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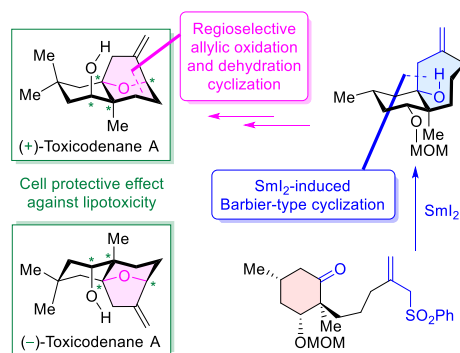
# Asymmetric Total Synthesis of Toxicodenane A by Samarium Iodide-Induced Barbier-Type Cyclization and Its Cell Protective Effect against Lipotoxicity

Keisuke Nishikawa,<sup>\*,†</sup> Koki Kikuta,<sup>†</sup> Tomoki Tsuruta,<sup>†</sup> Hitoshi Nakatsukasa,<sup>†</sup> Sho Sugahara,<sup>‡</sup> Shinji Kume,<sup>‡</sup> and Yoshiki Morimoto<sup>\*,†</sup>

<sup>†</sup>Department of Chemistry, Graduate School of Science, Osaka City University, Sumiyoshi-ku, Osaka 558-8585, Japan.

<sup>‡</sup>Department of Medicine, Shiga University of Medical Science, Tsukinowacho, Seta, Otsu, Shiga 520-2192, Japan.

Supporting Information Placeholder

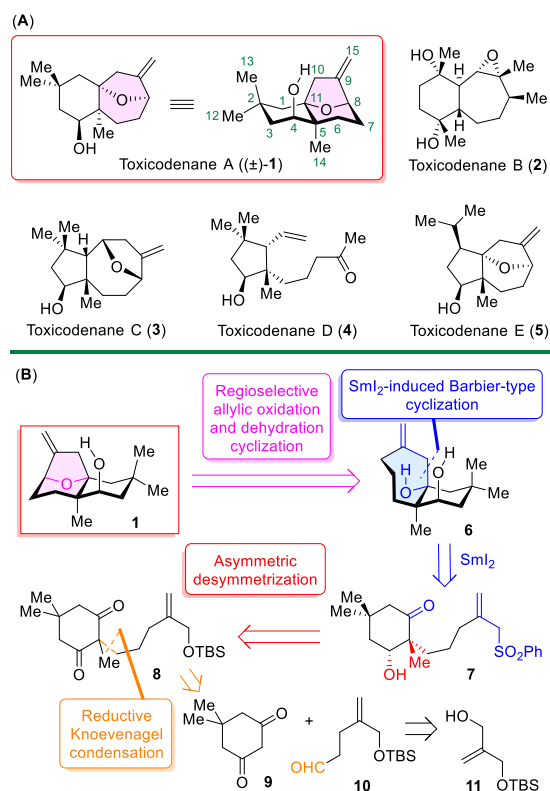


**ABSTRACT:** The asymmetric total synthesis of toxicodenane A, a sesquiterpenoid expected to be promising for diabetic nephropathy, was achieved. In the synthesis, a samarium iodide (SmI<sub>2</sub>)-induced Barbier-type cyclization and a regio- and stereoselective allylic oxidation followed by a dehydration cyclization were employed as key steps. Further, the first asymmetric syntheses of both enantiomers were accomplished using the abovementioned synthetic strategy. Finally, the synthetic compounds significantly inhibited lipotoxicity-mediated inflammatory and fibrotic responses in mouse renal proximal tubular cells.

