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Brief Communication

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# Lewis Acid Template-Catalyzed Asymmetric Diels–Alder Reaction

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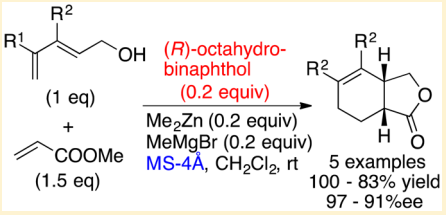
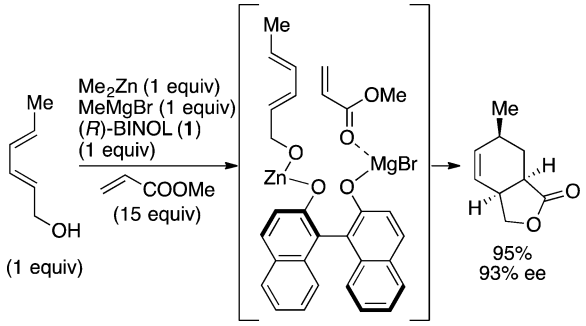
Supporting Information

**ABSTRACT:** An asymmetric Diels–Alder reaction of 2,4-dienols and methyl acrylate utilizing a chiral Zn(II)/Mg(II) bimetallic template with low catalyst loading was successfully achieved. The bimetallic Lewis acid template derived from (*R*)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol catalyzed the Diels–Alder reaction in the presence of molecular sieves 4 Å to afford various functionalized bicyclic γ-lactones with high enantiomeric purities.




The tethered Diels–Alder reaction is an efficient and powerful method for the stereoselective construction of functionalized cyclohexene derivatives.[1] Many advantages of the intramolecular Diels–Alder reaction have been extended to the intermolecular counterpart by linking the diene to the dienophile with a temporary tether.[2−8] In particular, Ward's enantioselective variant of the tethered Diels–Alder reaction is remarkable (Scheme 1).[9] They disclosed that the coordination

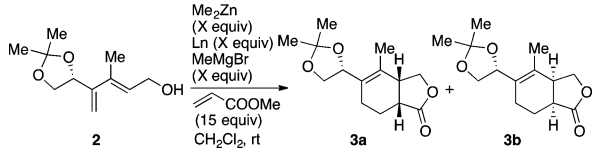
**Scheme 1. Ward's Enantioselective LACASA-DA**




of the diene and dienophile components to a bimetallic Lewis acid template derived from (*R*)-1,1′-bi-2-naphthol ((*R*)-BINOL) (**1**), $Me_2Zn$, and MeMgBr effectively controlled the Diels–Alder reaction to generate the bicyclic γ-lactone regio-, diastereo,- and enantioselectively in excellent yield. The reaction was referred to as LACASA-DA (Diels–Alder reaction based on a Lewis acid-catalyzed reaction of a self-assembled complex).[10−12] Ward's protocol has been tactically employed to enantioselectively construct functionalized cyclohexene intermediates for natural product synthesis.[13,14] This enantioselective reaction is highly effective, but it requires a stoichiometric quantity of BINOL–bimetallic complex to achieve an acceptable conversion. The tethered Diels–Alder reaction with low catalyst loading remains unexplored. Herein we report the first Lewis acid template-catalyzed asymmetric Diels–Alder reaction of dienols with methyl acrylate giving the highly functionalized bicyclic γ-lactones.

In the course of natural product synthesis, we examined the Diels–Alder reaction of **2** and methyl acrylate using (*R*)-BINOL (**1**) as a chiral ligand following Ward's protocol. In this particular case, the reaction provided a 4.8:1 diastereomeric mixture of **3a** and **3b** quantitatively (Table 1, entry 1).[15] A

**Table 1. Lewis Acid Template-Catalyzed Diels–Alder Reaction of 2 with Methyl Acrylate**




| entry | Ln | *X* (equiv) | time (h) | yield[a] (%) | **3a**: **3b**[b] |
|---|---|---|---|---|---|
| 1 | **1** | 1.0 | 3.5 | 100 | 4.8:1 |
| 2 | **4** | 1.0 | 20 | 94 | 4.6:1 |
| 3 | **5** | 1.0 | 24 | 98 | 9.9:1 |
| 4 | **5** | 0.5 | 2.5 | 99 | 10:1 |
| 5 | **5** | 0.2 | 4 | 96 | 10:1 |
| 6 | **5** | 0.1 | 24 | 88 | 8:1 |

[a]Isolated yield after chromatography. [b]Determined by $^1H$ NMR. The absolute structures of **3a** and **3b** were inferred by Ward's results.

