.0, 4.1 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 136.4, 129.2 (2C), 128.8 (2C), 87.7, 81.5, 71.1, 67.9, 32.2, 31.0, 29.3, 26.8, 25.9, 20.9; HRMS (ESI) calcd for $C_{16}H_{22}O_2SNa$ [(M + Na)$^+$] 301.1233, found 301.1233.



3i

3i (isolated and characterized as a 9:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{22}$ −8.3 (*c* 1.00, $CHCl_3$); IR (film) 2923, 2852, 1652, 1456, 1068 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$ major diastereomer) δ 7.37−7.33 (m, 4H), 7.27−7.21 (m, 6H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.54 (d, *J* = 2.8 Hz, 1H), 4.50 (d, *J* = 11.5 Hz, 1H), 3.84 (m, 1H), 3.69 (m, 1H), 3.26 (m, 1H), 3.21 (ddd, *J* = 10.6, 8.8, 4.6 Hz, 1H), 2.95 (ddd, *J* = 8.7, 8.7, 2.3 Hz, 1H), 1.96−1.88 (m, 2H), 1.78−1.71 (m, 2H), 1.66−1.58 (m, 2H), 1.41 (m, 1H), 1.31−1.23 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 132.53, 132.50, 129.0 (2C), 128.9 (2C), 128.2 (2C), 128.0 (2C), 127.6, 127.5, 82.1, 81.2, 72.7, 71.4, 67.7, 63.7, 33.6, 32.0, 31.5, 25.8, 22.0; HRMS (ESI) calcd for $C_{23}H_{28}O_3NaS$ [(M + Na)$^+$] 407.1651, found 407.1653.



3j

3j (isolated and characterized as a 12:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{22}$ −5.1 (*c* 1.00, $CHCl_3$); IR (film) 2927, 2856, 1540, 1092, 911 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 7.37 (m, 1H), 7.34 (m, 1H), 7.26−7.21 (m, 8H), 4.58 (d, *J* = 11.9 Hz, 1H), 4.55 (d, *J* = 3.2 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 3.85 (m, 1H), 3.69 (ddd, *J* = 8.2, 4.1, 3.2 Hz, 1H), 3.29−3.20 (m, 2H), 2.91 (ddd, *J* = 8.8, 8.8, 2.3 Hz, 1H), 2.05 (m, 1H), 1.92 (dddd, *J* = 14.2, 10.1, 5.9, 4.1 Hz, 1H), 1.76 (dddd, *J* = 9.2, 8.8, 5.0, 4.6 Hz, 1H), 1.70 (m, 1H), 1.66−1.60 (m, 2H), 1.40−1.26 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 132.6, 132.5, 128.99 (2C), 128.93 (2C), 128.3 (2C), 128.2 (2C), 127.7, 127.6, 81.9, 80.8, 72.5, 70.4, 67.5, 63.7, 32.9, 31.6, 31.3, 25.6, 21.7; HRMS (ESI) calcd for $C_{23}H_{28}O_3NaS$ [(M + Na)$^+$] 407.1651, found 407.1658.

3k (isolated and characterized as a 1:1 mixture of diastereomers): colorless crystals; mp 59−61 °C; $[\alpha]_D^{22}$ −9.9 (*c* 1.00, $CHCl_3$); IR

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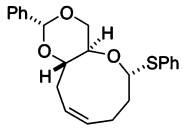
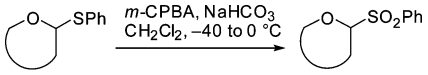


3k

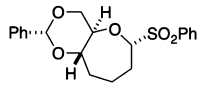
(film) 2953, 2855, 1472, 1157, 1092 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.53 (m, 1H), 7.49−7.43 (m, 3H), 7.38−7.30 (m, 11/2H), 7.23 (m, 1/2H), 5.84 (ddd, J = 10.5, 10.5, 7.3 Hz, 1/2H), 5.76 (ddd, J = 9.2, 9.2, 8.7 Hz, 1/2H), 5.68 (m, 1H), 5.48 (dd, J = 12.4, 4.1 Hz, 1/2H), 5.45 (s, 1/2H), 5.38 (s, 1/2H), 4.97 (dd, J = 11.5, 3.7 Hz, 1/2H), 4.88 (dd, J = 10.6, 4.6 Hz, 1/2H), 3.90 (ddd, J = 9.6, 9.6, 4.6 Hz, 1/2H), 3.79 (ddd, J = 9.2, 3.2, 3.2 Hz, 1/2H), 3.73 (dddd, J = 4.6, 4.6, 4.6, 4.1 Hz, 1/2H), 3.58 (dd, J = 10.6, 10.6 Hz, 1/2H), 3.46 (m, 1H), 2.93 (ddd, J = 11.0, 11.0, 2.3 Hz, 1/2H), 2.78 (ddd, J = 13.3, 9.2, 4.1 Hz, 1/2H), 2.47 (m, 1H), 2.38−2.25 (m, 3/2H), 2.17 (m, 1H), 2.10 (dddd, J = 14.2, 10.6, 3.7, 3.7 Hz, 1/2H), 2.02 (dddd, J = 14.2, 13.3, 7.3, 0.9 Hz, 1/2H), 1.95 (m, 1/2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.8 (1/2C), 137.5 (1/2C), 135.4 (1/2C), 134.2, 133.6 (1/2C), 132.7 (1/2C), 132.5 (1/2C), 131.9 (1/2C), 129.5, 129.0, 128.9, 128.8 (1/2C), 128.3 (1/2C), 128.19, 128.16, 126.4 (1/2C), 126.3 (1/2C), 126.07, 126.05, 124.6 (1/2C), 101.3, 94.0 (1/2C), 86.5 (1/2C), 80.2 (1/2C), 79.5 (1/2C), 79.3 (1/2C), 77.2 (1/2C), 70.7 (1/2C), 69.9 (1/2C), 35.1 (1/2C), 32.2 (1/2C), 30.9 (1/2C), 28.2 (1/2C), 24.4 (1/2C), 21.9 (1/2C); HRMS (ESI) calcd for $C_{22}H_{24}O_3SNa$ $[(M + Na)^+]$ 391.1338, found 391.1343.



3a–c
3h,3k

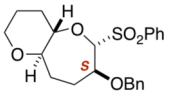
4a–c
4h,4k

General Procedure for Preparation of Sulfones 4a–c, 4h, and 4k.



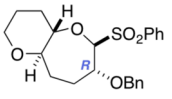
4a

To a solution of thioacetal **3a** (213 mg, 0.622 mmol) in CH_2Cl_2 (5 mL) at −40 °C were added $NaHCO_3$ (261 mg, 3.11 mmol) and *m*-CPBA (322 mg, 1.87 mmol), and the resultant mixture was stirred at 0 °C for 2 h. The resultant mixture was diluted with EtOAc and washed with saturated aqueous Na_2SO_3 solution and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 20−40% EtOAc/hexanes) gave sulfone **4a** (202 mg, 87%, dr 2.5:1). A small portion of this material was subjected to a second round of flash column chromatography (silica gel, 5% Et_2O/benzene) to separate 2,7-*cis* and 2,7-*trans* isomers of **4a** for analytical purposes. Data for 2,7-*cis*-isomer of **4a**: colorless crystals; mp 82−84 °C; $[\alpha]_D^{22}$ +37.1 (c 1.00, $CHCl_3$); IR (film) 2943, 2854, 1449, 1353, 1238, 1095 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.93−7.88 (m, 2H), 7.66 (m, 1H), 7.58−7.54 (m, 2H), 7.41−7.38 (m, 2H), 7.35−7.30 (m, 3H), 5.39 (s, 1H), 4.58 (dd, J = 6.4, 6.4 Hz, 1H), 3.89 (dd, J = 11.0, 5.0 Hz, 1H), 3.59 (ddd, J = 10.5, 9.2, 4.6 Hz, 1H), 3.53 (dd, J = 10.1, 10.1 Hz, 1H), 3.26 (ddd, J = 10.1, 9.2, 5.0 Hz, 1H), 2.52 (m, 1H), 2.18−2.12 (m, 2H), 1.88 (m, 1H), 1.73 (m, 1H), 1.55 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.2, 136.7, 134.0, 129.4 (2C), 129.0, 128.9 (2C), 128.3 (2C), 126.0 (2C), 101.0, 93.1, 81.5, 75.4, 68.6, 33.4, 26.4, 18.8; HRMS (ESI) calcd for $C_{20}H_{22}O_5SNa$ $[(M + Na)^+]$ 397.1080, found 397.1078. Data for 2,7-*trans*-isomer of **4a**: colorless crystals; mp 86−88 °C; $[\alpha]_D^{22}$ +49.5 (c 1.00, $CHCl_3$); IR (film) 2945, 2858, 1447, 1306, 1131 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.90−7.87 (m, 2H), 7.66 (m, 1H), 7.59−7.55 (m, 2H), 7.44−7.42 (m, 2H), 7.36−7.30 (m, 3H), 5.36 (s, 1H), 4.65 (dd, J = 12.4, 5.0 Hz, 1H), 4.27 (m, 1H), 4.26 (dd, J = 6.9, 6.9 Hz, 1H), 3.50 (ddd, J = 11.0, 8.7, 4.6 Hz, 1H), 3.43 (dd, J = 12.4, 12.4 Hz, 1H), 2.50 (ddd, J = 14.2, 7.7, 5.5 Hz, 1H), 2.26−2.19 (m, 2H), 2.07 (m, 1H), 1.58 (m, 1H), 1.50 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.6, 137.5, 134.0, 129.2 (2C), 129.1, 128.9 (2C), 128.3 (2C), 126.2 (2C), 100.8, 92.3, 80.7, 68.8, 68.1, 35.1, 25.1, 19.7; HRMS (ESI) calcd for $C_{20}H_{22}O_5SNa$ $[(M + Na)^+]$ 397.1080, found 397.1078.