Toxicodenane A ((±)-**1**, [Scheme 1A](#)) is a tricyclic sesquiterpenoid isolated from the dried resin of the lacquer tree, *Toxicodendron vernicifluum*, by Cheng et al. in 2013, along with toxicodenanes B (**2**) and C (**3**).<sup>1</sup> Further, Cheng et al. isolated two new sesquiterpenoids; toxicodenanes D (**4**) and E (**5**), from the same resin in 2015.<sup>2</sup> Natural products **2** and **3** could significantly inhibit the overproduction of fibronectin, collagen IV, and interleukin-6 in high-glucose-induced mesangial cells in a dose- and time- dependent manner, showing their potential in diabetic nephropathy. However, the bioactivity of toxicodenane A has not been reported yet. The natural product (±)-**1** has a condensed bicyclic framework and a unique tricyclic skeleton with a bridged ether moiety and an *exo*-olefin moiety. Its characteristic tricyclic skeleton is unprecedented among other sesquiterpenoids and attractive from the perspective of synthetic chemistry. However it is confirmed via an X-ray analysis that natural toxicodenane A is isolated as a racemic compound from nature.<sup>1</sup> Therefore, the quantitative supply of optically active toxicodenane A, which cannot be obtained from nature, was demanded to investigate its

bioactivity. Previously, the racemic total synthesis of toxicodenane A was achieved by the ring-closing metathesis of a diene compound by Ito et al. in 2017.<sup>3a</sup> In 2020, efforts toward its total synthesis using an intramolecular oxidopyrylium-based [5+2] cycloaddition were reported by Mitchell et al.<sup>3b</sup> And recently, the first enantioselective total synthesis of (+)-toxicodenane A has been reported through a Lewis acid-mediated intramolecular transacetalation followed by a Prins cascade reaction by Han et al.<sup>3c</sup> However, an asymmetric synthesis of (-)-toxicodenane A and the evaluation of biological activities using a synthetic sample provided by its asymmetric synthesis have not been reported. In this communication, our group reports the asymmetric total synthesis of both enantiomers of toxicodenane A in 15 steps from the known compound by samarium iodide (SmI<sub>2</sub>)-induced Barbier-type cyclization and regio- and stereoselective allylic oxidation, followed by dehydration cyclization, to construct the characteristic tricyclic framework. In addition, cell protective effects against lipotoxicity with both enantiomers of toxicodenane A were also evaluated.

### Scheme 1. (A) Chemical Structures of Toxicodenanes and (B) Retrosynthetic Analysis of Toxicodenane A (1)



Our retrosynthetic analysis of toxicodenane A (**1**) is shown in [Scheme 1B](#). A bridged ether moiety in **1** would be constructed through the allylic oxidation of bicyclic product **6**, followed by dehydration cyclization. A seven-membered ring with an *exo*-olefin moiety in **6** would be constructed by the SmI<sub>2</sub>-induced Barbier-type cyclization<sup>4</sup> of allyl sulfone **7**. The cyclization precursor **7** would be synthesized by the asymmetric desymmetrization of diketone **8**, and **8** would be synthesized by the reductive Knoevenagel condensation between 5,5-dimethyl-1,3-cyclohexanedione (**9**) and aldehyde **10** using Hantzsch's ester. Compound **10** would be converted from the known silyl ether **11** in 2 steps, including the Claisen rearrangement.

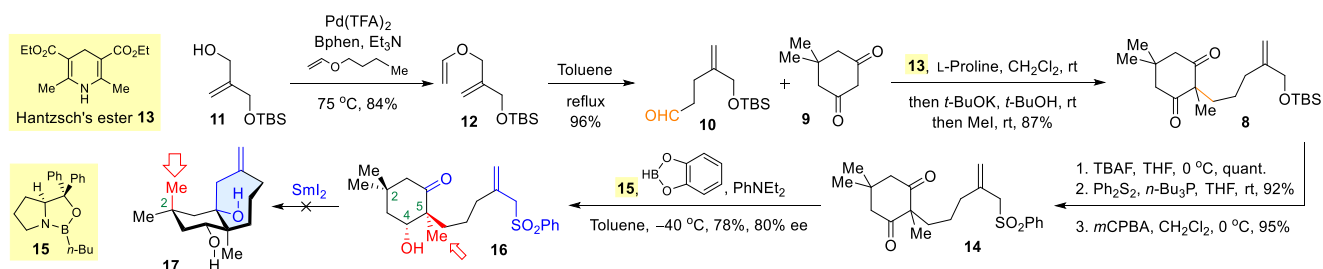
The total synthesis commenced with the known silyl ether **11** derived from commercially available 2-methylene-1,3-propanediol ([Scheme 2](#)).<sup>5</sup> Vinylation of **11**, using Pd(TFA)<sub>2</sub> and bathophenanthroline (Bphen), and the following Claisen rearrangement, provided the desired aldehyde **10**.<sup>6</sup> Diketone **8** was synthesized by the one-pot method including the reductive Knoevenagel condensation

