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# Enantioselective Total Synthesis of (+)-Ophiobolin A

**Kazuhiro Tsuna, Naoyoshi Noguchi, and Masahisa Nakada*[a]**

**Abstract:** The enantioselective total synthesis of (+)-ophiobolin A is described. This total synthesis features the construction of the spiro CD ring of (+)-ophiobolin A through a stereoselective intramolecular Hosomi–Sakurai cyclization reaction, the joining of the A ring to the CD ring by using a reaction reported by Utimoto, and the construction of the ophiobolin eight-membered carbocyclic ring through ring-closing metathesis (RCM), which was performed for the first time in this study. This successful RCM reaction required the use of a substrate that contained either a benzyloxy or a methoxymethoxy group at the C5 position and either an isopropenyl group or its hydroxylated form at the C6 position.

**Keywords:** cyclization · natural products · ophiobolin A · spiro compounds · total synthesis

## Introduction

The isolation of a number of terpenoids with a 5-8-5-membered carbocyclic ring system, such as ophiobolins (Figure 1) and fusicoccins, has been reported. These compounds have attracted considerable attention as synthetic targets[1,2] because of their complex structures and interesting biological activities.[3] In 1958, Ishibashi and Nakamura isolated (+)-ophiobolin A (Figure 1) as the first naturally occurring sesterterpene from a culture broth of the pathogenic plant fungus *Ophiobolus miyabeanus*.[4] The absolute structure of (+)-ophiobolin A was elucidated by Nozoe et al. in 1965 by X-ray crystallographic analysis of its derivative.[5] (+)-Ophiobolin A contains a unique 5-8-5-5 tetracyclic ring system, including a tetrahydrofuran ring, which contains a total of eight stereogenic centers. The five-membered A ring incorporates three successive stereogenic centers, with a chiral tertiary alcohol and two contiguous stereogenic centers at the *cis*-fused AB ring junction. The CD ring system is a spirocyclic ether with a total of five stereogenic centers, four of which are successive and one of which is an all-carbon quaternary stereogenic center at the *trans*-fused BC ring junction. Recent biological studies have shown that (+)-ophiobolin A induces apoptotic cell-death in the L1210 cell-line,[6] inhibits calmodulin-activated cyclic nucleotide phosphodiesterase, and also shows cytotoxicity to cancer cell-lines A-549, Mel-20, and P-335, with $IC_{50}$ values that range from 62.5 to 125 nM.[7]

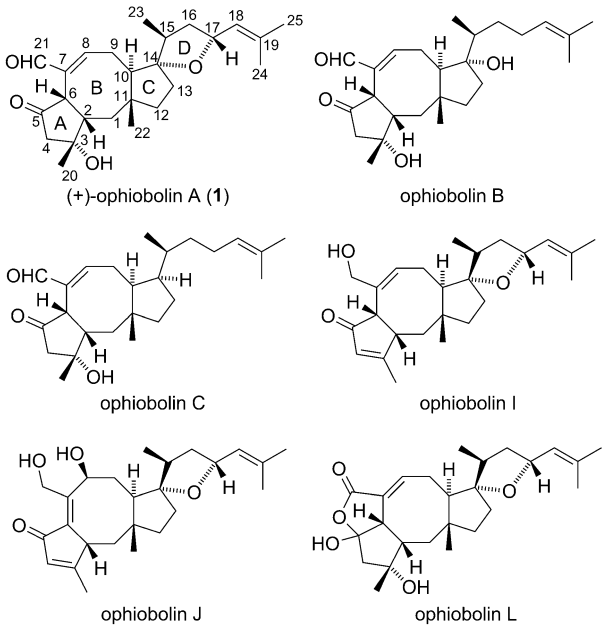


Figure 1. Structures of ophiobolins.

The complex structure and potent bioactivity of (+)-ophiobolin A (**1**) have made it an attractive synthetic target. Several synthetic studies of ophiobolins[2] and total syntheses of related compounds have been reported. However, studies on the total synthesis of ophiobolins have been limited to that of (+)-ophiobolin C, which was reported by Kishi and co-workers,[3c] and there are no other reports on the total synthesis of compound **1**. We recently reported the convergent and enantioselective total synthesis of (+)-ophiobolin A[8] and details of the synthetic sequence that culminates in its total synthesis are reported herein.

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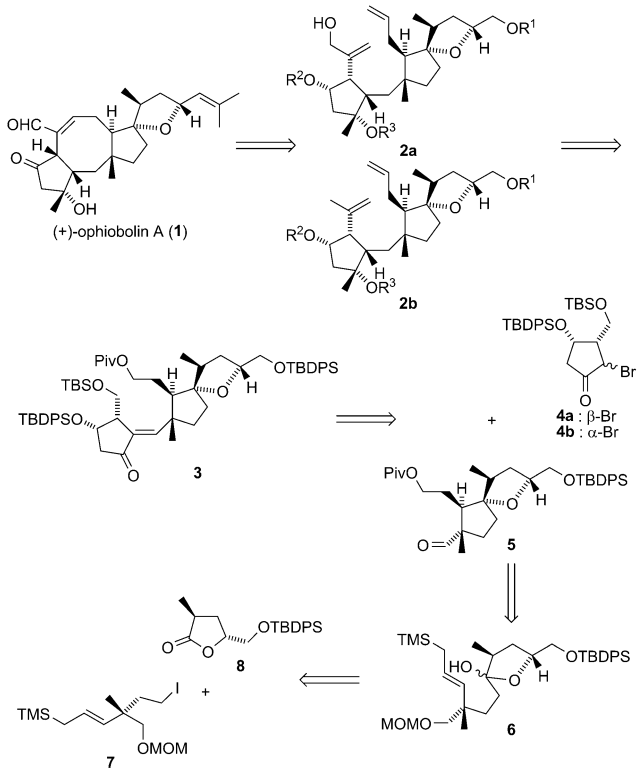
## Results and Discussion

**Retrosynthetic analysis of (+)-ophiobolin A**: To address the difficulties in forming the medium-sized, eight-membered carbocyclic ring in the total synthesis of (+)-ophiobolin A (1), we planned to employ ring-closing metathesis (RCM).[9] The formation of medium-sized, eight-membered carbocyclic rings by using RCM has attracted interest because medium-sized carbocyclic rings are typically difficult to construct, thus posing a synthetic challenge.[10] Indeed, the RCM reaction has become one of the most useful methods for the synthesis of complex natural products; however, the application of RCM reactions for the construction of eight-membered carbocyclic rings in the synthesis of natural products has been limited.[10a,c,d,i] Moreover, the construction of a complex ophiobolin skeleton by employing RCM has never been reported. The adoption of RCM in a late stage of a natural-product synthesis may be challenging, but successful precedents for the formation of relatively simple eight-membered carbocyclic rings by using RCM have encouraged us to implement a RCM reaction in the total synthesis of compound **1**.

Our retrosynthetic analysis of compound **1** is shown in Scheme 1. As mentioned above, we decided to construct the eight-membered B ring by using RCM. Thus, compound **2** was selected as the substrate, which would be derived from enone **3** through stereoselective hydrogenation and methylation. Compound **3** was expected to be prepared by using a stereoselective Reformatsky-type reaction between compounds **4** and **5**, followed by dehydration. Aldehyde **5** was expected to be obtained from an intramolecular Hosomi–Sakurai reaction[11] of allylsilane **6**, which would, in turn, be prepared by a coupling reaction between fragments **7** and **8**.



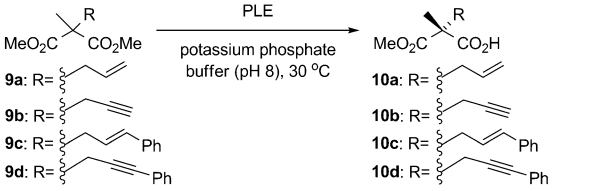

Scheme 1. Retrosynthetic analysis of (+)-ophiobolin A.