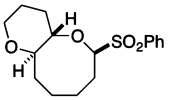
4b

4b (isolated and characterized as a 8:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{22}$ +22.3 (c 1.00, $CHCl_3$); IR (film) 2941, 2852, 1445, 1319, 1144, 1096 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 7.57−7.54 (m, 3H), 7.40 (m, 1H), 7.27−7.22 (m, 2H), 7.10−7.02 (m, 4H), 4.94 (d, J = 7.6 Hz, 1H), 4.71 (d, J = 11.5 Hz, 1H), 4.06 (ddd, J = 7.7, 3.7, 3.7 Hz, 1H), 3.17 (ddd, J = 10.6, 9.2, 4.6 Hz, 1H), 3.07 (ddd, J = 12.4, 11.5, 2.3 Hz, 1H), 2.95 (ddd, J = 8.7, 8.7, 2.8 Hz, 1H), 2.60 (m, 1H), 2.37−2.26 (m, 2H), 1.86 (m, 1H), 1.64 (m, 1H), 1.49 (ddddd, J = 13.3, 13.3, 13.3, 4.6, 4.1 Hz, 1H), 1.29 (m, 1H), 1.18 (dddd, J = 12.8, 12.8, 11.0, 4.1 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 138.1, 135.1, 134.9, 132.6 (2C), 128.9 (2C), 128.23 (2C), 128.20 (2C), 127.6, 82.4, 80.9, 72.7, 70.5, 67.4, 63.8, 32.8, 28.5, 27.7, 25.6; HRMS (ESI) calcd for $C_{22}H_{26}O_5SNa$ $[(M + Na)^+]$ 425.1393, found 425.1396.



4c

4c (isolated and characterized as a 8:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{22}$ +25.1 (c 1.00, $CHCl_3$); IR (film) 2936, 2854, 1541, 1300, 1095 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 7.92−7.89 (m, 2H), 7.58 (m, 1H), 7.50−7.46 (m, 4H), 7.36−7.31 (m, 2H), 7.27 (m, 1H), 4.69 (d, J = 11.9 Hz, 1H), 4.66 (d, J = 11.9 Hz, 1H), 4.56 (dd, J = 7.3, 4.6 Hz, 1H), 4.51 (d, J = 4.6 Hz, 1H), 4.34 (ddd, J = 10.6, 10.1, 5.5 Hz, 1H), 3.81 (m, 1H), 3.22 (ddd, J = 12.4, 11.0, 2.3 Hz, 1H), 2.96 (ddd, J = 10.6, 10.6, 5.5 Hz, 1H), 2.29 (m, 1H), 2.08 (m, 1H), 1.90−1.77 (m, 2H), 1.70−1.57 (m, 2H), 1.45 (ddd, J = 14.6, 13.7, 2.8 Hz, 1H), 1.31 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 139.5, 137.5, 133.4, 128.9 (2C), 128.8 (2C), 128.2 (2C), 128.0 (2C), 127.6, 94.9, 80.5, 75.6, 74.5, 72.6, 67.1, 30.8, 27.0, 25.0, 23.8; HRMS (ESI) calcd for $C_{22}H_{26}O_5SNa$ $[(M + Na)^+]$ 425.1393, found 425.1393.



4h

4h (isolated and characterized as a 10:1 mixture of diastereomers): colorless crystals; mp 66−69 °C; $[\alpha]_D^{22}$ −44.3 (c 1.00, $CHCl_3$); IR (film) 2939, 2859, 1723, 1446, 1305, 1149, 1096 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 7.91−7.89 (m, 2H), 7.65 (m, 1H), 7.57−7.54 (m, 2H), 4.67 (dd, J = 12.4, 1.9 Hz, 1H), 3.98 (ddd, J = 10.1, 10.1, 4.6 Hz, 1H), 3.83 (dddd, J = 11.5, 4.6, 1.4, 1.4 Hz, 1H), 3.23 (ddd, J = 11.5, 11.5, 2.8 Hz, 1H), 2.95 (ddd, J = 9.7, 9.7, 4.1 Hz, 1H), 2.34 (dddd, J = 15.6, 4.1, 4.1, 2.3 Hz, 1H), 2.28−2.17 (m, 2H), 1.91−1.79 (m, 2H), 1.76−1.63 (m, 2H), 1.61−1.53 (m, 2H), 1.48 (dddd, J = 14.2, 8.3, 8.3, 1.4 Hz, 1H), 1.46 (m, 1H), 1.32 (dddd, J = 12.8, 12.8, 11.0, 4.1 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 137.6, 133.7, 129.02 (2C), 129.00 (2C), 94.1, 80.6, 74.0, 67.8, 31.8, 31.1, 26.5, 26.0, 20.9, 20.7; HRMS (ESI) calcd for $C_{16}H_{22}O_4SNa$ $[(M + Na)^+]$ 333.1131, found 333.1135.

4k (isolated and characterized as a 1:1 mixture of diastereomers): colorless crystals; mp 68−71 °C; $[\alpha]_D^{22}$ −44.3 (c 1.00, $CHCl_3$); IR (film) 2921, 2850, 1734, 1476, 1237, 1068 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.63−7.58 (m, 2H), 7.49 (m, 1H), 7.37 (m, 1H), 7.20−7.15

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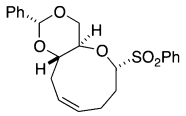
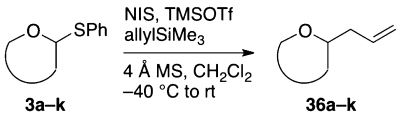


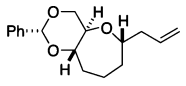
4k

(m, 5/2H), 7.13−7.02 (m, 5/2H), 6.98 (m, 1H), 5.63 (m, 1H), 5.49 (ddd, J = 10.6, 10.6, 6.9 Hz, 1/2H), 5.34 (ddd, J = 9.7, 9.7, 7.4 Hz, 1/2H), 5.26 (s, 1/2H), 5.23 (s, 1/2H), 5.11 (dd, J = 12.4, 4.6 Hz, 1/2H), 5.03 (dd, J = 10.5, 4.6 Hz, 1/2H), 4.52 (dd, J = 12.0, 3.7 Hz, 1/2H), 4.02 (dd, J = 10.5, 5.0 Hz, 1/2H), 3.86 (ddd, J = 9.6, 9.6, 4.6 Hz, 1/2H), 3.54 (ddd, J = 9.2, 3.2, 3.2 Hz, 1/2H), 3.46 (m, 1H), 3.40 (dd, J = 10.6, 10.6 Hz, 1/2H), 3.29 (ddd, J = 9.6, 9.6, 4.6 Hz, 1/2H), 2.81 (m, 1/2H), 2.64 (ddd, J = 13.7, 9.2, 4.1 Hz, 1/2H), 2.33 (m, 1/2H), 2.23 (ddd, J = 13.7, 6.4, 3.2 Hz, 1/2H), 2.11 (m, 1/2H), 2.00 (m, 1/2H), 1.85−1.58 (m, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 139.0 (1/2C), 138.8 (1/2C), 136.5 (1/2C), 134.6 (2C), 133.8 (1/2C), 133.3 (1/2C), 132.9 (1/2C), 132.0, 129.5 (1/2C), 129.09, 129.07, 128.81 (1/2C), 128.79 (1/2C), 128.3 (1/2C), 128.23, 128.21, 126.70, 126.66 (1/2C), 126.4 (1/2C), 101.3, 93.1 (1/2C), 86.3 (1/2C), 80.6 (1/2C), 79.9 (1/2C), 79.3, 71.0 (1/2C), 70.2 (1/2C), 35.2 (1/2C), 32.2 (1/2C), 31.2 (1/2C), 28.5 (1/2C), 24.6 (1/2C), 22.0 (1/2C); HRMS (ESI) calcd for $C_{22}H_{24}O_5SNa$ [(M + Na)$^+$] 423.1237, found 423.1241.