between the commercially available 5,5-dimethyl-1,3-cyclohexanedione (**9**) and **10** using Hantzsch's ester **13**,<sup>7</sup> followed by methylation using iodomethane (MeI). Sulfone **14** was obtained from **8** via the 3-step reaction sequence: (1) deprotection of a *tert*-butyldimethylsilyl group, (2) sulfidation of a primary hydroxy group, and (3) sulfonylation using *m*-chloroperoxybenzoic acid (*m*CPBA). Asymmetric desymmetrization of **14** by Corey-Bakshi-Shibata reduction using a chiral oxazaborolidine catalyst **15**<sup>8</sup> afforded cyclization precursor **16** as a single diastereomer in 78% and 80% ee.<sup>9a</sup> The synthesized **16** had a stereochemistry that was different from what Corey et al. reported and we envisioned,<sup>8,9b,c</sup> and thus, the next cyclization was challenging. We examined various conditions for the SmI<sub>2</sub>-induced radical cyclization<sup>4</sup> of **16**,<sup>9d</sup> but unfortunately, the by-product was obtained as a major product without the desired cyclic product **17**. This is presumably because the Barbier-type cyclization was strongly affected by the steric hindrance of the upper methyl group in the C2 position.

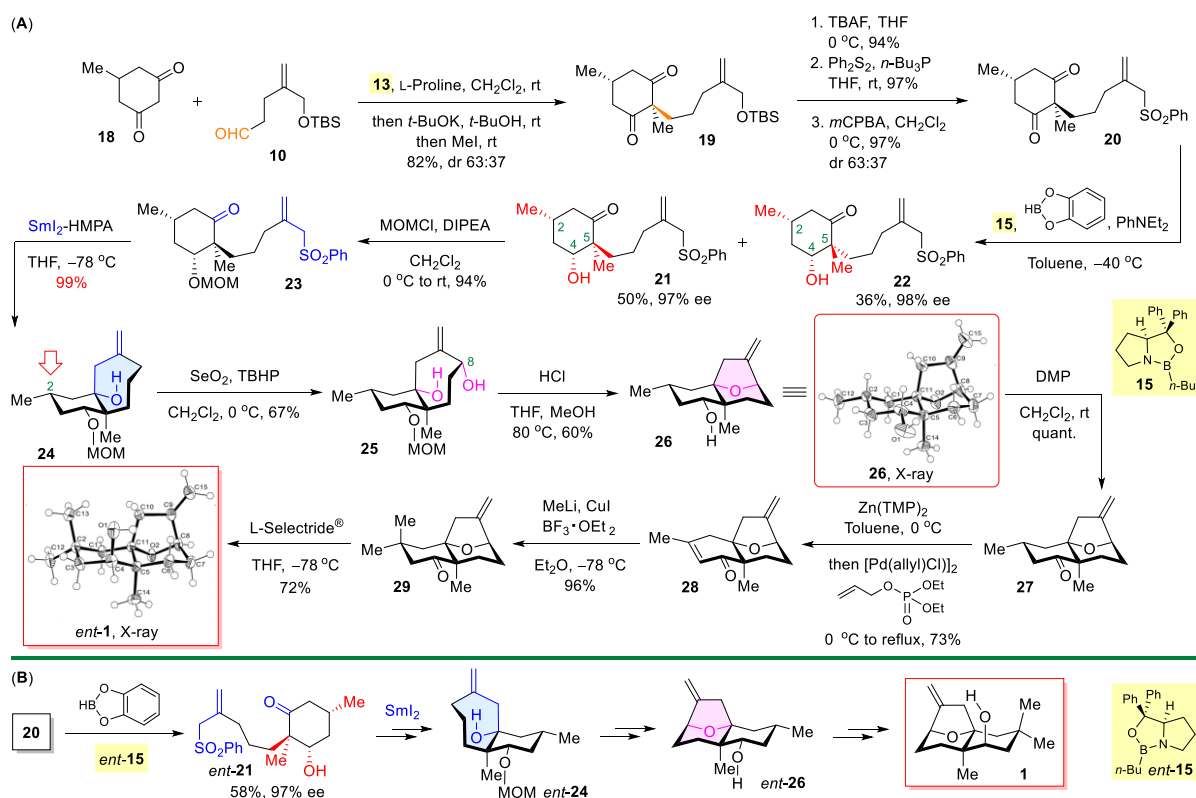
We have revised the synthetic plan of toxicodenane A. Using the commercially available 5-methyl-1,3-cyclohexanedione (**18**) with one less methyl group than **9**, we would synthesize *ent*-**1** via the introduction of a methyl group after the construction of the bicyclic framework by the Barbier-type cyclization ([Scheme 3A](#)). According to the same synthetic pathway as shown in [Scheme 2](#), the reductive Knoevenagel condensation<sup>7</sup> between the synthesized **10** and **18** followed by the methylation, provided an inseparable mixture of diastereomers **19** in dr 63:37. After the conversion of a siloxy group to a sulfonyl group, the asymmetric desymmetrization of **20** yielded the enantiopure alcohol **21** (50%, 97% ee), with diastereomer **22** as a minor product (36%, 98% ee).<sup>9a,b,c</sup> The subsequent synthesis proceeded using **21** obtained as a major product. After the methoxymethyl (MOM) protection of a secondary hydroxy group, the bicyclic product **24** with a *cis* configuration was stereoselectively synthesized through SmI<sub>2</sub>-induced Barbier-type cyclization; 99% yield was obtained.<sup>4,9e</sup> Diastereoselectivity in the cyclization was explained by considering chair-like  $\pi$ -allyl samarium species as the reaction intermediate.<sup>10</sup>

Next, we tried to construct the bridged ether moiety in toxicodenane A ([Scheme 3A](#)). The regio- and stereoselective allylic oxidation of **24** using SeO<sub>2</sub><sup>11</sup> afforded diol **25** as a major product in 67% yield, with a C8 epimer of **25** and the C8 hemiketal as minor products (2% and 9%, respectively).<sup>9f</sup> Heating **25** under the acidic conditions, tricyclic skeleton **26** with the desired bridged ether moiety was obtained by the dehydration cyclization. The relative configuration of **26** was determined through the X-ray