**Preparation of fragment 6**: The total synthesis of compound **1** began with the preparation of fragment **7**, which contained an all-carbon quaternary stereogenic center at the C11 position. Although many chiral starting materials are commercially available, there are none that contain a methyl-substituted, all-carbon quaternary stereogenic center. Therefore, we decided to prepare the chiral starting material for the synthesis of compound **7** on a relatively large scale because the total synthesis of compound **1** was envisioned to be a multi-step synthesis.

We elected to prepare the chiral starting material through a biocatalyst-mediated reaction, because it proceeded in aqueous solvent in air, even on a large scale. Enzymatic reactions are valuable catalytic asymmetric reactions and they have been used to promote a wide range of enantioselective transformations in organic synthesis. Specifically, the use of hydrolytic enzymes, lipases, and esterases is especially attractive because these enzymes can be used for a wide range of substrates and they afford high enantioselectivities. Furthermore, these hydrolytic enzymes do not require expensive and unstable co-enzymes. Hence, we started to prepare a new useful chiral building block that contained a methyl-substituted all-carbon quaternary stereogenic center through a pig liver esterase (PLE)-mediated hydrolysis of malonates (**9a–9d**), because malonates that possess such a quaternary carbon can be readily generated by alkylation.

As summarized in Table 1, diesters **9a** (R = allyl) and **9b** (R = propargyl) were quantitatively converted into their corresponding half-esters (**10a** and **10b**, respectively), but their enantioselectivities were unsatisfactory (Table 1, entries 1 and 2). However, diester **9c** (R = cinnamyl) was converted into half-ester **10c** in quantitative yield and 89% *ee* (Table 1, entry 3). In the case of compounds **9c′** or **9d**, the enantioselectivity was lower (Table 1, entries 4 and 5). All attempts to increase the enantioselectivity of half-ester **10c**

Table 1. PLE-mediated hydrolysis of diesters **9a–9d**.



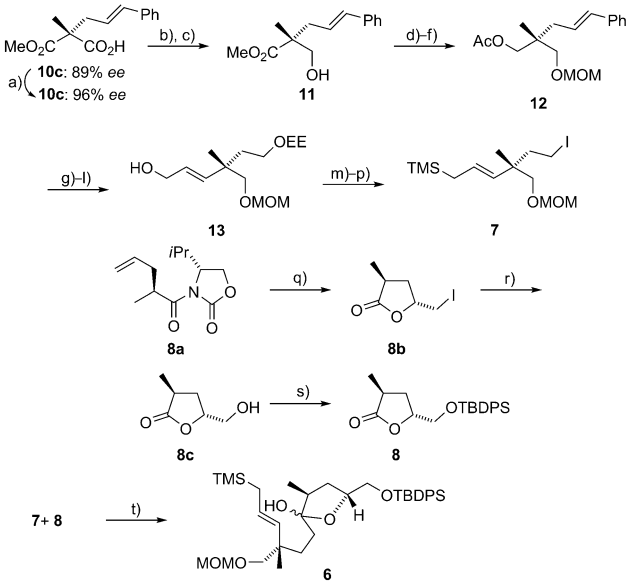

| Entry | Substrate | *t* [h] | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|
| 1 | **9a** | 18 | 100 | 37 (*S*) |
| 2 | **9b** | 22 | 96 | 58 (*S*) |
| 3 | **9c** | 9 | 100 | 89 (*R*) |
| 4 | **9c′**[c] | 23 | 82 | 76 (*R*) |
| 5 | **9d** | 7.5 | 56 | 13 (*R*) |

[a] Yield of isolated product; [b] for the determination of *ee* value and absolute configuration, see the Supporting Information; [c] diethyl ester was used.

by altering the hydrolysis conditions were unsuccessful. Therefore, we considered kinetic resolution to improve the *ee* value. In general, the hydrolysis of half-esters does not occur in the PLE-catalyzed enantioselective hydrolysis of σ-symmetric prochiral diesters. However, we found that half-ester **10c** (89% *ee*) underwent PLE-catalyzed hydrolysis when compound **10c** (89% *ee*) was gradually added to a suspension of PLE in potassium phosphate buffer (pH 8.0) by using a syringe pump, thus leading to the kinetic resolution of compound **10c**. Thus, 88% of ester **10c** (96% *ee*) was obtained by using this procedure.

Subsequently, we prepared compound **7** from **10c** as outlined in Scheme 2. Ester **10c** was converted into alkyl iodide **7** by using standard procedures in a 15-step sequence that began with the conversion of compound **10c** into its corresponding acid chloride, which was reduced with $NaBH_4$ to afford compound **11**. Alcohol **11** was protected as a MOM ether, followed by reduction with $LiAlH_4$ and acetylation to afford compound **12**. Compound **12** was subjected to ozonolysis, followed by reductive work-up to afford the corresponding alcohol. The obtained alcohol was protected as an ethoxyethyl ether, followed by removal of the acetyl group, Parrikh–Doering oxidation, a Horner–Wadsworth–Emmons reaction, and DIBAL-H reduction to give compound **13**. Treatment of compound **13** with lithium chloride and methanesulfonyl chloride afforded the corresponding allylic chloride and subsequent Still's reaction successfully introduced the allyltrimethylsilane. Subsequent removal of the ethoxyethyl group and conversion of the resultant alcohol into the corresponding iodide furnished fragment **7**.




Scheme 2. Preparation of compound **6**: a) PLE, KPB 8, 30 °C, 7 days, 88% yield, 96% *ee*; b) $(COCl)_2$, DMF (cat.), $CH_2Cl_2$, 0 °C to RT; c) $NaBH_4$, MeOH, THF, −30 °C to RT, 86% yield (2 steps); d) MOMCl, DIPEA, NaI, $CH_2Cl_2$, reflux, 99% yield; e) $LiAlH_4$, $Et_2O$, RT; f) $Ac_2O$, Py, DMAP, $CH_2Cl_2$, RT, quantitative yield (2 steps); g) $O_3$, MeOH, −78 °C, then $NaBH_4$, −78 to 0 °C, 94% yield; h) ethyl vinyl ether, PPTS, $CH_2Cl_2$, RT, 96% yield; i) $K_2CO_3$, MeOH, RT, quantitative yield; j) $SO_3$•Py, DMSO, $Et_3N$, 0 °C, 98% yield; k) *t*BuOK, $(EtO)_2P(O)CH_2CO_2Et$, THF, −78 °C to RT, quantitative yield; l) DIBAL-H, $CH_2Cl_2$, −78 °C, 99% yield; m) MsCl, 2,6-lutidine, LiCl, DMF, 0 °C, 98% yield; n) $Me_3SiSiMe_3$, MeLi, $Et_2O$/HMPA (4:1), −60 °C, 88% yield; o) PPTS, EtOH, RT, quantitative yield; p) $PPh_3$, imidazole, $I_2$, benzene, RT, 94% yield; q) NCS, $NaHCO_3$, NaI, EtOAc/$H_2O$ (2:1), RT, 92% yield (>30:1); r) $CF_3CO_2Na$, DMF, 90 °C, then $Et_2NH$, RT, 63% yield; s) TBDPSCl, imidazole, $CH_2Cl_2$, RT, 97% yield; t) compound **7**, *t*BuLi, $Et_2O$, −78 °C, 15 min, then compound **8**, −78 °C, 2 h, 84% yield, d.r. = 1:1. MOMCl = methoxymethyl chloride, DIPEA = *N*,*N*-diisopropylethylamine, Py = pyridine, DMAP = 4-dimethylaminopyridine, PPTS = pyridinium *para*-toluenesulfonate, DIBAL-H = diisobutylaluminium hydride, MsCl = methanesulfonyl chloride, HMPA = hexamethylphosphoramide, NCS = *N*-chlorosuccinimide, TBDPSCl = *tert*-butyldiphenylsilyl chloride, KPB 8 = pH 8.0 potassium phosphate buffer.