similar selectivity was observed when (*R*)-3,3′-dibromo-1,1′-bi-2-naphthol (**4**) was used in place of (*R*)-BINOL (**1**) (entry 2). On the other hand, the reaction using a stoichiometric amount of the bimetallic complex generated from (*R*)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol (**5**), $Me_2Zn$, and MeMgBr exhibited higher selectivity to provide **3a** and **3b** in a ratio of 9.9:1 in 98% yield (entry 3). It should be noted that the reaction mediated by 0.5 equiv of bimetallic complex with **5** was completed within 2 h to afford **3a** in excellent yield and high diastereoselectivity, which were similar to those observed for the stoichiometric reaction (entry 4).[16] Encouraged by this result, we examined the reaction at lower catalyst loading.

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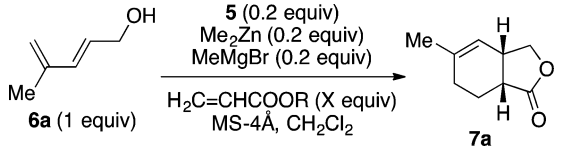
Consequently, the use of even 0.2 equiv of the catalyst was found to effectively promote the high asymmetric induction (entry 5), whereas lowering the catalyst loading of **5** to 0.1 equiv slightly diminished the yield and selectivity (entry 6).

Next, we explored the cycloaddition reaction of 4-methyl-2,4-pentadienol (**6a**), an achiral substrate, with various acrylates (Table 2). When **6a** was reacted with methyl acrylate using 0.2 equiv of bimetallic complex with **5** at rt for 3 d, the cycloaddition proceeded with moderate enantioselectivity to afford bicyclic γ-lactone **7a** in 83% yield and 52% ee (entry 1). A lower temperature did not improve the enantioselectivity (entry 2). On the other hand, the addition of molecular sieves 4 Å resulted in a dramatic rate acceleration (entry 3). Thus, in the presence of molecular sieves 4 Å, the reaction was completed within 1 day to afford **7a** in 100% yield and 84% ee. It must be noted that decreasing the amount of methyl acrylate markedly improved the enantioselectivity (entries 4–6). To our delight, the chiral template reaction of **6a** and 1.5 equiv of methyl acrylate using **5** in the presence of molecular sieves 4 Å provided **7a** in 98% yield and 92% ee. The reaction at 0 °C was sluggish, and the enantioselectivity became moderate (entry 7). Interestingly, even at a higher temperature (40 °C), the reaction proceeded without any loss of the enantioselectivity to give **7a** almost quantitatively (entry 8). A similar level of asymmetric induction was obtained with ethyl acrylate (entries 6 and 9); however, the reactions with other acrylates exhibited moderate enantioselectivities (entries 10–14). Concerning the solvent, apart from $CH_2Cl_2$, $CHCl_3$, PhH, PhMe, $Et_2O$, THF, and hexane turned out to be suboptimal for this asymmetric cycloaddition.

A variety of substituted 2,4-dienols were investigated to explore the generality of this protocol (Scheme 2). The reaction of simple 2,4-pentadienol **6b** afforded bicyclic γ-lactone **7b** in 83% yield and 94% ee. Notably, both of 3-methyl-2,4-pentadienol **6d** and 3,4-dimethyl-2,4-pentadienol **6f** were found to afford **7d** and **7f** in good yields and good enantioselectivities, respectively.[17] On the other hand, the reaction of 2,4-hexadienol **6c** exhibited the poor enantioselectivity, although the yield was acceptable. Furthermore, 2-methyl-2,4-pentadienol **6e** was found to be a less reactive substrate possibly for steric reasons. It is noteworthy that the reaction of the substrates bearing alkyl groups at the C-3 and 4 positions provided the cycloadducts in excellent yields and enantioselectivities (**7a**, **7d**, **7f**, and **7g**). In contrast, substituted acrylates such as methyl methacrylate and methyl crotonate were incompatible with this cycloaddition reaction of **6a** (**7h** and **7i**).

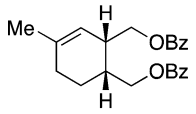
A plausible mechanism for the catalytic tethered Diels–Alder reaction is depicted in Scheme 3. As Ward's LACASA-DA mechanism,[9,18] magnesium octahydrobinaphthoate **A** and zinc dienolate **B** would form bimetallic Lewis acid **C**, which reacts with methyl acrylate to afford self-assembled intermediate **D**. The tethered intermediate **D** undergoes Diels–Alder reaction in endomode (**E**), followed by lactonization (**F**). The ligand exchange of **F** with methyl acrylate would release γ-lactone product **7**. The second exchange of the resulting **G** by dienol **6** regenerates **D** and releases methanol. The molecular sieves would play an important role for the capture of the methanol to accelerate the catalytic cycle.