### Scheme 2. Examination for the Construction of the Bicyclic Skeleton of Toxicodenane A



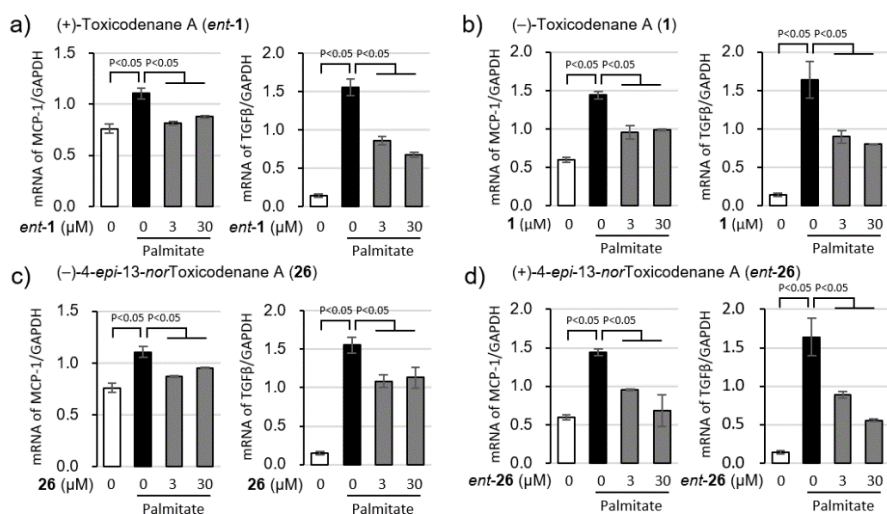
### Scheme 3. Asymmetric Total Syntheses of (A) (+)-Toxicodenane A (*ent-1*) and (B) (-)-Toxicodenane A (**1**)<sup>a</sup>



<sup>a</sup>In ORTEP drawings of **26** and *ent-1*, thermal ellipsoids are drawn at the 50% probability level.

analysis.<sup>9g</sup> Finally, we induced *ent-1* from **26** by the insertion of a methyl group and stereoinversion of a secondary hydroxy group. After the Dess-Martin oxidation of **26**,  $\alpha,\beta$ -unsaturated ketone **28** was obtained via one-step reaction; the formation of zinc enol ether using Zn(TMP)<sub>2</sub>

as the base, followed by the  $\alpha,\beta$ -dehydrogenation utilizing allyl-palladium catalysis.<sup>12</sup> After the nucleophilic conjugate addition of a methyl group to **28**, the asymmetric total synthesis of (+)-toxicodenane A (*ent-1*) was achieved by the



**Figure 1.** The effects of four different compounds on inflammatory and fibrotic responses in the cultured mouse renal proximal tubular cells (RPTECs) exposed to palmitate, a lipotoxic stimulus. a–d) mRNA expression levels of MCP-1 (an inflammatory marker) and TGFβ (a fibrotic marker) in the cultured RPTECs exposed to palmitate (150 μM) with/without the pre-treatment of the indicated compounds; a) (+)-toxicodenane A (*ent-1*), b) (-)-toxicodenane A (**1**), c) (-)-4-*epi*-13-nortoxicodenane A (**26**), and d) (+)-4-*epi*-13-nortoxicodenane A (*ent-26*). Data are expressed as mean ± SE. MCP-1, monocyte chemoattractant protein-1; TGFβ, transforming growth factor-β.

stereoselective reduction of **29** using L-Selectride®. The spectral data of synthetic *ent*-**1** were identical to those of the natural sample. Furthermore, the relative stereochemistry of *ent*-**1** was confirmed by X-ray diffraction analysis.<sup>9g</sup> The asymmetric total synthesis of *ent*-**1** was elaborated in 15 steps with 6% overall yield from **11**. As shown in Scheme 3B, we also synthesized the enantiomer (-)-toxicodenane A (**1**) from sulfone **20** by the same synthetic procedure; the asymmetric desymmetrization of **20** using *ent*-**15** followed by the SmI<sub>2</sub>-induced Barbier-type cyclization.