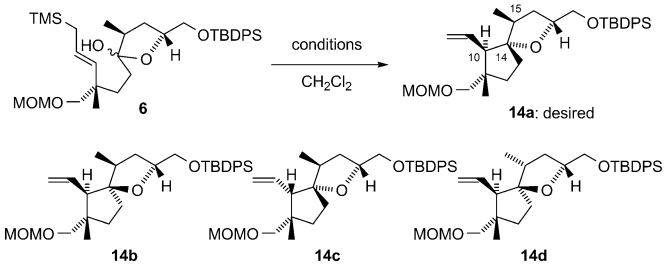
Fragment **8** (Scheme 2) was prepared from known compound **8a**[12] as follows: Iodolactonization[13] of compound **8a** efficiently afforded compound **8b**, which was converted into the corresponding trifluoroacetate, followed by removal of the trifluoroacetate by using diethylamine to give alcohol **8c**. The protection of compound **8c** as a TBDPS ether finally afforded compound **8**.[14] Treatment of compound **7** with *t*BuLi generated the corresponding organolithium intermediate, which was treated with compound **8** to generate **6** as a mixture of two diastereomers (d.r. = 1:1).

**Intramolecular Hosomi–Sakurai reaction of compound 6**: Then, we examined the intramolecular Hosomi–Sakurai reaction of compound **6** to construct the complex spirocyclic CD ring (Table 2). Treatment of **6** with $TiCl_4$ or $Ti(OiPr)_4$ did not yield compound **14**, probably because of unsuitable acidity (Table 2, entries 1 and 2). However, treatment with $TiCl_3(OiPr)$ afforded compounds **14a**, **14b**, and **14c** in 29, 31, and 40% yield, respectively (Table 2, entry 3). The use of the less-acidic $TiCl_2(OiPr)_2$ provided an unexpected C15 *epi* diastereomer (**14d**) in 57% yield, and treatment with $TiCl(OiPr)_3$ afforded compound **14d** as the sole product in 84% yield (Table 2, entries 4 and 5). The structure of compound **14d** was confirmed by X-ray crystallography (Figure 2). Treatment of **6** with $BF_3$•$OEt_2$ afforded the desired compound (**14a**) as the major product in 45% yield (Table 2, entry 6). Various Lewis acids were investigated to improve the yield of compound **14a** (Table 2, entries 7–10),[15] but only fruitless results were obtained. Moreover, neither reaction temperature nor quantity of Lewis acid altered the selectivity.

The observed stereoselectivity in the formation of compounds **14a**–**14c** may be explained by the proposed transition states shown in Figure 3. Among the four possible transition states, only **TS1**–**TS3** were considered because the other possible transition state (not shown) generated severe steric strain between the allylsilane group and the C15 methyl group. Transition state **TS1**, which would afford compound **14a**, is ideal, because the reaction of allylsilane at the C14 position may circumvent the steric strain between the allylsilane and the THF ring. On the other hand, the steric strain in transition states **TS2** and **TS3** may be relatively large, because the allylsilane group is located on the THF ring. However, transition states **TS2** and **TS3** could be stabilized by secondary orbital interactions,[16] which arise from

Table 2. Intramolecular Hosomi–Sakurai reaction of compound **6**.




| Entry | Lewis acid[a] | $T$ [°C] | $t$ [h][b] | Yield [%][c] | | | |
|---|---|---|---|---|---|---|---|
| | | | | **14a** | **14b** | **14c** | **14d** |
| 1 | $TiCl_4$ | −78 | 2 | decomposition | | | |
| 2 | $Ti(OiPr)_4$ | −78, −50, −20, RT | 2, 5, 12, 2 | no reaction | | | |
| 3 | $TiCl_3(OiPr)$ | −78 | 4 | 29 | 31 | 40 | 0 |
| 4 | $TiCl_2(OiPr)_2$ | −78, −50 | 4, 1.5 | 18 | 0 | 19 | 57 |
| 5 | $TiCl(OiPr)_3$ | −78, −50, −20 | 2, 2, 12 | 0 | 0 | 0 | 84 |
| 6 | $BF_3{\cdot}OEt_2$ | −78 | 4 | 45 | 25 | 27 | 0 |
| 7 | $ZnCl_2$ | −78, −50 | 2, 8 | 25 | 22 | 27 | 0 |
| 8 | $EtAlCl_2$ | −78 | 6 | 20 | 40 | 40 | 0 |
| 9 | $Et_2AlCl$ | −78, −50, −20 | 5, 8, 12 | 25 | 36 | 36 | 0 |
| 10 | $SnCl_4$ | −78 | 2 | 25 | 24 | 49 | 0 |

[a] Lewis acid (3.0 equiv); [b] multiple values correspond to the time at each temperature; [c] yield of isolated product.

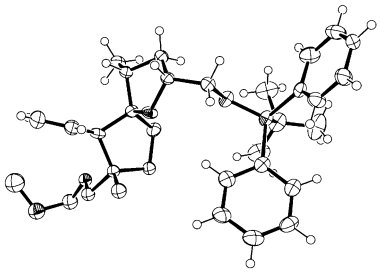


Figure 2. ORTEP diagram of compound **14d**; thermal ellipsoids are set at 50% probability. CCDC-612491 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

the overlap between the bonding orbital of the C–Si bond (HOMO) and the anti-bonding orbital of the oxonium ion that is derived from compound **6** (LUMO). Thus, although transition states **TS2** and **TS3** are energetically unfavorable because of steric strain, they could be stabilized by non-bonding interactions, which do not occur in transition state **TS1**, to afford compounds **14b** and **14c**, respectively.

Figure 4 shows a proposed mechanism for the formation of compound **14d**. Epimerization at the C15 position was only observed in the reactions with $TiCl_2(OiPr)_2$ and $TiCl(OiPr)_3$. Therefore, the basic ligand ($iPrO^-$) on these catalysts may have abstracted the C15 hydrogen atom to cause epimerization prior to the C–C bond-forming reaction, that is, epimerization is faster than the intramolecular reaction through transition state **TS2**, because of the steric interactions between the allylsilane moiety and the β-oriented C15 methyl group. The presumed transition state (**TS4**) that yields compound **14d**, is preferred over others because two substituents, namely Me and $CH_2OTBDPS$, on the THF ring have a 1,3-*cis* relationship, thereby facilitating the reaction on the less-hindered side. In addition, a secondary orbital interaction may participate in the stabilization of transition state **TS4**.

We also investigated the reaction of (*Z*)-allylsilane (**18**, Scheme 3). Compound **18** was prepared in a six-step sequence from compound **15**, which was derived from compound **12** (Scheme 2), as follows: Compound **15** was treated with the Ohira–Bestmann reagent, followed by lithiation of the terminal alkyne group and treatment with (iodomethyl)trimethylsilane to afford compound **16**. Lindlar reduction compound of **16**, removal of the ethoxyethyl ether, and iodination gave compound **17**. Finally, treatment of compound **17** with *t*BuLi generated the corresponding organolithium intermediate, which was reacted with compound **8** to afford compound **18** as a mixture of two diastereomers (d.r. = 1:1). Interestingly, treatment of compound **18** with $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$ at −78 °C afforded compound

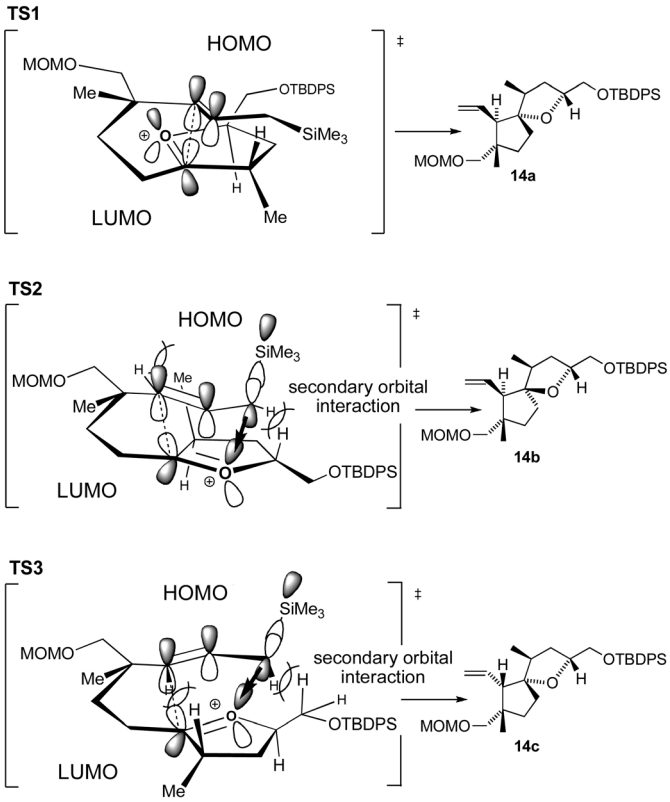



Figure 3. Proposed transition states **TS1**, **TS2**, and **TS3**.