**Table 2. Evaluation of Asymmetric Diels–Alder Reaction of 6a with Acrylates**



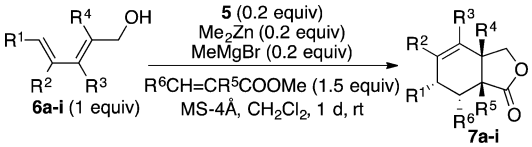

| entry | R | X (equiv) | temp (°C) | time (d) | yield[c] (%) | ee[d] (%) |
|---|---|---|---|---|---|---|
| 1[a] | Me | 15 | rt | 3 | 83 | 52 |
| 2[a] | Me | 15 | 0 | 3 | 43 | 53 |
| 3[b] | Me | 15 | rt | 1 | 100 | 84 |
| 4[b] | Me | 5 | rt | 1 | 100 | 88 |
| 5[b] | Me | 2.5 | rt | 1 | 100 | 92 |
| 6[b] | Me | 1.5 | rt | 1 | 98 | 92 |
| 7[b] | Me | 1.5 | 0 | 3 | 84 | 70 |
| 8[b] | Me | 1.5 | 40 | 1 | 98 | 94 |
| 9[b] | Et | 1.5 | rt | 1 | 100 | 92 |
| 10[b] | HFIPA | 1.5 | rt | 1 | 100 | 51 |
| 11[b] | *t*-Bu | 1.5 | rt | 1 | 16 | |
| 12[b] | isobutyl | 1.5 | rt | 1 | 98 | 78 |
| 13[b] | 1-naphthyl | 1.5 | rt | 1 | 98 | 71 |
| 14[b] | 2-naphthyl | 1.5 | rt | 1 | 79 | 41 |

[a]The reaction was performed without MS 4 Å. [b]MS 4 Å (200 mg) for **6a** (1.0 mmol). [c]Determined by $^1$H NMR. [d]Determined by chiral HPLC as bisbenzoylated compound (**SI-1**) after $LiAlH_4$ reduction and benzoylation.

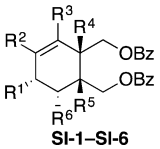



**SI-1**

**Scheme 2. Catalytic Asymmetric Diels–Alder Reaction of 6 with Methyl Acrylate Using 5[a]**




**6a,7a,SI-1**: R[1], R[3], R[4], R[5], R[6]= H; R[2]=Me; 98%, 93% ee
**6b,7b,SI-2**: R[1], R[2], R[3], R[4], R[5], R[6]= H; 83%, 94% ee
**6c,7c,SI-3**[b]: R[2], R[3], R[4], R[5], R[6]= H; R[1]=Me; 74%, 43% ee
**6d,7d,SI-4**: R[1], R[2], R[4], R[5], R[6]= H; R[3]=Me; 100%, 97% ee
**6e,7e**[c,d]: R[1], R[2], R[3], R[5], R[6]= H; R[4]=Me; trace
**6f,7f,SI-5**: R[1], R[4], R[5], R[6]= H; R[2], R[3]=Me; 94%, 94% ee
**6g,7g,SI-6**:
R[1], R[3], R[4], R[5], R[6]= H; R[2]=$CH_2CH_2OBn$; 100%, 91% ee
**6h,7h**[d,e]: R[1], R[3], R[4],R[6]= H; R[2], R[5]=Me; 8%
**6i,7i**[b,d,f]: R[1], R[3], R[4], R[5]= H; R[2], R[6]=Me; 3%




**SI-1–SI-6**

[a]MS 4 Å (200 mg) for **6** (1.0 mmol). Yield was determined by $^1$H NMR, and ee value was determined by chiral HPLC as bisbenzoylated compounds (**SI-1**–**SI-6**) after $LiAlH_4$ reduction and benzoylation. The absolute configuration of Diels–Alder adduct **7b** was determined by comparison with the optical rotation of known compound,[14c] and other products were assigned by analogy. [b]The reaction was performed for 3 days. [c]The reaction was performed for 5 days. [d]The ee value was not determined. [e]Methyl methacrylate was used. [f]Methyl crotonate was used.