Finally, a biological significance and a therapeutic potency of synthetic (+)-toxicodenane A (*ent*-**1**) and (-)-toxicodenane A (**1**) were examined along with the synthetic intermediates; (-)-4-*epi*-13-*nortoxicodenane* A (**26**) and (+)-4-*epi*-13-*nortoxicodenane* A (*ent*-**26**) as shown in Figure 1. Because lipotoxicity is focused as a pathological factor in obesity-related and diabetic kidney diseases, the effects of these compounds were examined in the cultured renal proximal tubular cells (RPTECs) exposed to palmitate, a saturated fatty acid that can cause cell-toxicity.<sup>13</sup> The palmitate stimulation significantly increased mRNA expression levels of monocyte chemoattractant protein-1 (MCP-1), an inflammatory cytokine, and transforming growth factor-β (TGFβ), a fibrotic cytokine, which were significantly inhibited by the pre-treatment of each compound *ent*-**1**, **1**, **26**, or *ent*-**26**. Thus, all four compounds protect RPTECs against lipotoxicity-mediated inflammation and fibrosis, and thus may serve as a novel therapeutic agent against lipotoxicity-related kidney diseases. These results clearly suggest that the absolute configuration of toxicodenane A has no effect on the biological activity.

In summary, the first asymmetric syntheses of both enantiomers of toxicodenane A were completed by the SmI<sub>2</sub>-induced Barbier-type cyclization and regio- and stereoselective allylic oxidation followed by the dehydration cyclization to construct the characteristic tricyclic framework. Furthermore, it was revealed that both enantiomers have almost the same cell protective effect against lipotoxicity. Further application of the synthetic strategy to the synthesis of other toxicodenanes is currently under investigation.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI.

All experimental procedures, the spectroscopic data, and copies of <sup>1</sup>H-, <sup>13</sup>C-, and <sup>19</sup>F-NMR spectra (PDF).

### Accession Codes

CCDC 2036421–2036423 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.ca-m.ac.uk/data\\_request/cif](http://www.ccdc.ca-m.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

## AUTHOR INFORMATION

### Corresponding Authors

**Keisuke Nishikawa** – Department of Chemistry, Graduate School of Science, Osaka City University, Sumiyoshi-ku, Osaka 558-8585, Japan; [orcid.org/0000-0002-3170-8023](https://orcid.org/0000-0002-3170-8023); Email: [kni-shi@osaka-cu.ac.jp](mailto:kni-shi@osaka-cu.ac.jp)

**Yoshiki Morimoto** – Department of Chemistry, Graduate School of Science, Osaka City University, Sumiyoshi-ku, Osaka 558-8585, Japan; [orcid.org/0000-0002-4770-3091](https://orcid.org/0000-0002-4770-3091); Email: [morimoto@sci.osaka-cu.ac.jp](mailto:morimoto@sci.osaka-cu.ac.jp)

### Authors

**Koki Kikuta** – Department of Chemistry, Graduate School of Science, Osaka City University, Sumiyoshi-ku, Osaka 558-8585, Japan

**Tomoki Tsuruta** – Department of Chemistry, Graduate School of Science, Osaka City University, Sumiyoshi-ku, Osaka 558-8585, Japan

**Hitoshi Nakatsukasa** – Department of Chemistry, Graduate School of Science, Osaka City University, Sumiyoshi-ku, Osaka 558-8585, Japan

**Sho Sugahara** – Department of Medicine, Shiga University of Medical Science, Tsukinowacho, Seta, Otsu, Shiga 520-2192, Japan

**Shinji Kume** – Department of Medicine, Shiga University of Medical Science, Tsukinowacho, Seta, Otsu, Shiga 520-2192, Japan

### Notes

The authors declare no competing financial interest.