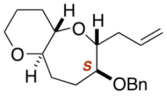
3a–k 36a–k

General procedure for nucleophilic allylation of 3a−k.



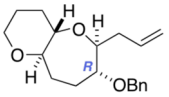
36a

To a mixture of thioacetal **3a** (19.5 mg, 0.0569 mmol), freshly activated 4 Å molecular sieves (30 mg), and allyltrimethylsilane (0.035 mL, 0.29 mmol) in CH_2Cl_2 (1 mL) at −40 °C were added NIS (19 mg, 0.085 mmol) and TMSOTf (0.10 M solution in CH_2Cl_2, 0.057 mL, 0.0057 mmol), and the resultant mixture was stirred at −40 °C for 10 min. The reaction mixture was warmed to room temperature, stirred at room temperature for 12 h, and then diluted with saturated aqueous $NaHCO_3$ solution, saturated aqueous Na_2SO_3 solution, and EtOAc. The organic layer was separated and washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 2% EtOAc/hexanes) gave allylated product **36a** (12.5 mg, 80%, dr >20:1) as a colorless oil: $[\alpha]_D^{23}$ +45.4 (c 0.50, $CHCl_3$); IR (film) 2934, 2851, 1437, 1241, 1096 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47−7.45 (m, 2H), 7.35−7.30 (m, 3H), 5.79 (dddd, J = 17.4, 10.6, 6.8, 6.8 Hz, 1H), 5.43 (s, 1H), 5.06 (ddd, J = 17.4, 2.6, 1.8 Hz, 1H), 5.04 (ddd, J = 10.8, 1.8, 1.8 Hz, 1H), 4.16 (dd, J = 10.1, 4.1 Hz, 1H), 3.78 (m, 1H), 3.60−3.51 (m, 3H), 2.29 (m, 1H), 2.22−2.14 (m, 2H), 1.94 (m, 1H), 1.76 (m, 1H), 1.55−1.41 (m, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 141.3, 139.1, 133.0 (2C), 126.8 (2C), 126.1, 113.0, 101.6, 80.1, 80.0, 71.6, 70.6, 33.7, 31.2, 23.3, 21.4; HRMS (ESI) calcd for $C_{17}H_{22}O_3Na$ [(M + Na)$^+$] 297.1461, found 297.1455.



36b

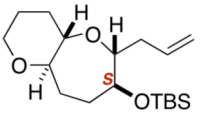
36b (isolated and characterized as a 15:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{23}$ +27.7 (c 0.80, $CHCl_3$); IR (film) 2932, 2848, 1414, 1230, 1095 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 7.24−7.22 (m, 2H), 7.17−7.14 (m, 2H), 7.09 (m, 1H), 5.94 (dddd, J = 16.9, 10.1, 6.9, 6.9 Hz, 1H), 5.07 (m, 1H), 5.03 (m, 1H), 4.34 (d, J = 11.5 Hz, 1H), 4.07 (d, J = 11.5 Hz, 1H), 3.75 (ddd, J = 9.7, 8.7, 3.2 Hz, 1H), 3.69 (dddd, J = 11.5, 4.6, 1.9, 1.4 Hz, 1H), 3.06−2.97 (m, 4H), 2.44 (m, 1H), 2.20 (m, 1H), 2.13 (m, 1H), 1.88 (m, 1H), 1.82−1.72 (m, 2H), 1.45−1.30 (m, 3H), 1.21 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 138.9, 128.32 (2C), 128.29 (2C), 127.8, 127.4, 117.3, 82.4, 82.3, 80.7, 70.5, 70.0, 67.5, 32.8, 31.1, 28.0, 27.4, 25.6; HRMS (ESI) calcd for $C_{19}H_{26}O_3Na$ [(M + Na)$^+$] 325.1774, found 325.1770.



36c

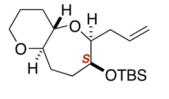
36c (dr >20:1): a colorless oil; $[\alpha]_D^{23}$ +16.0 (c 0.90, $CHCl_3$); IR (film) 2934, 2854, 1452, 1093, 1062 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34−7.26 (m, 5H), 5.86 (dddd, J = 17.4, 10.1, 7.3, 6.4 Hz, 1H), 5.08−5.02 (m, 2H), 4.61 (d, J = 11.5 Hz, 1H), 4.37 (d, J = 11.5 Hz, 1H), 3.81 (dddd, J = 11.0, 4.1, 1.8, 1.4 Hz, 1H), 3.54 (ddd, J = 9.7, 9.7, 3.2 Hz, 1H), 3.29−3.22 (m, 2H), 3.09 (ddd, J = 10.6, 9.2, 5.0 Hz, 1H), 3.04 (ddd, J = 10.6, 9.2, 5.5 Hz, 1H), 2.42 (m, 1H), 2.27 (m, 1H), 2.12 (m, 1H), 1.97−1.92 (m, 2H), 1.80 (dddd, J = 13.7, 13.3, 10.5, 2.3 Hz, 1H), 1.63−1.53 (m, 2H), 1.38−1.23 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.0, 135.8, 128.4 (2C), 128.0 (2C), 127.8, 116.6, 83.9, 80.8, 79.8, 71.4, 71.1, 67.3, 36.4, 32.4, 31.5, 26.1, 25.7; HRMS (ESI) calcd for $C_{19}H_{26}O_3Na$ [(M + Na)$^+$] 325.1774, found 325.1770.

36d: A 3:1 mixture of 2,7-*cis* and 2,7-*trans* isomers of **36d** was separated by flash column chromatography using silica gel (8% EtOAc/hexanes) and characterized individually.



2,7-*cis* isomer of **36d**

2,7-*cis* isomer of **36d**: colorless oil; $[\alpha]_D^{24}$ +10.2 (c 1.00, $CHCl_3$); IR (film) 2931, 2857, 1407, 1310, 1210, 1079 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.87 (dddd, J = 17.4, 9.6, 7.4, 6.4 Hz, 1H), 5.09−5.03 (m, 2H), 3.81 (m, 1H), 3.50 (ddd, J = 10.1, 8.2, 2.3 Hz, 1H), 3.39 (ddd, J = 10.5, 8.7, 2.7 Hz, 1H), 3.27 (m, 1H), 3.12 (ddd, J = 10.5, 9.2, 4.5 Hz, 1H), 3.03 (ddd, J = 10.5, 9.2, 5.5 Hz, 1H), 2.41 (m, 1H), 2.22 (m, 1H), 2.02 (dddd, J = 13.8, 5.9, 5.9, 2.3 Hz, 1H), 1.95 (m, 1H), 1.88 (dddd, J = 13.8, 13.8, 8.2, 2.3 Hz, 1H), 1.67−1.57 (m, 3H), 1.38−1.31 (m, 2H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.2, 116.5, 81.8, 80.9, 77.1, 71.3, 67.4, 36.2, 32.1, 31.6, 31.5, 29.8, 25.8 (3C), 17.9, −4.0, −4.7; HRMS (ESI) calcd for $C_{18}H_{34}O_3SiNa$ [(M + Na)$^+$] 349.2169, found 349.2171.

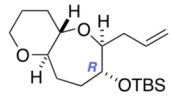


2,7-*trans* isomer of **36d**

2,7-*trans* isomer of **36d**: colorless oil; $[\alpha]_D^{24}$ +18.3 (c 1.00, $CHCl_3$); IR (film) 2935, 2849, 1420, 1267, 1170, 1097 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 6.10 (dddd, J = 17.4, 10.1, 6.8, 6.8 Hz, 1H), 5.23 (m, 1H), 5.16 (m, 1H), 3.78 (dddd, J = 11.0, 4.6, 1.8, 1.4 Hz, 1H), 3.71 (ddd, J = 10.6, 7.8, 2.8 Hz, 1H), 3.53 (ddd, J = 10.1, 8.3, 1.4 Hz, 1H), 3.18−3.09 (m, 3H), 2.59 (m, 1H), 2.29 (m, 1H), 2.18 (m, 1H), 2.07−1.97 (m, 2H), 1.72 (dddd, J = 13.7, 5.9, 2.3, 1.8 Hz, 1H), 1.58 (dddd, J = 13.3, 13.3, 10.1, 2.8 Hz, 1H), 1.53 (m, 1H), 1.42 (m, 1H), 1.31 (m, 1H), 1.01 (s, 9H), 0.084 (s, 3H), 0.083 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 136.7, 116.1, 81.7, 81.3, 77.6, 71.5, 67.1, 36.6, 32.5, 32.0, 31.9, 26.0, 25.8 (3C), 17.8, −4.1, −4.8; HRMS (ESI) calcd for $C_{18}H_{34}O_3SiNa$ [(M + Na)$^+$] 349.2169, found 349.2164.