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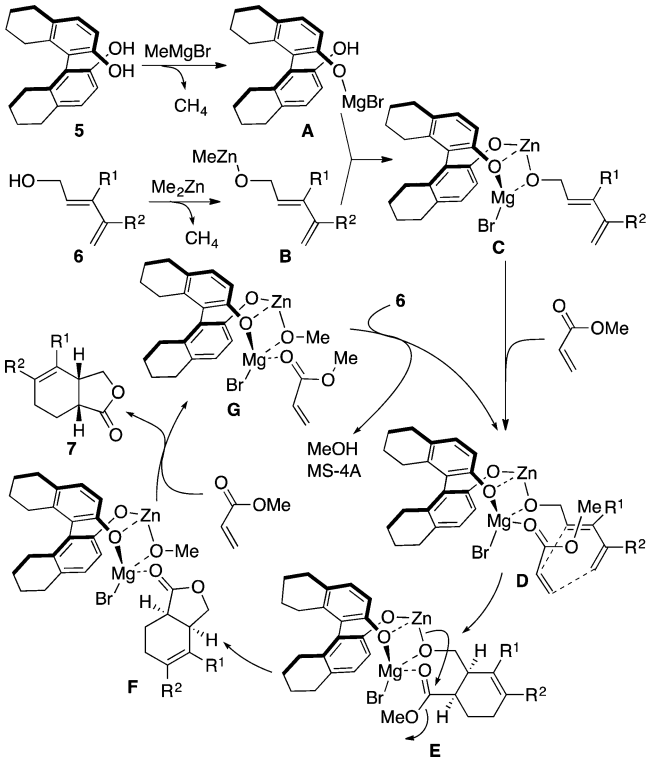
**Scheme 3. Plausible Mechanism for Tethered Diels−Alder Reaction**




In conclusion, we have successfully developed the catalytic version of Ward's LACASA-DA reaction for the first time. The use of a Zn(II)/Mg(II)−(*R*)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthoate template together with molecular sieves was found to effectively create the catalytic reaction system. The present method is highly practical in terms of yield, enantioselectivity, and mild reaction conditions. Further synthetic application for biologically active compounds is undertaken in our laboratory.

## EXPERIMENTAL SECTION

**General Methods.** Where appropriate, reactions were performed in flame-dried glassware under argon atmosphere. All extracts were dried over $MgSO_4$ and concentrated by rotary evaporation below 30 °C at 25 Torr. Commercial reagents and solvents were used as supplied with following exceptions. Tetrahydrofuran (THF) and diethyl ether ($Et_2O$) were purified by filtration through a column of activated alumina under an argon atmosphere.[19] Dichloromethane ($CH_2Cl_2$), chloroform ($CHCl_3$), benzene (PhH), toluene (PhMe), hexane, pyridine, and triethylamine ($Et_3N$) were distilled from calcium hydride. Compounds **6a**,[20] **6b**,[21] **6d**,[22] **6e**,[23] and **6f**[24] were prepared according to the literature procedure. Compound **6c** is commercially available. HRMS spectra were taken in EI (dual focusing sector field), ESI (TOF), or FAB (dual-focusing sector field) mode.

**Preparation of (*R*,*E*)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-3-methylpenta-2,4-dien-1- ol (2).** From commercially available (−)-methyl (*S*)-2,2-dimethyl-1,3-dioxolane-4-carboxylate, **2** was synthesized as shown below.

*Diethyl (1-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-1-oxopropan-2-yl)phosphonate.* To a solution of diethyl ethylphosphonate (8.31 g, 50.0 mmol) in THF (37 mL) was added *n*-BuLi (2.66 M in hexane solution; 18.8 mL, 49.9 mmol) at −78 °C, and the mixture was stirred for 2 h. To the mixture was added a solution of (−)-methyl (*S*)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (6.15 g, 38.4 mmol) in THF (62 mL), and stirring was continued for 1 h. The mixture was diluted with saturated $NH_4Cl$ (100 mL) and extracted with $Et_2O$ (100 mL) and AcOEt (100 mL). The combined organic extracts were washed with brine (100 mL), dried, and concentrated. The residue was subjected to chromatography ($SiO_2$ 300 g, hexane−AcOEt, 1:1) to furnish diethyl (1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-oxopropan-2-yl)-phosphonate. Colorless oil, 10.8 g, 95% yield, dr 2:1. IR (neat): 3476, 2986, 1721, 1453, 1378, 1248, 1156, 1023, 963, 845 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 4.74 (t, $J$ = 7.0 Hz, 0.35 × 1H), 4.69 (dd, $J$ = 7.0, 4.4 Hz, 0.65 × 1H), 4.27−3.96 (m, 6H + 0.65 × 1H), 3.59 (dq, $J_{HP}$ = 22.0, 7.3 Hz, 0.35 × 1H), 1.53 (s, 0.35 × 3H), 1.43−1.31 (m, 12H + 0.65 × 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 206.1, 205.1, 111.3, 110.5, 80.0, 79.9, 66.1, 65.7, 62.8, 62.4, 42.1, 41.9, 40.8, 40.6, 26.0, 25.8, 25.1, 25.0, 16.2, 11.7, 11.6, 10.6, 10.5. MS (EI): $m/z$ 166 (100), 193, 294 ($M^+$). HRMS (EI): $m/z$ calcd for $C_{12}H_{23}O_6$ P 294.1233, found 294.1240 ($M^+$).