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## REFERENCES

- (1) He, J.-B.; Luo, J.; Zhang, L.; Yan, Y.-M.; Cheng, Y.-X. Sesquiterpenoids with New Carbon Skeletons from the Resin of *Toxicodendron vernicifluum* as New Types of Extracellular Matrix Inhibitors. *Org. Lett.* **2013**, *15*, 3602–3605.
- (2) He, J.-B.; Lu, Q.; Cheng, Y.-X. Two New Sesquiterpenes from the Resin of *Toxicodendron vernicifluum*. *Helv. Chim. Acta* **2015**, *98*, 1004–1008.
- (3) (a) Kobayashi, T.; Yamanoue, K.; Abe, H.; Ito, H. Diastereoselective Total Synthesis of (±)-Toxicodenane A. *Eur. J. Org. Chem.* **2017**, 6693–6699. (b) Grabowski, J. P.; Ferrence, G. M.; Mitchell, T. A. Efforts toward the Total Synthesis of (±)-Toxicodenane A Utilizing an Oxidopyrylium-Based [5+2] Cycloaddition of a Silicon-Tethered BOC-Pyranone. *Tetrahedron Lett.* **2020**, *61*, 152324–152326. (c) Qin, X.-L.; Wu, G.-J.; Han, F.-S. Enantioselective Total Synthesis and Absolute Configuration Assignment of (+)-Toxicodenane A. *Org. Lett.* **2021**, *23*, 8570–8574.
- (4) (a) Kan, T.; Nara, S.; Ito, S.; Matsuda, F.; Shirahama, H. Stereoselective Cyclization Mediated by Samarium(II) Iodide Using Allyl Sulfides and Sulfones as Ketyl Radical Acceptors. *J. Org. Chem.* **1994**, *59*, 5111–5113. (b) Claydent, J.; Julia, M. Homoallylic Alcohols from Samarium Diiodide-Mediated Coupling of Allylic Sulfones with Carbonyl Compounds. *J. Chem. Soc., Chem. Commun.* **1994**, 2261–2262. (c) Tamiya, H.; Goto, K.; Matsuda, F. Efficient Medium-Ring Cyclization under Non-High-Dilution Conditions Using SmI<sub>2</sub>. *Org. Lett.* **2004**, *6*, 545–547.
- (5) Senter, T. J.; Fadeyi, O. O.; Lindsley, C. W. Enantioselective Total Synthesis of (+)-Amabiline. *Org. Lett.* **2012**, *14*, 1869–1871.
- (6) (a) Bosch, M.; Schlaf, M. Synthesis of Allyl and Alkyl Vinyl Ethers Using an in Situ Prepared Air-Stable Palladium Catalyst.



Efficient Transfer Vinylation of Primary, Secondary, and Tertiary Alcohols. *J. Org. Chem.* **2003**, *68*, 5225–5227. (b) Marcé, P.; Díaz, Y.; Matheu, M. I.; Castellón, S. Synthesis of D- and L-Carbocyclic Nucleosides via Rhodium-Catalyzed Asymmetric Hydroacylation as the Key Step. *Org. Lett.* **2008**, *10*, 4735–4738.

(7) (a) Ramachary, D. B.; Kishor, M. Organocatalytic Sequential One-Pot Double Cascade Asymmetric Synthesis of Wieland–Miescher Ketone Analogues from a Knoevenagel/Hydrogenation/Robinson Annulation Sequence: Scope and Applications of Organocatalytic Biomimetic Reductions. *J. Org. Chem.* **2007**, *72*, 5056–5068. (b) Pichette, S.; Winter, D. K.; Lessard, J.; Spino, C. Converting Cycloalkanones into *N*-Heterocycles: Formal Synthesis of (–)-Gephyrotoxin 287C. *J. Org. Chem.* **2013**, *78*, 12532–12544. (c) Pasha, M. A.; Krishna, A. V.; Ashok, E.; Ramachary, D. B. Organocatalytic Reductive Propargylation: Scope and Applications. *J. Org. Chem.* **2019**, *84*, 15399–15416.