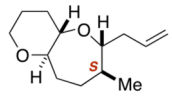
36e (isolated and characterized as a 20:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{23}$ +22.0 (c 1.20, $CHCl_3$); IR (film) 2935, 2850, 1387, 1219, 1093 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, major

dx.doi.org/10.1021/jo4025545 | J. Org. Chem. 2014, 79, 1656−1682



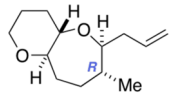
36e

diastereomer) δ 5.90 (dddd, J = 16.9, 10.1, 6.8, 6.4 Hz, 1H), 5.10−5.02 (m, 2H), 3.71 (m, 1H), 3.49−3.43 (m, 2H), 3.13 (ddd, J = 11.9, 11.5, 0.8 Hz, 1H), 3.07 (m, 1H), 3.00 (m, 1H), 2.42 (m, 1H), 2.19 (m, 1H), 2.02 (m, 1H), 1.63 (m, 1H), 1.50 (m, 1H), 1.44−1.22 (m, 5H), 0.89 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 136.3, 116.3, 81.7, 81.0, 77.1, 71.2, 67.2, 36.3, 32.2, 31.7, 31.6, 29.7, 25.7 (3C), 17.8, −4.2, −4.8; HRMS (ESI) calcd for $C_{18}H_{34}O_3SiNa$ [(M + Na)$^+$] 349.2169, found 349.2171.



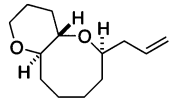
36f

36f (isolated and characterized as a 5:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{23}$ +15.5 (c 1.00, $CHCl_3$); IR (film) 2937, 2853, 1441, 1327, 1216, 1092 cm^{-1}; ^{1}H NMR (600 MHz, $(CD_3)_2CO$, major diastereomer) δ 5.91 (dddd, J = 17.4, 10.1, 7.2, 7.2 Hz, 1H), 5.06 (dddd, J = 17.4, 2.3, 1.4, 1.4 Hz, 1H), 4.97 (dddd, J = 10.1, 2.3, 1.4, 1.4 Hz, 1H), 3.72 (dddd, J = 11.0, 4.1, 1.8, 1.8 Hz, 1H), 3.24 (ddd, J = 11.0, 9.1, 5.0 Hz, 1H), 3.19 (ddd, J = 10.6, 10.6, 2.8 Hz, 1H), 3.16 (ddd, J = 9.6, 9.6, 2.8 Hz, 1H), 2.92 (ddd, J = 10.6, 8.7, 5.5 Hz, 1H), 2.33 (m, 1H), 2.26 (m, 1H), 1.99−1.91 (m, 2H), 1.59−1.49 (m, 4H), 1.37 (m, 1H), 1.32−1.25 (m, 2H), 0.92 (d, J = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $(CD_3)_2CO$, major diastereomer) δ 136.5, 116.2, 83.3, 81.2, 69.8, 67.2, 40.2, 36.9, 35.8, 31.6, 29.8, 25.6, 20.9; HRMS (ESI) calcd for $C_{13}H_{22}O_2Na$ [(M + Na)$^+$] 233.1512, found 233.1518.



36g

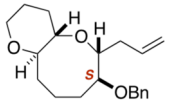
36g (dr >20:1): colorless oil; $[\alpha]_D^{23}$ +22.4 (c 1.00, $CHCl_3$); IR (film) 2940, 2843, 1421, 1371, 1088 cm^{-1}; ^{1}H NMR (600 MHz, $(CD_3)_2CO$) δ 5.91 (dddd, J = 17.4, 10.5, 6.9, 6.9 Hz, 1H), 5.06 (m, 1H), 4.97 (m, 1H), 3.72 (dddd, J = 11.0, 4.1, 19, 1.9 Hz, 1H), 3.24 (ddd, J = 11.0, 9.1, 5.0 Hz, 1H), 3.19 (ddd, J = 10.6, 10.6, 2.8 Hz, 1H), 3.16 (ddd, J = 9.6, 9.6, 2.8 Hz, 1H), 2.92 (ddd, J = 10.6, 9.2, 5.5 Hz, 1H), 2.33 (m, 1H), 2.26 (m, 1H), 1.99−1.90 (m, 2H), 1.59−1.49 (m, 4H), 1.37 (ddd, J = 12.4, 5.5, 2.3 Hz, 1H), 1.32−1.25 (m, 2H), 0.92 (d, J = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $(CD_3)_2CO$) δ 137.9, 115.8, 83.5, 82.0, 70.4, 67.3, 40.8, 37.4, 36.5, 32.4, 30.6, 26.2, 21.0; HRMS (ESI) calcd for $C_{13}H_{22}O_2Na$ [(M + Na)$^+$] 233.1512, found 233.1511.



36h

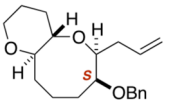
36h (dr >20:1): colorless crystals; mp 59−62 °C; $[\alpha]_D^{23}$ +37.1 (c 1.00, $CHCl_3$); IR (film) 2931, 2845, 1389, 1156, 1090 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.81 (dddd, J = 17.0, 10.6, 7.3, 6.4 Hz, 1H), 5.04 (m, 1H), 5.02 (m, 1H), 3.83 (dddd, J = 11.5, 4.6, 1.9, 1.3 Hz, 1H), 3.72 (m, 1H), 3.36 (ddd, J = 11.0, 9.2, 4.6 Hz, 1H), 3.28 (m, 1H), 3.36 (ddd, J = 9.7, 9.7, 4.1 Hz, 1H), 2.29 (m, 1H), 2.08 (m, 1H), 1.92−1.85 (m, 2H), 1.82−1.50 (m, 7H), 1.48−1.41 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.6, 116.6, 81.7, 78.2, 70.5, 67.8, 40.3, 32.6, 31.8, 28.7, 26.7, 26.2, 21.6; HRMS (ESI) calcd for $C_{13}H_{22}O_2Na$ [(M + Na)$^+$] 233.1512, found 233.1511.

36i: A 6:1 mixture of 2,8-*cis* and 2,8-*trans* isomers of **36i** was separated by flash column chromatography using silica gel (2−5% EtOAc/hexanes) and characterized individually.



2,8-*cis* isomer of **36i**

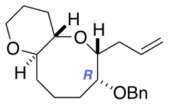
2,8-*cis*-isomer of **36i**: colorless oil; $[\alpha]_D^{23}$ +7.2 (c 0.70, $CHCl_3$); IR (film) 2937, 2848, 1331, 1277, 1096 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34−7.29 (m, 4H), 7.26 (m, 1H), 5.82 (dddd, J = 17.0, 10.1, 7.4, 6.4 Hz, 1H), 5.08−5.02 (m, 2H), 4.58 (d, J = 11.5 Hz, 1H), 4.34 (d, J = 11.5 Hz, 1H), 3.82 (m, 1H), 3.48 (ddd, J = 8.7, 8.7, 3.2 Hz, 1H), 3.31 (ddd, J = 8.7, 6.8, 2.3 Hz, 1H), 3.24 (m, 1H), 3.07−3.01 (m, 2H), 2.50 (m, 1H), 2.11−1.99 (m, 3H), 1.92−1.85 (m, 2H), 1.81 (m, 1H), 1.73 (m, 1H) 1.64−1.53 (m, 3H), 1.36 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.4, 135.5, 128.4 (2C), 127.9 (2C), 127.7, 117.0, 83.9, 83.2, 82.0, 81.7, 71.3, 67.8, 39.9, 34.8, 31.5, 27.5, 26.0, 19.8; HRMS (ESI) calcd for $C_{20}H_{28}O_3Na$ [(M + Na)$^+$] 339.1931, found 339.1925.



2,8-*trans* isomer of **36i**

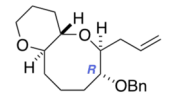
2,8-*trans*-isomer of **36i**: colorless oil; $[\alpha]_D^{23}$ +10.1 (c 0.80, $CHCl_3$); IR (film) 2926, 2855, 1508, 1456, 1099 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34−7.29 (m, 4H), 7.25 (m, 1H), 5.67 (dddd, J = 17.4, 10.1, 7.3, 7.3 Hz, 1H), 5.03−4.96 (m, 2H), 4.63 (d, J = 11.5 Hz, 1H), 4.31 (d, J = 11.5 Hz, 1H), 3.83 (m, 1H), 3.66−3.60 (m, 2H), 3.44 (ddd, J = 5.9, 2.3, 2.3 Hz, 1H), 3.32 (ddd, J = 9.6, 9.6, 4.1 Hz, 1H), 3.26 (m, 1H), 2.50 (ddd, J = 13.8, 7.8, 7.3 Hz, 1H), 2.32 (ddddd, J = 13.8, 6.9, 6.9, 1.4, 1.4 Hz, 1H), 2.18−2.10 (m, 2H), 1.95 (m, 1H), 1.85 (m, 1H), 1.72−1.63 (m, 3H), 1.55−1.47 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 135.4, 128.2 (2C), 127.8 (2C), 127.4, 116.9, 79.2, 77.3, 76.4, 75.8, 70.9, 68.0, 37.9, 34.1, 30.6, 28.5, 26.3, 17.3; HRMS (ESI) calcd for $C_{20}H_{28}O_3Na$ [(M + Na)$^+$] 339.1931, found 339.1933.