*(S,E)-4-(tert-Butyldimethylsiloxy)-1-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylbut-2-en-1-one.* To a solution of diethyl (1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-oxopropan- 2-yl)phosphonate (1.60 g, 5.02 mmol) in $Et_2O$ (35 mL) were added BaO (346 mg, 2.26 mmol) and water (0.08 mL) at 0 °C, and the mixture was stirred for 20 min. To this mixture was added dropwised a solution of [(*tert*-butyldimethylsilyl)oxy]acetaldehyde (1.05 g, 6.02 mmol) in $Et_2O$ (14 mL). The reaction mixture was stirred at 0 °C for 2.5 h and at rt for 22 h. The mixture was diluted with saturated $NH_4Cl$ (10 mL) and water (20 mL) and extracted with AcOEt (30 mL × 3). Combined organic extracts were dried and concentrated, and the residue was purified by flash chromatography ($SiO_2$ 100 g, hexane−AcOEt, 10:1) to afford a ketone. Colorless oil, 1.34 g, 85% yield. $[\alpha]^{26}_D$: −1.0 (*c* 1.40, $CHCl_3$). IR (neat): 2934, 2859, 1680, 1467, 1377, 1256, 1114, 1067, 841, 779 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 6.61 (t, $J$ = 4.8 Hz, 1H), 4.98 (t, $J$ = 6.8 Hz, 1H), 4.34 (d, $J$ = 5.1 Hz, 2H), 4.14 (dd, $J$ = 8.0, 6.8 Hz, 1H), 3.98 (dd, $J$ = 8.0, 6.8 Hz, 1H), 1.67 (s, 3H), 1.33 (s, 6H), 0.82 (s, 9H), 0.00 (s, 6H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 197.0, 144.7, 134.1, 110.7, 76.6, 66.7, 60.8, 25.9, 25.8, 25.6, 18.3, 11.7, −5.3. MS (ESI): $m/z$ 337 [(M + Na)$^+$]. HRMS (ESI): $m/z$ calcd for $C_{16}H_{30}NaO_4Si$ [(M + Na)$^+$] 337.1811, found 337.1820.

*(R,E)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-3-methylpenta-2,4-dien-1-ol (2).* To a suspension of methyltriphenylphosphonium bromide (2.79 g, 7.69 mmol), prepared by heating at 100 °C for 1 h, in THF (17 mL) was added *n*-BuLi (2.69 M in hexane solution; 2.5 mL, 6.75 mmol), and the mixture was stirred at 0 °C for 1 h. To this mixture was added a solution of the above-mentioned ketone (1.34 g, 4.26 mmol) in THF (26 mL). The reaction mixture was stirred at 0 °C for 12 h. The mixture was diluted with saturated $NH_4Cl$ (25 mL) and water (10 mL) and extracted with AcOEt (30 mL × 3). The combined organic extracts were dried and concentrated to afford crude diene (3.81 g).

To a solution of the diene (3.81 g) in THF (20 mL) was added tetrabutylammonium fluoride (1 M in THF solution; 6.4 mL, 6.4 mmol) at 0 °C, and the mixture was stirred at rt for 3 h. The reaction mixture was concentrated in vacuo, and the residue was subjected to silica gel column chromatography ($SiO_2$ 100 g, hexane−AcOEt, 2:1 to 1:1) to afford **2**. Yellow oil, 36 mg, 97%. $[\alpha]^{27}_D$: −39.8 (*c* 1.04, $CHCl_3$). IR (neat): 3412, 2987, 1611, 1378, 1216, 1158, 1065, 910, 861, 515 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 5.59 (t, $J$ = 6.3 Hz, 1H), 5.47 (s, 1H), 5.24 (s, 1H), 4.90 (dd, $J$ = 6.9, 6.3 Hz, 1H), 4.31−4.26 (m, 3H), 3.58 (dd, $J$ = 6.9, 6.3 Hz, 1H), 1.85 (s, 3H), 1.48 (s, 3H), 1.44 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 146.8, 135.4, 126.2, 111.4, 109.1, 75.4, 70.3, 59.7, 26.3, 25.6, 14.9. MS (EI): $m/z$ 167 (100), 183, 198 ($M^+$). HRMS (EI): $m/z$ calcd for $C_{11}H_{18}O_3$ ($M^+$) 198.1256, found 198.1254.