**14b** from compound **17** as the single product in 65% overall yield. Transition state **TS5**, which also provides compound **14b**, may be more suitable than other transition states that

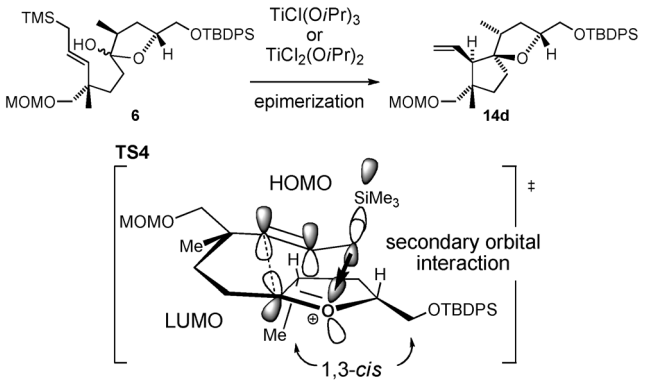
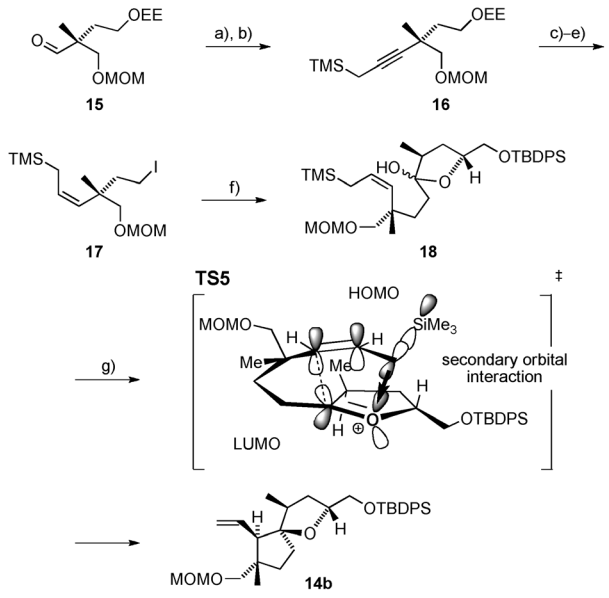



Figure 4. Proposed mechanism for the formation of compound **14d**.

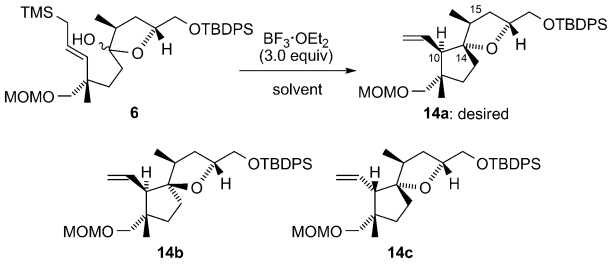



Scheme 3. Preparation and reaction of compound **18**: a) $K_2CO_3$, Ohira–Bestmann reagent, MeOH, RT; b) *n*BuLi, (iodomethyl)trimethylsilane, THF, 50 °C, 72 % yield (2 steps); c) $Pd/BaSO_4$ (5 wt. %), quinoline, MeOH, RT; d) PPTS, EtOH, RT; e) $PPh_3$, imidazole, $I_2$, benzene, RT, 80 % yield (3 steps); f) compound **17**, *t*BuLi, $Et_2O$, −78 °C, then compound **8**, −78 °C; g) $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, −78 °C, 65 % yield (2 steps).

correspond **TS1** and **TS3** because transition state **TS5** would be stabilized by the secondary orbital interactions.

To improve the ratio of compound **14a**, the effect of solvent on the intramolecular Hosomi–Sakurai reaction of compound **6** was examined in the presence of $BF_3{\cdot}OEt_2$ as an optimal Lewis acid (Table 3). Treatment of **6** in MeCN at −40 °C only resulted in its decomposition (Table 3, entry 2). The reaction in *n*-heptane afforded compound **14c** as the major product (Table 3, entry 3), whereas the reaction in toluene (Table 3, entry 4) improved the ratio of compounds **14a**/**14b**/**14c** to 63:7:20. Moreover, the use of $Et_2O$ (Table 3, entry 5) resulted in the formation of trace amounts of compound **14c** and the ratio of compounds **14a**/**14b** changed to 56:30. Treatment of compound **6** in a mixed solvent system of toluene and $Et_2O$ was examined, with the expectation

Table 3. Effect of the solvent on the intramolecular Hosomi–Sakurai reaction of compound **6**.

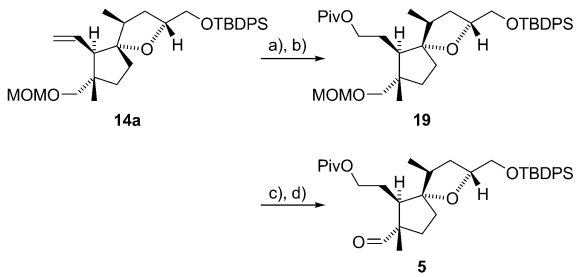



| Entry | Solvent | $T$ [°C] | $t$ [h] | Yield [%][a] | | |
|---|---|---|---|---|---|---|
| | | | | **14a** | **14b** | **14c** |
| 1 | $CH_2Cl_2$ | −78 | 4 | 45 | 25 | 27 |
| 2 | MeCN | −40 | 12 | decomposition | | |
| 3 | *n*-heptane | −60 | 12 | 9 | 22 | 46 |
| 4 | toluene | −60 | 12 | 63 | 7 | 20 |
| 5 | $Et_2O$ | −60 | 12 | 56 | 30 | trace |
| 6 | $Et_2O$/toluene (4:1) | −60 | 12 | 56 | 28 | 4 |
| 7 | $Et_2O$/toluene (1:4) | −60 | 12 | 51 | 30 | 10 |
| 8 | $Et_2O$/toluene (1:1) | −60 | 12 | 68 | 17 | trace |

[a] Yield of isolated product.

that a cooperative effect between toluene and $Et_2O$ would be observed (Table 3, entries 6–8). Indeed, the reaction in $Et_2O$/toluene (1:1) at −60 °C afforded the desired product (**14a**) in 68 % yield and good selectivity (**14a**/**14b**, 4:1; Table 3, entry 8). Although it is not well-understood why the ratio of compound **14a** was improved by changing the solvent, various solvents may disturb transition states **TS2** and **TS3** by solvation.