36j: A 5:1 mixture of 2,8-*trans* and 2,8-*cis* isomers of **36j** was separated by flash column chromatography using silica gel (2% EtOAc/hexanes) and characterized individually.



2,8-*cis* isomer of **36j**

2,8-*cis*-isomer of **36j**: colorless oil; $[\alpha]_D^{23}$ +5.9 (c 1.00, $CHCl_3$); IR (film) 2933, 2851, 1331, 1134, 1088 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.32−7.30 (m, 2H), 7.19−7.15 (m, 2H), 7.09 (m, 1H), 5.80 (dddd, J = 17.0, 9.6, 6.8, 6.8 Hz, 1H), 5.08 (m, 1H), 5.03 (m, 1H), 4.43 (d, J = 11.9 Hz, 1H), 4.05 (d, J = 11.9 Hz, 1H), 3.85 (ddd, J = 11.5, 9.7, 4.1 Hz, 1H), 3.71 (dddd, J = 11.5, 4.6, 1.8, 1.4 Hz, 1H), 3.53 (ddd, J = 6.9, 6.9, 2.8 Hz, 1H), 3.25−3.20 (m, 2H), 3.04 (ddd, J = 11.5, 11.5, 2.3 Hz, 1H), 2.58 (ddd, J = 13.7, 7.3, 7.3 Hz, 1H), 2.51 (ddddd, J = 13.7, 6.9, 6.9, 1.4, 1.4 Hz, 1H), 2.16 (m, 1H), 2.06−1.94 (m, 3H), 1.84 (m, 1H), 1.51−1.42 (m, 2H), 1.37 (m, 1H), 1.28 (dddd, J = 15.1, 8.3, 2.3, 1.8 Hz, 1H), 1.23 (m, 1H); ^{13}C NMR (150 MHz, C_6D_6) δ 139.3, 136.2, 128.5 (2C), 128.3 (2C), 127.7, 116.5, 80.6, 79.1, 77.4, 75.2, 71.1, 67.8, 37.9, 34.6, 31.8, 29.2, 26.8, 18.2; HRMS (ESI) calcd for $C_{20}H_{28}O_3Na$ [(M + Na)$^+$] 339.1931, found 339.1932.

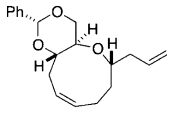


2,8-*trans* isomer of **36j**

2,8-*trans*-isomer of **36j**: colorless oil; $[\alpha]_D^{23}$ +13.3 (c 1.00, $CHCl_3$); IR (film) 2932, 2849, 1338, 1231, 1092 cm^{-1}; ^{1}H NMR (600 MHz,

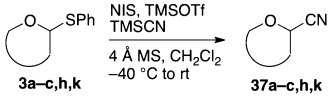
dx.doi.org/10.1021/jo4025545 | J. Org. Chem. 2014, 79, 1656−1682

$CDCl_3$) δ 7.34−7.29 (m, 4H), 7.27 (m, 1H), 5.85 (dddd, J = 16.9, 10.1, 7.8, 6.8 Hz, 1H), 5.06−5.01 (m, 2H), 4.57 (d, J = 11.5 Hz, 1H), 4.35 (d, J = 11.5 Hz, 1H), 3.82 (dddd, J = 11.0, 4.1, 4.1, 1.8 Hz, 1H), 3.59 (ddd, J = 9.1, 6.4, 4.1 Hz, 1H), 3.43 (ddd, J = 9.1, 6.7, 3.2 Hz, 1H), 3.34 (ddd, J = 11.0, 9.6, 4.1 Hz, 1H), 3.27 (ddd, J = 10.1, 10.1, 3.2 Hz, 1H), 3.25 (m, 1H), 2.46 (m, 1H), 2.30 (ddd, J = 14.2, 7.3, 6.4 Hz, 1H), 1.97−1.91 (m, 2H), 1.87 (m, 1H), 1.79−1.73 (m, 3H), 1.68−1.63 (m, 2H), 1.59−1.51 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.4, 135.3, 128.4 (2C), 127.9 (2C), 127.7, 117.0, 80.5, 79.7, 76.3, 75.8, 71.4, 68.0, 38.1, 34.8, 31.1, 30.1, 26.4, 19.3; HRMS (ESI) calcd for $C_{20}H_{28}O_3Na$ [(M + Na)$^+$] 339.1931, found 339.1935.



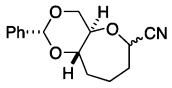
36k

36k (isolated and characterized as a 2:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{23}$ −13.8 (c 1.00, $CHCl_3$); IR (film) 2935, 2855, 1329, 1177, 1089 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.68−7.64 (m, 2H), 7.21−7.17 (m, 2H), 7.12 (m, 1H), 5.71 (m, 1H), 5.63 (ddd, J = 17.0, 10.6, 5.0 Hz, 2/3H), 5.61 (m, 1/3H), 5.52 (m, 1H), 5.32 (s, 1/3H), 5.31 (s, 2/3H), 5.03 (ddd, J = 17.0, 1.4, 1.4 Hz, 2/3H), 4.89 (ddd, J = 17.5, 1.4, 1.4 Hz, 1/3H), 4.85 (ddd, J = 10.6, 1.8, 1.4 Hz, 2/3H), 4.80 (ddd, J = 10.6, 1.4, 1.4 Hz, 1/3H), 4.27 (dd, J = 10.5, 4.6 Hz, 1/3H), 4.22 (dd, J = 10.5, 5.0 Hz, 2/3H), 3.87 (m, 1/3H), 3.71 (ddd, J = 9.2, 9.2, 4.1 Hz, 1/3H), 3.61 (m, 1/3H), 3.59 (dd, J = 10.1, 10.1 Hz, 1/3H), 3.56 (dd, J = 9.2, 4.6 Hz, 2/3H), 3.50 (m, 2/3H), 3.48 (dd, J = 10.6, 10.6 Hz, 2/3H), 3.38 (ddd, J = 10.1, 9.1, 5.0 Hz, 2/3H), 2.80 (m, 1H), 2.46 (m, 1H), 2.26 (m, 1H), 2.03 (m, 1/3H), 1.82 (m, 2/3H), 1.42−1.22 (m, 4H); ^{13}C NMR (150 MHz, C_6D_6) δ 141.3 (2/3C), 141.0 (1/3C), 140.5 (1/3C), 139.0 (2/3C), 133.0 (2/3C), 130.6 (1/3C), 128.8 (4/3C), 128.6 (2/3C), 126.78 (2/3C), 126.76 (4/3C), 126.1 (2/3C), 125.4 (1/3C), 115.4 (1/3C), 113.0 (2/3C), 101.8 (1/3C), 101.6 (2/3C), 80.04 (2/3C), 79.98 (1/3C), 77.2 (1/3C), 72.3 (1/3C), 71.6 (2/3C), 70.60 (2/3C), 70.58 (2/3C), 65.6 (1/3C), 33.73 (1/3C), 33.65 (2/3C), 31.9 (1/3C), 31.3 (2/3C), 24.2 (1/3C), 23.3 (2/3C), 21.3 (2/3C), 20.6 (1/3C); HRMS (ESI) calcd for $C_{19}H_{24}O_3Na$ [(M + Na)$^+$] 323.1618, found 323.1622.



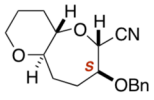
3a–c,h,k **37a–c,h,k**

General Procedure for Nucleophilic Cyanation of 3a−c, 3h, and 3k.



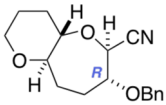
37a

To a mixture of thioacetal **3a** (22.8 mg, 0.0666 mmol), freshly activated 4 Å molecular sieves (30 mg), and TMSCN (0.040 mL, 0.33 mmol) in CH_2Cl_2 (1 mL) at −40 °C were added NIS (22 mg, 0.10 mmol) and TMSOTf (0.1 M solution in CH_2Cl_2, 0.055 mL, 0.0055 mmol), and the resultant mixture was stirred at −40 °C for 30 min. The reaction mixture was warmed to room temperature, stirred at room temperature for 12 h, and then diluted with saturated aqueous $NaHCO_3$ solution, saturated aqueous Na_2SO_3 solution, and EtOAc. The organic layer was separated and washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 2−5% EtOAc/hexanes) gave cyanated product **37a** (13.3 mg, 77%, dr 1:1) as a colorless oil. The following data were collected as a 1:1 mixture of diastereomers: $[\alpha]_D^{24}$ −7.7 (c 1.00, $CHCl_3$); IR (film) 2925, 2853, 2280, 1461, 1282, 1104 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50−7.41 (m, 3H), 7.37−7.31 (m, 2H), 5.44 (s, 1H), 4.69 (dd, J = 6.4, 3.7 Hz, 1/2H), 4.55 (dd, J = 11.5, 6.8 Hz, 1/2H), 4.31 (dd, J = 11.0, 5.5 Hz, 1/2H), 4.25 (dd, J = 11.0, 5.5 Hz, 1/2H), 3.79 (ddd, J = 9.7, 9.7, 6.0 Hz, 1/2H), 3.68 (m, 1/2H), 3.64−3.54 (m, 3/2H), 3.48 (m, 1/2H), 2.31−2.00 (m, 4H), 1.93−1.76 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.4 (1/2C), 136.9 (1/2C), 129.2 (1/2C), 129.1 (1/2C), 128.33, 128.29, 126.14, 126.08, 100.9 (1/2C), 100.6 (1/2C), 81.0 (1/2C), 80.5 (1/2C), 71.7 (1/2C), 69.1 (1/2C), 69.0 (1/2C), 68.64 (1/2C), 68.63 (1/2C), 67.0 (1/2C), 66.7 (1/2C), 66.0 (1/2C), 34.9 (1/2C), 34.2 (1/2C), 33.3 (1/2C), 33.2 (1/2C), 19.2 (1/2C), 18.5 (1/2C); HRMS (ESI) calcd for $C_{15}H_{17}NO_3Na$ [(M + Na)$^+$] 282.1101, found 282.1108.