**(3a*R*,7a*R*)-5-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-4-methyl-3a,6,7,7a-tetrahydroisobenzofuran-1(3*H*)-one (3a).** To a solution of **2** (121 mg, 0.61 mmol) in $CH_2Cl_2$ (3 mL) was added dimethylzinc (0.92 M in hexane; 0.13 mL, 0.12 mmol) at 0 °C, and the mixture was stirred for 5 min. In another vessel, MeMgBr (1.0 M in THF; 0.12 mL, 0.12 mmol) was added to a solution of (*R*)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol (36 mg, 0.12 mmol) in $CH_2Cl_2$ (0.6 mL) at 0 °C, and the mixture was stirred for 5 min. The former mixture was added to the latter mixture, and stirring was continued for 5 min. The combined mixture was diluted with $CH_2Cl_2$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(1.5 mL), and methyl acrylate (0.8 mL, 9.1 mmol) was added. After being stirred at rt for 24 h, the mixture was diluted with satd $NaHCO_3$ (5 mL) and filtered through Celite. The filtrate was dried and concentrated, and the residue was subjected to chromatography ($SiO_2$ 10 g, hexane−AcOEt, 1:1) to afford **3a**. White crystals, 148 mg, 96%. Mp: 90.5−91.5 °C. $[\alpha]^{27}_D$: −121.7 (*c* 0.92, $CHCl_3$). IR (neat): 2984, 1933, 1768, 1449, 1374, 1297, 1209, 1154, 1056, 862 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ 5.01 (t, *J* = 7.3 Hz, 1H), 4.48 (t, *J* = 8.3 Hz, 1H), 4.10 (dd, *J* = 8.8, 5.9 Hz, 1H), 4.03 (dd, *J* = 8.0, 7.3 Hz, 1H), 3.54 (dd, *J* = 8.0, 7.3 Hz, 1H), 3.00−2.96 (m, 1H), 2.77−2.74 (m, 1H), 2.29−2.20 (m, 1H), 2.00−1.89 (m, 2H), 1.85−1.76 (m, 1H), 1.73 (s, 3H), 1.45 (s, 3H), 1.39 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 178.8, 131.3, 127.6, 109.2, 74.3, 70.9, 67.0, 41.0, 38.5, 26.3, 25.5, 21.0, 20.7, 16.7. MS (EI): *m*/*z* 72 (100), 252 ($M^+$). HRMS (EI): *m*/*z* calcd for $C_{14}H_{20}O_4$ ($M^+$) 252.1362, found 252.1374.

**Preparation for Dienol 6g.** From known 4-(benzyloxy)-2-methylenebutanal,[25] compound **6g** was synthesized as shown below.

*Ethyl (E)-6-(Benzyloxy)-4-methylenehex-2-enoate.* To a solution of (carbethoxymethylene)triphenylphosphorane 6.38 g (18.3 mmol) in $CH_2Cl_2$ (100 mL) was added a solution of 4-(benzyloxy)-2-methylenebutanal (2.32 g, 12.2 mmol) in $CH_2Cl_2$ (22 mL). The reaction mixture was refluxed for 13 h. The mixture was diluted with $H_2O$ (50 mL), extracted with $Et_2O$ (50 mL × 3), dried, and concentrated. The residue was subjected to chromatography ($SiO_2$ 100 g, hexane−AcOEt, 5:1) to furnish the titled ester. Colorless oil, 2.89 g, 91% yield. $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.34−7.30 (m, 6H), 5.94 (d, *J* = 16.0 Hz, 1H), 5.46 (s, 1H), 5.40 (s, 1H), 4.52 (s, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.62 (t, *J* = 6.8 Hz, 2H), 2.57 (t, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 6.8 Hz, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 167.1, 146.4, 141.5, 138.2, 128.4, 127.6, 124.6, 118.4, 100.5, 73.0, 68.5, 60.4, 31.9, 14.3. IR (neat): 2863, 1717, 1631, 1454, 1366, 1275, 1105, 914, 869, 741 $cm^{-1}$. MS (EI): *m*/*z* 61, 88, 91, 126, 139, 154, 169, 187, 215, 230, 242, 260. HRMS (EI): *m*/*z* calcd for $C_{16}H_{20}O_3$ ($M^+$) 260.1413, found 260.1411.