**Preparation of aldehyde 5**: Because the spirocyclic CD ring that contained the correct C10 and C14 stereogenic centers was constructed successfully in good yield, we prepared aldehyde **5** from compound **14a** (Scheme 4). Hydroboration

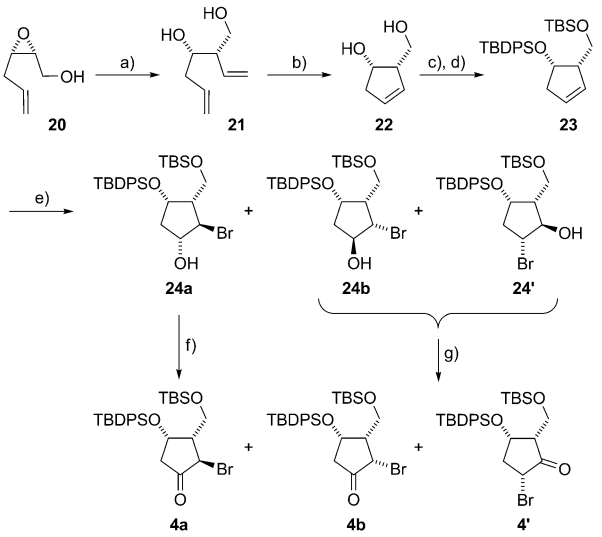



Scheme 4. Preparation of aldehyde **5**: a) 9-BBN, THF, RT, 3 h, then 3 M NaOH, 30 % $H_2O_2$ aq., RT, 3 h, quantitative yield; b) PivCl, Py, DMAP, $CH_2Cl_2$, RT, 12 h, quantitative yield; c) $BF_3{\cdot}OEt_2$, $Me_2S$, $CH_2Cl_2$, −30 °C, 3 h, 92 % yield; d) Dess–Martin periodinane, $CH_2Cl_2$, RT, 2 h, 94 % yield. 9-BBN = 9-borabicyclo[3.3.1]nonane, PivCl = pivaloyl chloride.

of compound **14a** and subsequent treatment with pivaloyl chloride afforded **19**. Cleavage of the MOM ether of compound **19** and subsequent Dess–Martin oxidation yielded aldehyde **5**.

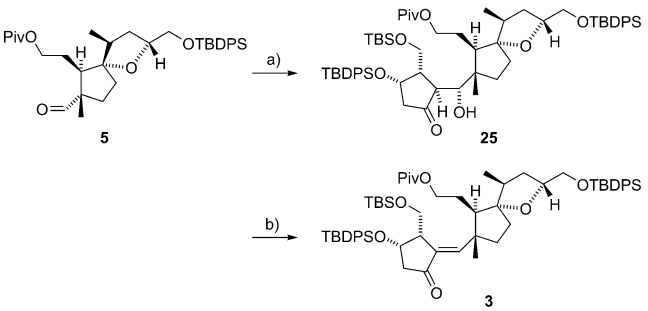
**Preparation of compounds 4a and 4b**: Compounds **4a** and **4b** were thought to be obtained by oxidation of the corresponding bromohydrins (**24a** and **24b**), which would be prepared from alkene **23** in a regioselective manner (Scheme 5). Alkene **23** was obtained from known compound **20**[17] through a regioselective epoxide-opening reaction with vinylmagnesium bromide and subsequent RCM.




Scheme 5. Preparation of compounds **4a** and **4b**: a) $H_2C$=CHMgBr, CuI, $Et_2O$/THF, −25 °C, 68% yield; b) Grubbs II, $CH_2Cl_2$, RT, 92% yield; c) TBSCl, imidazole, $CH_2Cl_2$, 0 °C, 87% yield; d) TBDPSCl, imidazole, DMAP, $CH_2Cl_2$/DMF (10:1), RT, 98% yield; e) NBS, acetone/$H_2O$ (3:1), RT, 58% yield of **24a**, 25% **24b**+**24′**, (**24a**+**24b**)/**24′** = 8.2:1 (16% **24b**, 9% **24′**); f) Dess–Martin periodinane, $CH_2Cl_2$, RT, 98% yield; g) Dess–Martin periodinane, $CH_2Cl_2$, RT, 61% **4b**, 34% **4**. TBSCl = *tert*-butyldimethylsilyl chloride, NBS = *N*-bromosuccinimide.

As expected, treatment of compound **20** with vinylmagnesium bromide in the presence of CuI afforded compound **21** with high regioselectivity.[18] The RCM reaction of compound **21** proceeded efficiently and the primary and secondary hydroxy groups in compound **22** were protected as TBS and TBDPS ethers, respectively. Moreover, as expected, treatment of compound **23** with NBS in aqueous acetone afforded bromohydrin **24a** as the major product. Although an inseparable mixture of compounds **24b** and **24′** was obtained as a minor component, this mixture was separated with ease from compound **24a** and was subjected to Dess–Martin oxidation to afford a separable mixture of compounds **4b** and **4′**. Compound **24a** was converted into compound **4a** by Dess–Martin oxidation in 98% yield.

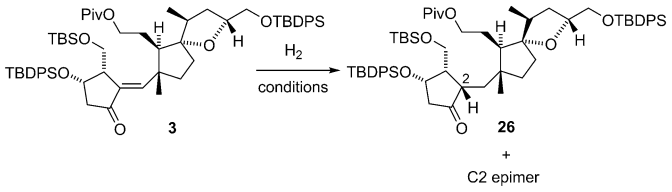
**Coupling reaction between compounds 4 and 5**: Then, we investigated the coupling reaction shown in Scheme 6. The classic Reformatsky reaction between compounds **4** and **5** yielded no products; therefore, we examined the coupling procedure reported by Utimoto and co-workers.[19] This reaction, which involves a bulky aldehyde, proceeds efficiently under mild conditions because of the boron enolate that is generated in situ. The reaction between compounds **4a** and **5** with triphenyltin hydride and triethylborane in benzene proceeded at room temperature to afford compound **25** as a single product in 90% yield. Treatment of compound **4b** with compound **5** also provided compound **25** (83%) as a single product. Our study may be the first example of the use of Utimoto's coupling reaction in natural product synthesis. Notably, this coupling reaction proceeded without β-elimination of the siloxy group, which sometimes occurs in a β-substituted cyclopentenone such as this one. Although the dehydration of compound **25** with conventional reagents[20] resulted in low yields, treatment of compound **25** with Burgess reagent[21] successfully afforded the desired enone (**3**) in 92% yield as a single product.




Scheme 6. Preparation of compound **3**: a) Compound **4**, $Ph_3SnH$, $Et_3B$, benzene, RT, 90% yield (from **4a**), 83% yield (from **4b**); b) Burgess reagent, benzene, RT, 92% yield.

To construct the C2 and C3 stereogenic centers, we first examined the stereoselective hydrogenation of compound **3** (Table 4). Thus, the hydrogenation of **3** in EtOH in the presence of palladium on carbon afforded a mixture of com-

Table 4. Stereoselective hydrogenation of compound **3** to construct the C2 stereogenic center.



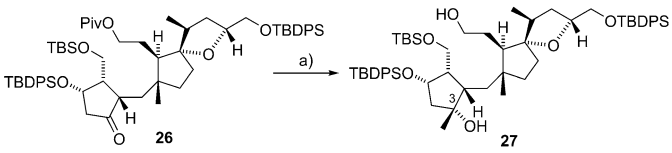

| Entry | Catalyst | Solvent | *T* [°C] | *t* [h] | Yield [%][a] | |
|---|---|---|---|---|---|---|
| | | | | | **26** | C2 epimer |
| 1 | Pd/C | EtOH | 50 | 12 | 62 | 25 |
| 2 | $Pd(OH)_2$/C | EtOH | 50 | 12 | 56 | 32 |
| 3 | $PtO_2$ | EtOH | 50 | 3 | decomposition | |
| 4 | $PtO_2$ | EtOAc | 50 | 3 | 40 | 40 |
| 5 | Raney Ni | EtOH | RT | 5 | 74 | 14 |
| 6 | Raney Ni | EtOH/THF (1:1) | RT | 9 | 87 | 9 |
| 7 | Raney Ni | MeOH/THF (1:1) | RT | 3 | 82 | 2 |
| 8 | Raney Ni | THF | RT | 12 | no reaction | |
| 9 | Raney Ni | EtOAc | RT | 12 | no reaction | |

[a] Yield of isolated product.