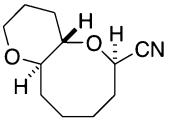
37b

37b (isolated and characterized as a 18:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{24}$ +18.4 (c 1.00, $CHCl_3$); IR (film) 2925, 2851, 2298, 1581, 1479, 1438, 1093 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 7.33−7.24 (m, 5H), 5.14 (d, J = 6.4 Hz, 1H), 4.58 (d, J = 11.9 Hz, 1H), 4.47 (d, J = 11.9 Hz, 1H), 3.86 (ddd, J = 11.5, 4.6, 1.8 Hz, 1H), 3.73 (ddd, J = 6.4, 4.6, 1.8 Hz, 1H), 3.40 (ddd, J = 10.0, 9.1, 4.1 Hz, 1H), 3.30 (ddd, J = 11.9, 11.9, 3.2 Hz, 1H), 2.93 (ddd, J = 9.6, 9.6, 4.1 Hz, 1H), 2.09−1.99 (m, 2H), 1.88−1.74 (m, 3H), 1.72−1.61 (m, 2H), 1.42 (dd, J = 11.5, 5.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 138.2, 136.2, 128.3 (2C), 127.6, 127.5 (2C), 100.5, 83.1, 80.8, 79.4, 71.5, 67.9, 30.6, 27.4, 26.1, 21.2; HRMS (ESI) calcd for $C_{17}H_{21}NO_3Na$ [(M + Na)$^+$] 310.1414, found 310.1412.



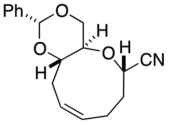
37c

37c (dr >20:1): colorless oil; $[\alpha]_D^{24}$ +10.3 (c 0.75, $CHCl_3$); IR (film) 2938, 2850, 2277, 1489, 1442, 1092 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33−7.31 (m, 2H), 7.25−7.22 (m, 3H), 5.08 (d, J = 5.9 Hz, 1H), 4.46 (d, J = 11.9 Hz, 1H), 4.36 (d, J = 11.9 Hz, 1H), 3.82 (ddd, J = 11.5, 4.6, 1.8 Hz, 1H), 3.72 (ddd, J = 11.5, 4.6, 1.4 Hz, 1H), 3.63 (ddd, J = 9.7, 5.9, 4.6 Hz, 1H), 3.06 (ddd, J = 11.5, 11.5, 2.3 Hz, 1H), 2.94 (ddd, J = 11.5, 9.6, 3.2 Hz, 1H), 2.20 (m, 1H), 2.10 (dd, J = 13.3, 11.5 Hz, 1H), 1.93−1.86 (m, 2H), 1.74−1.67 (m, 2H), 1.49−1.39 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.0, 136.2, 128.1 (2C), 127.4, 127.3 (2C), 100.2, 82.9, 80.5, 79.2, 71.3, 67.4, 30.4, 27.2, 25.4, 20.9; HRMS (ESI) calcd for $C_{17}H_{21}NO_3Na$ [(M + Na)$^+$] 310.1414, found 310.1418.



37h

37h (dr 10:1): colorless crystals; mp 65−68 °C; $[\alpha]_D^{23}$ +33.8 (c 1.00, $CHCl_3$); IR (film) 2959, 2838, 2251, 1462, 1216, 1116, 1096 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 4.50 (dd, J = 12.8, 3.2 Hz, 1H), 3.85 (dddd, J = 11.0, 4.6, 1.9, 1.4 Hz, 1H), 3.53 (ddd, J = 11.0, 9.6, 4.6 Hz, 1H), 3.29 (ddd, J = 11.0, 11.0, 3.2 Hz, 1H), 3.00 (ddd, J = 10.1, 10.1, 4.1 Hz, 1H), 2.28 (m, 1H), 2.14 (m, 1H), 1.92 (dddd, J = 14.2, 11.0, 4.6, 0.9 Hz, 1H), 1.79−1.57 (m, 7H), 1.49−1.42 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 118.8, 80.8, 74.5, 67.8, 67.3, 31.3, 30.6, 28.2, 25.9, 25.4, 21.0; HRMS (ESI) calcd for $C_{11}H_{17}NO_2Na$ [(M + Na)$^+$] 218.1151, found 218.1158.



37k

37k (isolated and characterized as a 4:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{24}$ −9.3 (c 0.80, $CHCl_3$); IR (film) 2921, 2850, 2310,

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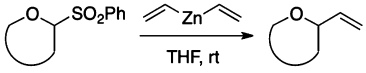
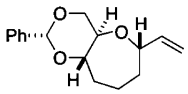
1455, 1252, 1070 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.51 (m, 1H), 7.47−7.41 (m, 4H), 5.85 (m, 1/5H), 5.81 (ddd, J = 11.0, 11.0, 5.0 Hz, 4/5H), 5.59 (ddd, J = 11.0, 10.5, 5.9 Hz, 4/5H), 5.56 (m, 1/5H), 5.25 (s, 4/5H), 5.24 (s, 1/5H), 4.87 (m, 1H), 4.19 (m, 1H), 3.79 (dd, J = 11.0, 8.7 Hz, 4/5H), 3.77 (dd, J = 11.5, 2.8 Hz, 1/5H), 3.71 (ddd, J = 6.4, 6.4, 2.8 Hz, 1H), 3.56 (dd, J = 11.0, 5.0 Hz, 1H), 2.13 (m, 4/5H), 2.10−1.85 (m, 6/5H), 1.87−1.80 (m, 2H), 1.78−1.74 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.6 (4/5C), 135.5 (1/5C), 130.0 (1/5C), 129.8 (4/5C), 129.1 (8/5C), 129.0 (2/5C), 127.3 (2/5C), 127.2 (8/5C), 125.80 (4/5C), 125.75 (1/5C), 118.1 (1/5C), 118.0 (4/5C), 117.3 (1/5C), 116.7 (4/5C), 102.1 (4/5C), 100.9 (1/5C), 81.7 (4/5C), 79.7 (1/5C), 74.1 (4/5C), 74.0 (1/5C), 72.3 (1/5C), 72.2 (4/5C), 64.7 (4/5C), 64.6 (1/5C), 31.4 (4/5C) 30.5 (1/5C), 21.9 (1/5C), 21.3 (4/5C), 13.9 (4/5C), 13.4 (1/5C); HRMS (ESI) calcd for $C_{17}H_{19}NO_3Na$ [(M + Na)$^+$] 308.1257, found 308.1251.



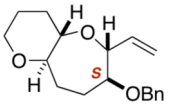
4a-c,h,k **38a-c,h,k**

General Procedure for Nucleophilic Alkenylation of 4a−c, 4h, and 4k.



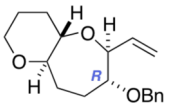
38a

To a suspension of $ZnBr_2$ (95%, 23 mg, 0.095 mmol) in THF (0.5 mL) was added vinylmagnesium bromide (1.0 M solution in THF, 0.19 mL, 0.19 mmol), and the resultant mixture was stirred at room temperature for 30 min. To the resultant suspension was added a solution of sulfone **4a** (23.8 mg, 0.0636 mmol) in THF (0.5 mL), and the resultant mixture was stirred at room temperature for 10 h. The reaction mixture was diluted with saturated aqueous NH_4Cl solution and EtOAc. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5% EtOAc/hexanes) gave alkenylated product **38a** (13.2 mg, 80%, dr 18:1) as a colorless oil. The following data were collected as a 18:1 mixture of diastereomers: $[\alpha]_D^{24}$ −22.9 (c 1.00, $CHCl_3$); IR (film) 2953, 2846, 1462, 1331, 1210, 1092 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 7.47−7.45 (m, 2H), 7.35−7.29 (m, 3H), 5.85 (ddd, J = 17.5, 10.6, 4.6 Hz, 1H), 5.44 (s, 1H), 5.18 (ddd, J = 17.5, 1.8, 1.4 Hz, 1H), 5.12 (ddd, J = 10.6, 1.8, 1.4 Hz, 1H), 4.24−4.20 (m, 2H), 3.62−3.55 (m, 3H), 2.21 (dddd, J = 13.3, 5.5, 5.5, 1.4 Hz, 1H), 2.00 (m, 1H), 1.81 (m, 1H), 1.64−1.58 (m, 2H), 1.46 (ddd, J = 12.8, 10.1, 2.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 138.7, 137.9, 128.9, 128.3 (2C), 126.1 (2C), 114.6, 100.7, 81.7, 77.4, 70.2, 65.6, 35.6, 33.7, 20.1; HRMS (ESI) calcd for $C_{16}H_{20}O_3Na$ [(M + Na)$^+$] 283.1305, found 283.1311.