*(E)-6-(Benzyloxy)-4-methylenehex-2-en-1-ol (**6g**).* To a solution of the above-mentioned ester (2.89 g, 11.1 mmol) in $CH_2Cl_2$ (110 mL) was added DIBAL (1.02 M in hexane; 23.7 mL, 24.2 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 15 h, saturated aqueous Rochelle salt (100 mL) was added, and the mixture was stirred at room temperature for 3 h. The mixture was extracted with $Et_2O$ (100 mL × 3), dried, and concentrated. The residue was subjected to chromatography ($SiO_2$ 100 g, hexane−AcOEt, 2:1) to furnish **6g**. Pale yellow oil, 2.00 g, 83% yield. $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.34−7.28 (m, 5H), 6.27 (d, *J* = 16.0 Hz, 1H), 5.86 (dt, *J* = 16.0, 5.6 Hz, 1H), 5.09 (s, 1H), 5.04 (s, 1H), 4.53 (s, 2H), 4.19 (t, *J* = 5.6 Hz, 2H), 3.62 (t, *J* = 7.2 Hz, 2H), 2.56 (t, *J* = 7.2 Hz, 2H), 1.47 (br, 1H). $^{13}C$ NMR (400 MHz, $CDCl_3$): δ 142.1 138.4, 133.2, 128.4, 128.0, 127.7, 127.6, 117.1, 72.9, 68.9, 63.6, 32.4. IR (neat): 3368, 2860, 1606, 1365, 1096, 971, 894, 741 $cm^{-1}$. MS (EI): *m*/*z* 41, 65, 79, 83, 91, 112, 127, 143, 155, 174, 187, 200, 218. HRMS (EI): *m*/*z* calcd for $C_{14}H_{18}O_2$ ($M^+$) 218.1307, found 218.1313.

**General Procedure for Lewis Acid Template-Catalyzed Diels−Alder Reactions.** To a solution of **6** (1.00 mmol) in $CH_2Cl_2$ (5 mL) was added dimethylzinc (1.02 M in hexane solution; 0.196 mL, 0.20 mmol) at 0 °C, and the mixture was stirred for 30 min. In another vessel, MeMgBr (3.0 M in $Et_2O$ solution; 0.067 mL, 0.20 mmol) was added to a mixture of (*R*)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol (58.9 mg, 0.20 mmol) and dried MS-4 Å powder (200 mg) in $CH_2Cl_2$ (1.0 mL) at 0 °C, and the mixture was stirred for 30 min. The former mixture and washings with $CH_2Cl_2$ (1.6 mL) were added to the latter one, and stirring was continued for 30 min. The combined mixture was diluted with $CH_2Cl_2$ (2.4 mL), methyl acrylate (0.135 mL, 1.5 mmol) was added, and stirring was continued at rt for 24 h, The reaction mixture was diluted with satd $NaHCO_3$ (5 mL) and filtered through Celite. The filtrate was dried and concentrated and the residue was subjected to chromatography ($SiO_2$ 10 g, hexane−AcOEt, 15:1 or PhMe−AcOEt, 5:1) to afford the desired product.

*(3aS,7aR)-5-Methyl-3a,6,7,7a-tetrahydroisobenzofuran-1(3H)-one (**7a**).* Colorless oil, 149 mg, 98% yield. $[\alpha]^{25}_D$: −163.5 (*c* 1.83, MeOH). $^1H$ NMR (400 MHz, $CDCl_3$): δ 5.30 (s, 1H), 4.34 (dd, *J* = 8.8, 6.4 Hz, 1H), 4.02 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.04 (s, 1H), 2.80−2.76 (m, 1H), 2.15−1.69 (m, 4H), 1.69 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 201.4, 138.1, 119.4, 72.5, 37.5, 35.7, 25.9, 24.0, 20.1. IR (neat): 3520, 2931, 1785, 1163, 821, 713, 639, 520, 475. MS (EI): *m*/*z* 41, 55, 77, 79, 94, 107, 117, 137, 152. HRMS (EI): *m*/*z* calcd for $C_9H_{12}O_2$ ($M^+$) 152.0838, found 152.0821.