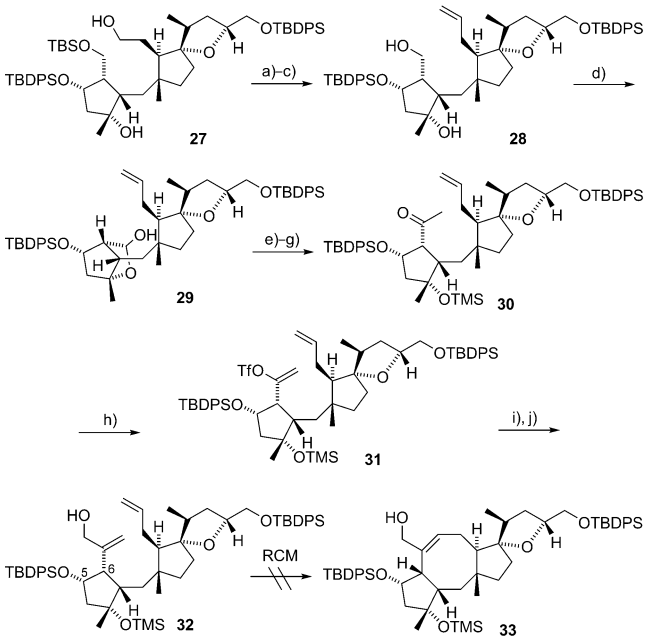
pound **26** and its C2 epimer (d.r. = 62:25; Table 4, entry 1), but this ratio decreased to 56:32 when using Pearlman's catalyst ($Pd(OH)_2/C$; Table 4, entry 2). In the reaction with Adams catalyst, no selectivity was observed (Table 4, entries 3 and 4). However, the reaction with Raney Ni in EtOH improved the ratio to 74:14 (Table 4, entry 5). Further optimization showed that the hydrogenation of compound **3** with Raney Ni in a mixed solvent system (MeOH or EtOH/THF, 1:1) afforded compound **26** with high selectivity and yield (Table 4, entries 6 and 7).[22] Interestingly, no products were obtained from hydrogenation with Raney Ni in THF or EtOAc (Table 4, entries 8 and 9). In addition, we observed no epimerization at the C2 stereogenic center when compound **26** and its C2 epimer were treated under the same conditions.

Next, we examined the reaction of methyl lithium with ketone **26**. As expected, the reaction occurred on the less-hindered side, along with removal of the pivaloyl group, to afford compound **27** as a single product (98% yield), thus furnishing all of the stereogenic centers that exist in compound **1** (Scheme 7).



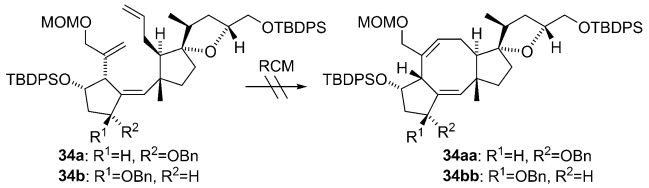

Scheme 7. Stereoselective reaction of methyl lithium with ketone **26**: a) MeLi, $Et_2O$, −78 to 0 °C, 98% yield.

After establishing all of the stereogenic centers in compound **1**, we focused on constructing the eight-membered carbocyclic ring (Scheme 8). Swern oxidation of compound **27** afforded the corresponding aldehyde, followed by a Wittig reaction and removal of the TBS group to yield **28**. Although the Swern oxidation of compound **28** caused dehydration of the tertiary alcohol, IBX oxidation[23] of compound **28** successfully proceeded without dehydration to afford lactol **29**. Treatment of compound **29** with methyl lithium and subsequent Dess–Martin oxidation and treatment with TMSCl afforded ketone **30**. Although the conversion of compound **30** into enol triflate **31** was successfully performed by using Comins' reagent,[24] compound **31** was found to be unstable. Indeed, decomposition of compound **31** was observed during storage, even at −30 °C. Thus, the palladium-mediated transformation of compound **31** into the methyl ester posed an unexpected challenge because of the sensitivity of compound **31**. Among the various reagents that were tested for the palladium-mediated formation of the methyl ester, the combination of $[Pd(PPh_3)_4]$ and $Et_3N$ in MeOH/toluene under a CO atmosphere generated the desired compound with good reproducibility. The reduction of the methyl ester in *n*-hexane with DIBAL-H effectively generated compound **32**, whilst the reduction in toluene yielded the 1,4-reduced product as the major component.




Scheme 8. Preparation of compound **32** and attempted RCM reaction: a) $(COCl)_2$, DMSO, $CH_2Cl_2$, −78 °C, then $Et_3N$, RT, 98% yield; b) $Ph_3P^+MeBr^-$, *t*BuOK, THF, 0 °C, 99% yield; c) PPTS, EtOH, RT, quantitative yield; d) IBX, DMSO, RT; e) MeLi, $Et_2O$, 0 °C; f) Dess–Martin periodinane, $CH_2Cl_2$, RT, 78% (3 steps); g) TMSCl, imidazole, DMF, RT, quantitative yield; h) Comins' reagent, KHMDS, THF, −78 °C; i) $[Pd(PPh_3)_4]$, $Et_3N$, CO (1 atm), MeOH/toluene (20:1), 50 °C; j) DIBAL-H, *n*-hexane, −78 °C, 47% yield (3 steps). IBX = 2-iodoxybenzoic acid.

Then, we examined the use of RCM to construct the eight-membered B ring. First, we attempted the RCM of compound **32** with Grubbs II catalyst, but no desired products were obtained. Reactions with Hoveyda–Grubbs II catalyst and modified Grubbs II catalyst,[25] which have been reported to be effective in the RCM reactions of hindered alkenes, also yielded no products. Moreover, the RCM reactions of compounds **34a** and **34b** (Scheme 9), which were designed to have an alkene on the eight-membered ring to decrease the transannular interactions in the transition state, also failed to afford the desired product.




Scheme 9. Attempted RCM reactions of compounds **34a** and **34b**.

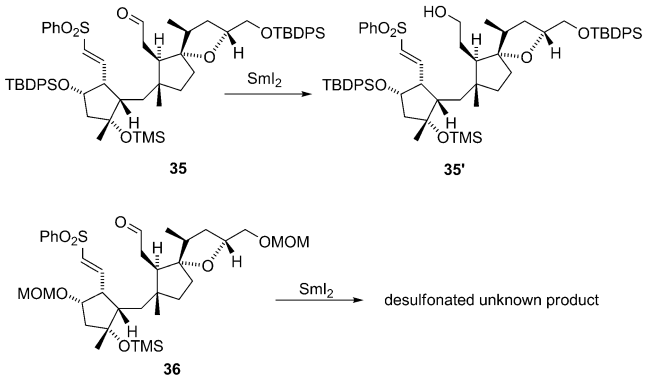
In all of the RCM reactions, most of the starting material remained at the end of the reactions and small amounts of styrene derivatives were formed. Styrene derivatives are derived from the cross-metathesis of the terminal alkene with the catalyst. Hence, we speculated that the ring-closing step

may have been the problem in this RCM reaction and that it would be affected by the bulky TBDPS group on the C5 hydroxy moiety, that is, the bulky TBDPS group may push the alkene of the *cis*-substituted C6 substituent into a position that is inaccessible to the carbene intermediate that is formed in situ from the reaction between monosubstituted alkene group in compound **32** and the catalyst.