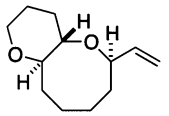
38b

38b (isolated and characterized as a 8:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{24}$ −7.7 (c 1.00, $CHCl_3$); IR (film) 2924, 2851, 1239, 1096, 1038 cm^{-1}; ^1H NMR (600 MHz, C_6D_6, major diastereomer) δ 7.24−7.08 (m, 5H), 6.02 (ddd, J = 17.5, 11.0, 3.7 Hz, 1H), 5.40 (ddd, J = 17.5, 1.9, 1.9 Hz, 1H), 5.12 (ddd, J = 11.0, 1.9, 1.9 Hz, 1H), 4.33 (d, J = 11.5 Hz, 1H), 4.26 (m, 1H), 4.10 (d, J = 11.5 Hz, 1H), 3.66 (m, 1H), 3.22 (ddd, J = 10.6, 8.7, 1.4 Hz, 1H), 3.08−2.98 (m, 3H), 2.13 (m, 1H), 1.96 (m, 1H), 1.82 (dddd, J = 13.3, 13.3, 10.1, 1.9 Hz, 1H) 1.75 (m, 1H), 1.40−1.28 (m, 4H); ^{13}C NMR (150 MHz, C_6D_6, major diastereomer) δ 138.0, 128.4, 128.3 (2C), 127.9 (2C), 127.5, 115.1, 83.9, 81.4, 80.5, 72.7, 71.3, 67.2, 33.0, 32.4, 26.4, 26.1; HRMS (ESI) calcd for $C_{18}H_{24}O_3Na$ [(M + Na)$^+$] 311.1618, found 311.1611.



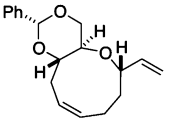
38c

38c (dr >20:1): colorless oil; $[\alpha]_D^{24}$ +17.7 (c 0.75, $CHCl_3$); IR (film) 2938, 2850, 1489, 1442, 1092 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33−7.24 (m, 5H), 5.96 (ddd, J = 17.4, 10.6, 4.1 Hz, 1H), 5.32 (ddd, J = 17.4, 1.8, 1.8 Hz, 1H), 5.19 (ddd, J = 10.6, 1.8, 1.8 Hz, 1H), 4.62 (d, J = 11.5 Hz, 1H), 4.41 (d, J = 11.5 Hz, 1H), 4.00 (m, 1H), 3.81 (m, 1H), 3.39 (ddd, J = 10.5, 9.2, 1.3 Hz, 1H), 3.28 (ddd, J = 11.5, 11.5, 3.2 Hz, 1H), 3.10−3.04 (m, 2H), 2.14 (m, 1H), 2.02 (m, 1H), 1.96 (m, 1H), 1.85 (dddd, J = 13.3, 13.3, 10.6, 2.3 Hz, 1H) 1.64−1.54 (m, 2H), 1.39 (m, 1H), 1.28 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.0, 128.4 (2C), 127.9 (2C), 127.78, 127.75, 115.6, 83.3, 80.8, 80.2, 72.3, 71.5, 67.3, 32.4, 32.0, 26.1, 25.7; HRMS (ESI) calcd for $C_{18}H_{24}O_3Na$ [(M + Na)$^+$] 311.1618, found 311.1622.



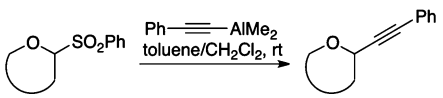
38h

38h (dr >20:1): colorless crystals; mp 71−73 °C; $[\alpha]_D^{24}$ +28.3 (c 0.91, benzene); IR (film) 2923, 2851, 1458, 1398, 1094 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.90 (ddd, J = 17.3, 10.6, 5.5 Hz, 1H), 5.16 (ddd, J = 17.3, 1.4, 1.4 Hz, 1H), 5.09 (ddd, J = 10.6, 1.4, 1.4 Hz, 1H), 4.14 (m, 1H), 3.83 (dddd, J = 11.5, 4.1, 1.8, 1.8 Hz, 1H), 3.33−3.26 (m, 2H), 3.06 (ddd, J = 10.6, 9.6, 4.1 Hz, 1H), 1.91−1.71 (m, 5H), 1.68−1.40 (m, 7H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.8, 115.3, 81.6, 77.8, 71.6, 67.9, 32.6, 31.7, 28.0, 26.2, 26.1, 21.8; HRMS (ESI) calcd for $C_{12}H_{20}O_2Na$ [(M + Na)$^+$] 219.1356, found 219.1363.



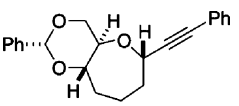
38k

38k (isolated and characterized as a 3:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{24}$ +15.1 (c 1.00, $CHCl_3$); IR (film) 2925, 2852, 1456, 1395, 1094 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 7.47−7.44 (m, 2H), 7.36−7.29 (m, 3H), 5.81 (ddd, J = 17.4, 10.6, 5.9 Hz, 1H), 5.75−5.67 (m, 2H), 5.43 (s, 1H), 5.16 (ddd, J = 17.4, 1.4, 1.4 Hz, 1H), 5.01 (ddd, J = 10.6, 1.4, 1.4 Hz, 1H), 4.20 (dd, J = 10.6, 4.6 Hz, 1H), 3.97 (m, 1H), 3.76−3.67 (m, 2H), 3.60 (dd, J = 10.1, 10.1 Hz, 1H), 2.75 (m, 1H), 2.58−2.39 (m, 2H), 2.20 (m, 1H), 1.74 (dddd, J = 14.2, 10.6, 3.7, 3.7 Hz, 1H), 1.58 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 140.5, 132.9, 131.3, 128.3 (2C), 126.15, 126.12 (2C), 113.7, 101.4, 79.8, 70.4, 63.8, 33.5, 29.5, 22.1; HRMS (ESI) calcd for $C_{18}H_{22}O_3Na$ [(M + Na)$^+$] 309.1461, found 309.1466.



4a-c,h,k **39a-c,h,k**

General Procedure for Nucleophilic Alkynylation of 4a−c, 4h, and 4k.



39a

To a solution of ethynylbenzene (0.012 mL, 0.11 mmol) in toluene (0.4 mL) at 0 °C was added n-BuLi (1.6 M solution in hexanes, 0.064 mL, 0.11 mmol), and the resultant solution was stirred at 0 °C

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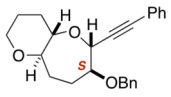
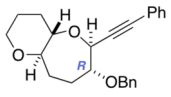
for 30 min. To the reaction mixture were added CH_2Cl_2 (0.4 mL) and Me_2AlCl (1.0 M solution in hexanes, 0.11 mL, 0.11 mmol) at 0 °C, and the resultant solution was stirred at room temperature for 30 min. To the resultant solution was added a solution of sulfone **4a** (28.1 mg, 0.0751 mmol) in CH_2Cl_2 (0.3 mL), and the resultant mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5% EtOAc/hexanes) gave alkynylated product **39a** (20.3 mg, 81%, dr 3:1) as a colorless oil. The following data were collected as a 3:1 mixture of diastereomers: $[\alpha]_D^{24}$ −32.0 (*c* 1.00, $CHCl_3$); IR (film) 2932, 2857, 1454, 1373, 1283, 1098 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.47−7.45 (m, 3/2H), 7.44−7.40 (m, 3/2H), 7.36−7.27 (m, 7H), 5.46 (s, 3/4H), 5.45 (s, 1/4H), 4.80 (dd, *J* = 5.9, 4.1 Hz, 1/4H), 4.65 (dd, *J* = 11.0, 6.8 Hz, 3/4H), 4.31 (dd, *J* = 11.0, 5.5 Hz, 1/4H), 4.29 (dd, *J* = 11.0, 5.5 Hz, 3/4H), 3.89 (m, 3/4H), 3.74−3.51 (m, 9/4H), 2.30−2.21 (m, 2H), 2.14 (m, 3/4H), 1.96−1.78 (m, 2H), 1.63−1.50 (m, 9/4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.8 (1/4C), 131.83 (3/4C), 131.76 (2C), 128.9, 128.4, 128.3 (5C), 128.2, 126.1 (2C), 122.5, 100.8, 88.8 (1/4C), 84.9 (1/4C), 81.6 (1/4C), 81.1 (3/4C), 69.9 (3/4C), 69.3 (1/4C), 67.7 (3/4C), 66.6 (3/4C), 36.1 (3/4C), 35.9 (1/4C), 35.4 (3/4C), 34.5 (1/4C), 19.6 (3/4C), 18.6 (1/4C); HRMS (ESI) calcd for $C_{22}H_{22}O_3Na$ [(M + Na)$^+$] 357.1461, found 357.1467.