(8) (a) Yeung, Y.-Y.; Chein, R.-J.; Corey, E. J. Conversion of Torgov's Synthesis of Estrone into a Highly Enantioselective and Efficient Process. *J. Am. Chem. Soc.* **2007**, *129*, 10346–10347. (b) Chein, R.-J.; Yeung, Y.-Y.; Corey, E. J. Highly Enantioselective Oxazaborolidine-Catalyzed Reduction of 1,3-Dicarbonyl Compounds: Role of the Additive Diethylaniline. *Org. Lett.* **2009**, *11*, 1611–1614. (c) Kobayashi, T.; Tomita, Y.; Kawamoto, Y.; Ito, H. Highly Stereocontrolled Total Synthesis of Secodolastane Diterpenoid Isolinearol. *Org. Biomol. Chem.* **2020**, *18*, 7316–7320.

(9) (a) For modified Mosher's analyses of **16**, **21**, and **22**, see the [Supporting Information \(SI\)](#). Each enantiomeric excess was determined via the <sup>19</sup>F-NMR data of MTPA esters. (b) The relative configurations of compounds **16**, **19**, **21**, **22**, **24**, and **25** were unambiguously determined by the NOESY spectra; see the [SI](#). (c) For diastereo- and enantioselectivity in the asymmetric desymmetrization of sulfones **14** and **20**, see the [SI](#). (d) For examination of the SmI<sub>2</sub>-initiated Barbier-type cyclization of **16**, see the [SI](#). We also examined the cyclization of a MOM protection

form of **16**, but the desired cyclic product was not obtained. (e) For the SmI<sub>2</sub>-initiated cyclization of sulfones **21** and **22** and their relative configurations of the obtained bicyclic products, see the [SI](#). (f) For stereoselectivity in the allylic oxidation of bicyclic product **24**, see the [SI](#). (g) For X-ray crystallographic analyses of the *p*-bromobenzoyl form of the cyclic product synthesized from **22** (CCDC 2036423), **26** (CCDC 2036421), and *ent*-**1** (CCDC 2036422), see the [SI](#).

(10) It is expected that the SmI<sub>2</sub>-induced Barbier-type cyclization takes place through the organo-samarium addition pathway as shown in ref. (4c). For the diastereoselectivity to give **24**, see the [SI](#). However, it is also likely that the cyclization proceeds through the pathway via the ketyl radical, or both. The reaction mechanism is currently under investigation.

(11) (a) Mehta, G.; Murthy, A. S. K. The First Total Synthesis of the Novel Triquinane Natural Products Pleurotellol and Pleurotellic Acid. *Tetrahedron Lett.* **2003**, *44*, 5243–5246. (b) Valente, C.; Organ, M. G. Assessing Synthetic Strategies: Total Syntheses of (±)-Neodolabellane-Type Diterpenoids. *Chem. - Eur. J.* **2008**, *14*, 8239–8245. (c) Liang, Y.; Jiang, X.; Fu, X.-F.; Ye, S.; Wang, T.; Yuan, J.; Wang, Y.; Yu, Z.-X. Total Synthesis of (+)-Asteriscanolide: Further Exploration of the Rhodium(I)-Catalyzed [(5+2)+1] Reaction of Ene-Vinylcyclopropanes and CO. *Chem. - Asian J.* **2012**, *7*, 593–604. (d) Pan, Z.; Zheng, C.; Wang, H.; Chen, Y.; Li, Y.; Cheng, B.; Zhai, H. Total Synthesis of (±)-Sculponeatin N. *Org. Lett.* **2014**, *16*, 216–219.

(12) Huang, D.; Zhao, Y.; Newhouse, T. R. Synthesis of Cyclic Enones by Allyl-Palladium-Catalyzed α,β-Dehydrogenation. *Org. Lett.* **2018**, *20*, 684–687.

(13) Tanaka, Y.; Kume, S.; Araki, H.; Nakazawa, J. Chin-Kanasaki, M.; Araki, S.; Nakagawa, F.; Koya, D.; Haneda, M.; Maegawa, H.; Uzu, T. 1-Methylnicotinamide Ameliorates Lipotoxicity-Induced Oxidative Stress and Cell Death in Kidney Proximal Tubular Cells. *Free Radic. Biol. Med.* **2015**, *89*, 831–841.