In another attempt to access the B ring, we examined $SmI_2$-mediated cyclization reactions[26,27] of the alkenyl sulfones **35** and **36** (Scheme 10). Although efforts to obtain the ring-closed products were made by examining a variety of additives, solvents, and reaction temperatures, no desired products were obtained. Compound **35** was converted only into alcohol **35′** and the reaction of **36**, which is protected with a MOM group at the C5 position, gave a desulfonated, structurally unknown component as the major product. These results suggest that the bulky C5 protecting group may also affect the reactivity of the C5 alkenyl sulfone.

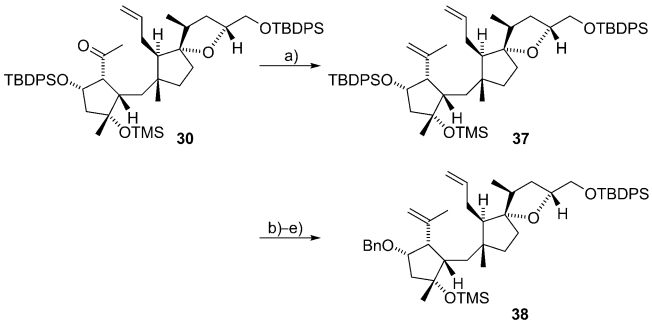
Consequently, we decided to examine the relationship between the structures of the substrates and the yields of the RCM reactions. In terms of the substrate structure, we focused on the C5 protecting group and the C6 substituent. Based on the results shown in Scheme 9 and Scheme 10, RCM substrate **38** was prepared with a relatively small Bn




Scheme 10. Attempted construction of the B ring through an $SmI_2$-mediated reaction.

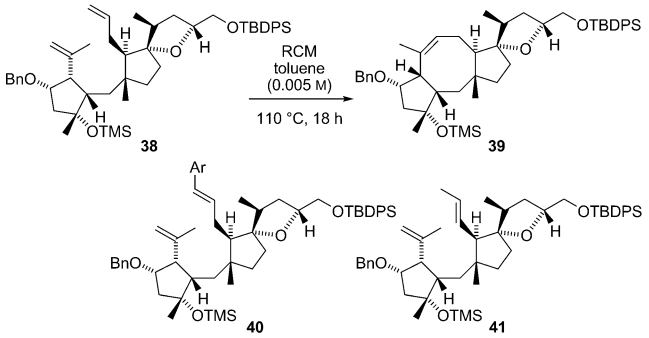
group on the C5 hydroxy group and an isopropenyl group at the C6 position (Scheme 11). Treatment of **30** with Takai's reagent[28] afforded compound **37**. This result was followed by the removal of all of the silyl groups, selective protection of the primary hydroxy group as a TBDPS ether and the secondary hydoxy group as a benzyl ether, and protection of the remaining tertiary hydroxy group as a TMS ether to afford compound **38**.

The RCM of compound **38** was examined by using Grubbs II and Hoveyda–Grubbs II catalysts (Table 5). The RCM reaction with Grubbs II was performed in toluene at 110 °C to afford the desired compound (**39**) in 58 % yield with a small amount of byproduct **40** (Table 5, entry 1). The reaction with Hoveyda–Grubbs II catalyst afforded compound **39** in 39 % yield, along with double-bond-isomerized




Scheme 11. Preparation of compound **38**: a) Zn, $PbCl_2$, $CH_2I_2$, $TiCl_4$, THF, 50 °C, 88 % yield; b) TBAF, THF, RT; c) TBDPSCl, imidazole, DMAP, $CH_2Cl_2$, −30 °C, 94 % yield (2 steps); d) BnBr, NaH, DMF, 0 °C; e) TMSCl, imidazole, DMF, RT, 91 % yield (2 steps). BnBr = benzyl bromide.

Table 5. RCM reactions of compound **38**.




| Entry | Catalyst (30 mol %) | Additive (equiv) | Yield of **39** [%][a] |
|---|---|---|---|
| 1 | Grubbs II | none | 58 |
| 2 | Hoveyda–Grubbs II | none | 39 |
| 3 | Hoveyda–Grubbs II | 1,4-benzoquinone (1) | 69 |
| 4 | Hoveyda–Grubbs II | 1,4-benzoquinone (10) | 91 |

[a] Yield of isolated product.

compound **41** as the major product. No byproduct (**40**) was observed (Table 5, entry 2). Several methods to suppress the isomerization of the terminal alkene have been reported.[29] Therefore, we examined the RCM reaction of compound **38** with Hoveyda–Grubbs II in the presence of 1.0 equivalent of 1,4-benzoquinone, which yielded compound **39** in 69 % yield. However, compound **41** was still formed (Table 5, entry 3). The RCM reaction with Hoveyda–Grubbs II catalyst and 10.0 equivalents of 1,4-benzoquinone improved the yield of compound **39** and showed no formation of compound **41** (Table 5, entry 4).

Subsequently, several substrates were prepared and subjected to RCM under the optimized conditions. Compounds **39**, **43**, **44**, **51**, and **52** were successfully obtained (Figure 5). The RCM reactions of substrates that contained a silyl group on the C5 hydroxy group (i.e., substrates that corresponded to compounds **42** and **48**) and those that contained a C6 substituent with a protected hydroxy group (i.e., substrates that corresponded to compounds **45**–**47**) did not afford the desired products. The RCM reactions of sub-

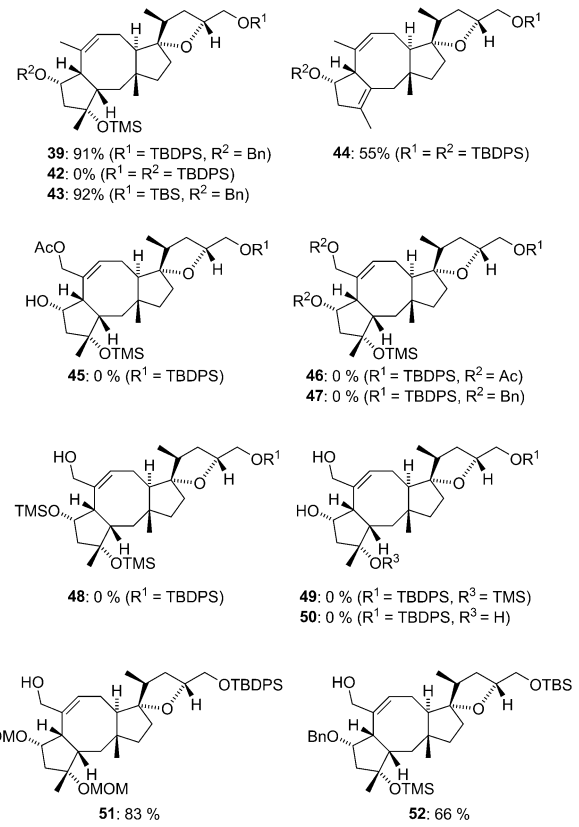
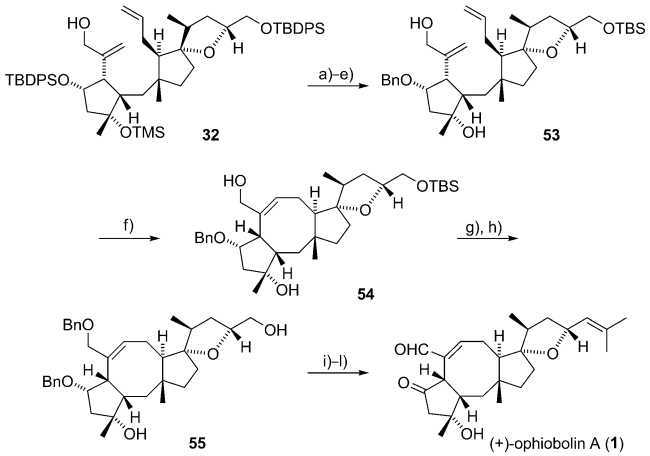



Figure 5. Results of the RCM reactions of the corresponding substrates.

strates that contained a free hydroxy group at the C5 position (i.e., substrates that corresponded to compounds **49** and **50**) only resulted in decomposition. Interestingly, the RCM of a substrate that contained an unsaturated A ring with a TBDPS group on the C5 hydroxy group afforded compound **44** in 55% yield. These results suggest that the unsuccessful RCM reactions may not only be caused by the bulkiness of the C5 substituent but also by structural features of the substrate. The unprotected hydroxy group on the C6 substituent of these substrates did not play a crucial role in the RCM reaction because compounds **39**, **43**, and **44** were formed by RCM. In summary, the successful RCM requires that the C5 hydroxy group be masked with a less-bulky protective group and, in addition, that the C6 substituent be either an isopropenyl group or its hydroxylated form.