39b

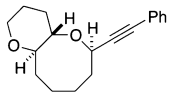
39b (isolated and characterized as a 7:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{24}$ +11.2 (*c* 1.00, $CHCl_3$); IR (film) 2938, 2859, 1490, 1442, 1086 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 7.52−7.49 (m, 2H), 7.44−7.41 (m, 2H), 7.36−7.32 (m, 2H), 7.29−7.22 (m, 3H), 7.17 (m, 1H), 5.30 (d, *J* = 5.0 Hz, 1H), 4.63 (d, *J* = 11.9 Hz, 1H), 4.46 (d, *J* = 11.9 Hz, 1H), 4.01 (dd, *J* = 6.4, 5.5 Hz, 1H), 3.91 (ddd, *J* = 10.6, 9.7, 5.0 Hz, 1H), 3.82 (m, 1H), 3.26 (ddd, *J* = 12.4, 10.1, 3.1 Hz, 1H), 3.08 (m, 1H), 2.03−1.98 (m, 2H), 1.86−1.80 (m, 2H), 1.69−1.60 (m, 2H), 1.55 (m, 1H), 1.29 (dddd, *J* = 12.8, 12.8, 11.0, 4.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 137.7, 136.6, 131.8, 131.0 (2C), 128.7 (2C), 128.3 (2C), 127.8 (2C), 127.71, 127.66, 126.5, 91.9, 80.3, 78.8, 72.0, 71.5, 67.3, 31.5, 26.7, 25.1, 23.8; HRMS (ESI) calcd for $C_{24}H_{26}O_3Na$ [(M + Na)$^+$] 385.1774, found 385.1783.



39c

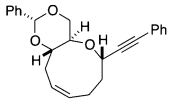
39c (isolated and characterized as a 6:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{24}$ −6.2 (*c* 1.00, $CHCl_3$); IR (film) 2936, 2855, 1481, 1396, 1089 cm^{-1}; ^1H NMR (600 MHz, C_6D_6, major diastereomer) δ 7.68−7.66 (m, 2H), 7.43−7.41 (m, 2H), 7.19−7.15 (m, 3H), 7.12−7.06 (m, 2H), 7.00 (m, 1H), 5.18 (d, *J* = 5.0 Hz, 1H), 4.36 (d, *J* = 11.9 Hz, 1H), 4.20 (d, *J* = 11.9 Hz, 1H), 4.17 (ddd, *J* = 10.6, 9.7, 5.0 Hz, 1H), 3.67 (m, 1H), 3.60 (dd, *J* = 6.4, 5.5 Hz, 1H), 3.13 (ddd, *J* = 10.5, 9.1, 5.5 Hz, 1H), 3.03 (ddd, *J* = 11.5, 11.5, 2.3 Hz, 1H), 2.06 (dddd, *J* = 13.7, 13.7, 10.6, 2.8 Hz, 1H), 1.99 (m, 1H), 1.88 (m, 1H), 1.63 (m, 1H), 1.38 (ddd, *J* = 14.2, 14.2, 2.3 Hz, 1H), 1.36−1.23 (m, 2H), 1.08 (m, 1H); ^{13}C NMR (150 MHz, C_6D_6, major diastereomer) δ 138.3, 138.2, 130.8 (2C), 128.9 (2C), 128.6 (2C), 128.5, 128.3 (2C), 126.4, 92.5, 91.9, 83.6, 80.9, 79.3, 72.2, 72.0, 67.2, 32.0, 27.4, 25.4, 23.9; HRMS (ESI) calcd for $C_{24}H_{26}O_3Na$ [(M + Na)$^+$] 385.1774, found 385.1776.

39h (dr >20:1): colorless crystals; mp 79−82 °C; $[\alpha]_D^{24}$ +33.4 (*c* 1.00, $CHCl_3$); IR (film) 2931, 2853, 1442, 1280, 1096 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.40−7.37 (m, 2H), 7.31−7.28 (m, 3H), 4.61



39h

(dd, *J* = 11.9, 2.8 Hz, 1H), 3.86 (m, 1H), 3.63 (ddd, *J* = 10.5, 9.6, 4.6 Hz, 1H), 3.31 (ddd, *J* = 11.5, 11.5, 2.8 Hz, 1H), 3.03 (ddd, *J* = 10.1, 10.1, 4.1 Hz, 1H), 2.20 (m, 1H), 2.14 (m, 1H), 1.91 (dddd, *J* = 14.7, 10.5, 4.1, 1.9 Hz, 1H), 1.84−1.56 (m, 7H), 1.54−1.42 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 131.6 (2C), 128.3 (2C), 128.2, 122.8, 88.9, 84.2, 81.7, 72.5, 69.2, 67.9, 32.5, 30.8, 30.4, 26.2, 25.8, 21.4; HRMS (ESI) calcd for $C_{18}H_{22}O_2Na$ [(M + Na)$^+$] 293.1512, found 293.1518.



39k

39k (isolated and characterized as a 1.2:1 mixture of diastereomers): colorless oil; $[\alpha]_D^{24}$ −4.2 (*c* 1.00, $CHCl_3$); IR (film) 2940, 2851, 1432, 1369, 1090 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.63−7.58 (m, 2H), 7.51−7.48 (m, 1H), 7.38−7.36 (m, 1H), 7.20−7.15 (m, 29/11H), 7.13−7.02 (m, 26/11H), 7.00−6.96 (m, 1H), 5.67−5.59 (m, 1H), 5.49 (ddd, *J* = 10.6, 10.6, 6.9 Hz, 5/11H), 5.34 (ddd, *J* = 9.7, 9.7, 7.3 Hz, 6/11H), 5.26 (s, 5/11H), 5.23 (s, 6/11H), 5.11 (dd, *J* = 12.4, 4.6 Hz, 6/11H), 5.03 (dd, *J* = 10.5, 4.6 Hz, 5/11H), 4.52 (dd, *J* = 9.6, 3.7 Hz, 6/11H), 4.02 (dd, *J* = 10.5, 5.0 Hz, 5/11H), 3.86 (ddd, *J* = 9.6, 9.6, 4.6 Hz, 6/11H), 3.53 (ddd, *J* = 9.2, 3.7, 3.7 Hz, 5/11H), 3.49−3.44 (m, 1H), 3.40 (dd, *J* = 10.6, 10.6 Hz, 5/11H), 3.29 (ddd, *J* = 14.2, 9.6, 4.6 Hz, 6/11H), 2.81 (ddd, *J* = 13.3, 10.6, 2.7 Hz, 6/11H), 2.64 (ddd, *J* = 13.8, 9.2, 4.1 Hz, 5/11H), 2.33 (ddd, *J* = 13.3, 7.8, 5.0 Hz, 6/11H), 2.22 (ddd, *J* = 13.8, 6.4, 3.7 Hz, 5/11H), 2.11 (m, 6/11H), 2.00 (m, 5/11H), 1.85−1.58 (m, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 139.0 (5/11C), 138.8 (6/11C), 136.5 (6/11C), 134.6 (12/11C), 133.4 (5/11C), 133.3 (6/11C), 132.9 (5/11C), 132.0 (10/11C), 129.5 (10/11C), 129.08 (12/11C), 129.07 (12/11C), 128.81 (6/11C), 128.78 (5/11C), 128.3 (6/11C), 128.22 (10/11C), 128.21 (12/11C), 127.6 (5/11C), 126.69 (10/11C), 126.65 (6/11C), 126.4 (5/11C), 101.6, 93.1 (5/11C), 86.3 (6/11C), 80.6 (5/11C), 79.9 (6/11C), 79.3, 71.0 (5/11C), 70.2 (6/11C), 35.2 (6/11C), 32.2 (5/11C), 31.2 (5/11C), 28.5 (6/11C), 24.6 (5/11C), 22.0 (6/11C); HRMS (ESI) calcd for $C_{22}H_{24}O_5SNa$ [(M + Na)$^+$] 423.1237, found 423.1233.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Stereochemical assignment of compounds **2a−k**, **3a−k**, **4a−c**, **4h**, **4k**, **36a−k**, **37a−c**, **37h**, **37k**, **38a−c**, **38h**, **38k**, **39a−c**, **39h**, and **39k**. Copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel/Fax: +81-22-217-6214. E-mail: hfuwa@m.tohoku.ac.jp.

Notes

The authors declare no competing financial interest.

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