Based on the results shown in Figure 5, we examined the synthesis of **1** by the RCM of compound **53** (Scheme 12). Compound **53** was prepared from compound **32** through protection of the primary hydroxy group as a pivalate, removal of all of the silyl groups, selective protection of the primary hydroxy group as a TBS ether and the secondary hydroxy group as the benzyl ether, and removal of the pivaloyl group by DIBAL-H. Thus, the RCM reaction of compound **53** successfully afforded the desired product (**54**). The dehydration of the tertiary hydroxy group of compound **54** occurs readily under acidic conditions; however, no dehydrated products were observed in the RCM reaction. The

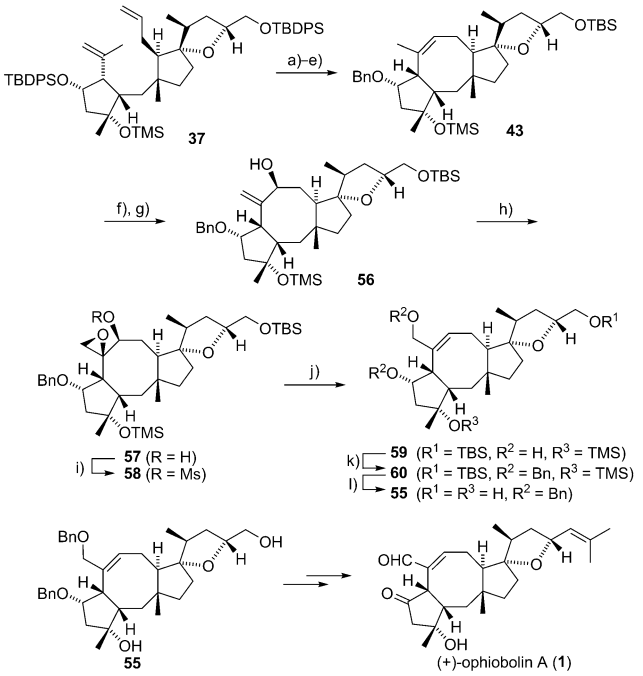



Scheme 12. Enantioselective total synthesis of (+)-ophiobolin A (**1**) from compound **32**: a) PivCl, Py, DMAP, $CH_2Cl_2$, RT; b) TBAF, THF, RT; c) TBSCl, DIPEA, DMAP, $CH_2Cl_2$, 0°C; d) BnBr, NaH, DMF, 0°C; e) DIBAL-H, *n*-hexane, −78°C, 76% yield (5 steps); f) Hoveyda–Grubbs II, 1,4-benzoquinone, toluene, 110°C; g) BnBr, NaH, DMF, 0°C; h) PPTS, EtOH, RT, 68% yield (3 steps); i) $(COCl)_2$, DMSO, $CH_2Cl_2$, −78°C, then $Et_3N$, RT; j) $(CH_3)_2CHP(C_6H_5)_3{}^+I^-$, *n*BuLi, THF, RT; k) Li, naphthalene, THF, −30°C; l) $(COCl)_2$, DMSO, $CH_2Cl_2$, −78°C, then $Et_3N$, RT, 49% yield (4 steps). TBAF = tetra-*n*-butylammonium fluoride.

primary hydroxy group on compound **54** was selectively protected as a benzyl ether and subsequent removal of the TBS group afforded compound **55**. The Swern oxidation of compound **55** proceeded effectively and subsequent Wittig reaction, removal of the benzyl group with lithium naphthalenide, and Swern oxidation afforded compound **1**. Synthetic compound **1** was found to be identical to (+)-ophiobolin A in all respects ($^1H$ and $^{13}C$ NMR and IR spectroscopy, MS, and $[\alpha]_D$), thus confirming that the enantioselective total synthesis of (+)-ophiobolin A had been achieved.

Because compound **43** was successfully obtained by using RCM, we also examined the total synthesis of compound **1** by an alternative route (Scheme 13). That is, all of the silyl groups in compound **37** were removed with TBAF, followed by the selective protection of the primary hydroxy group as a TBS ether and the secondary hydoxy group as a benzyl ether, protection of the remaining tertiary hydroxy group as a TMS ether, and RCM reaction with Hoveyda–Grubbs II in the presence of 1,4-benzoquinone in toluene at 110°C to afford **43**. To introduce an oxygen functionality at the C21 position of compound **43**, allylic oxidation of compound **43** at this position was attempted. However, no desired products were obtained, despite extensive studies. Therefore, we converted compound **43** into compound **56** and examined further transformations to afford (+)-ophiobolin A. Thus, treatment of compound **43** with *m*CPBA afforded the epoxide, which was converted into allylic alcohol **56** by being treated with lithium 2,2,6,6-tetramethylpiperidide. The allylic rearrangement of compound **56** by using a rhenium reagent[30] provided none of the desired products and the conversion of compound **57** into halides with an allylic rearrangement[31] was also unsuccessful. The allylic rearrange-




Scheme 13. Enantioselective total synthesis of (+)-ophiobolin A (**1**) from compound **37**: a) TBAF, THF, RT; b) TBSCl, DIPEA, DMAP, $CH_2Cl_2$, 0°C, 82% yield (2 steps); c) BnBr, NaH, DMF, 0°C, 93% yield; d) TMSCl, imidazole, DMF, RT, 93% yield; e) Hoveyda–Grubbs II, 1,4-benzoquinone, toluene, 110°C, 92% yield; f) *m*CPBA, $Na_2HPO_4$, $CH_2Cl_2$, 0°C; g) 2,2,6,6-tetramethylpiperidine, *n*BuLi, $Et_2AlCl$, toluene, 0°C, 70% yield (2 steps); h) *m*CPBA, $Na_2HPO_4$, $CH_2Cl_2$, 0°C; i) MsCl, $Et_3N$, DMAP, $CH_2Cl_2$, 0°C, 86% yield (2 steps); j) Li, naphthalene, THF, −30°C; k) BnBr, NaH, DMF, 0°C; l) PPTS, EtOH, RT, 70% yield (3 steps). *m*CPBA = *meta*-chloroperoxybenzoic acid.

ment of the acetate group in compound **56** was attempted under several conditions, but no desired products were obtained. Finally, we found that mesylate **58** was effectively converted into compound **59** by treatment with lithium naphthalenide in good yield.[32] The hydroxy group of compound **59** was protected as a benzyl ether and subsequent removal of the TBS and TMS groups under acidic conditions afforded compound **55**, which was subsequently converted into (+)-ophiobolin A (**1**) by using the four steps previously described.

## Conclusion

In summary, we have accomplished the enantioselective total synthesis of (+)-ophiobolin A for the first time through two separate routes. Our total synthesis features the construction of the spiro CD ring of (+)-ophiobolin A through a stereoselective intramolecular Hosomi–Sakurai cyclization reaction, the joining of the A ring to the CD ring by using the coupling reaction reported by Utimoto, and the construction of the ophiobolin eight-membered carbocyclic ring through a RCM reaction. The successful RCM reaction required that the hydroxy group at the C5 position be masked by a less-bulky protecting group and, in addition, that the substituent at the C6 position be either an isopropenyl group or its hydroxylated form. Further synthetic studies on ophiobolins are currently underway.

## Acknowledgements

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