*(3aS,7aR)-3a,6,7,7a-Tetrahydroisobenzofuran-1(3H)-one (**7b**).* Colorless oil, 115 mg, 83% yield. $[\alpha]^{22}_D$: −142.3 (*c* 1.175, $CHCl_3$) (lit.[14c] $[\alpha]^{22}_D$ −117.0 (*c* 1.00, $CHCl_3$)). $^1H$ NMR (400 MHz, $CDCl_3$): δ 5.93−5.91 (m, 1H), 5.59 (d, *J* = 10.0 Hz, 1H), 4.35 (td, *J* = 8.8, 2.4 Hz, 1H), 4.03 (dt, *J* = 8.8, 2.2 Hz, 1H), 3.06 (br, 1H), 2.82 (t, *J* = 5.6 Hz, 1H), 2.08−2.01 (m, 3H), 1.81−1.74 (m, 1H). $^{13}C$ NMR (400 MHz, $CDCl_3$): δ 178.5, 130.5, 125.1, 72.0, 37.9, 35.2, 20.9, 19.5. IR (neat): 2921, 1773, 1440, 1371, 1139, 1037, 991, 862, 772, 664 $cm^{-1}$. MS (EI): *m*/*z* 79, 80, 93, 107, 123, 138. HRMS (EI): *m*/*z* calcd for $C_8H_{10}O_2$ ($M^+$) 138.0681, found 138.0677.

*(3aS,6S,7aR)-6-Methyl-3a,6,7,7a-tetrahydroisobenzofuran-1(3H)-one (**7c**).* Pale yellow crystals, 112 mg, 74% yield. Mp: 35.0−37.0 °C. $[\alpha]^{28}_D$: −123.5 (*c* 1.00, $CHCl_3$), $^1H$ NMR (400 MHz, $CDCl_3$): δ 5.76 (d, *J* = 10.2 Hz, 1H), 5.58 (dt, *J* = 10.2, 2.8 Hz, 1H), 4.47 (t, *J* = 8.6 Hz, 1H), 3.92 (t, *J* = 8.6 Hz, 1H), 3.06 (br, 1H), 2.74−2.67 (m, 1H), 2.25 (br, 1H), 2.04 (dt, *J* = 13.2, 4.8 Hz, 1H), 1.63 (d, *J* = 7.2 Hz, 3H), 1.41−1.32 (m, 1H), $^{13}C$ NMR (100 MHz, $CDCl_3$): 179.4, 136.5, 122.6, 71.9, 38.2, 35.0, 28.9, 28.8, 21.2; IR (neat): 2957, 1790, 1454, 1041, 899, 746 $cm^{-1}$, MS (EI): *m*/*z* 43, 53, 77, 79, 94, 107, 124, 137, 152, HRMS (EI): *m*/*z* calcd for $C_9H_{12}O_2$ ($M^+$) 152.0837, found 152.0835.

*(3aR,7aR)-4-Methyl-3a,6,7,7a-tetrahydroisobenzofuran-1(3H)-one (**7d**).* Colorless oil, 152 mg, 100% yield. $[\alpha]^{29}_D$: −168.9 (*c* 1.01, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): δ 5.64 (s, 1H), 4.39 (dd, *J* = 8.8 Hz, 7.4 Hz, 1H), 4.15−4.12 (m, 1H), 2.92 (br, 1H), 2.82−2.77 (m, 1H), 2.01−1.87 (m, 3H), 1.80−1.72 (m, 1H), 1.70 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 179.1, 130.4, 125.2, 70.7, 39.4, 38.6, 21.9, 21.2, 20.2. IR (neat): 2931, 1792, 905, 652 $cm^{-1}$. MS (EI): *m*/*z* 41, 53, 77, 79, 94, 107, 124, 137, 152. HRMS (EI): *m*/*z* calcd for $C_9H_{12}O_2$ ($M^+$) 152.0837, found 152.0846.

*(3aR,7aR)-4,5-Dimethyl-3a,6,7,7a-tetrahydroisobenzofuran-1(3H)-one (**7f**).* White crystals, 156 mg, 94% yield. Mp: 46.0−49.0 °C. $[\alpha]^{26}_D$ −85.2 (*c* 0.750, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): δ 4.38 (dd, *J* = 9.0, 7.2 Hz, 1H), 4.10 (dd, *J* = 9.0, 4.4 Hz, 1H), 2.93 (br, 1H), 2.76 (br, 1H), 2.03−1.75 (m, 4H), 1.65 (s, 6H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 179.3, 130.5, 122.2, 71.3, 40.9, 38.8, 28.4, 20.7, 19.7, 16.8. IR (neat): 2916, 1774, 1444, 1376, 1299, 1159, 1026 $cm^{-1}$. MS (EI): *m*/*z* 41, 65, 77, 91, 93, 108, 121, 138, 151, 166 ($M^+$). HRMS (EI): *m*/*z* calcd for $C_{10}H_{14}O_2$ ($M^+$) 166.0994, found 166.0993.

*(3aS,7aR)-5-[2-(Benzyloxy)ethyl]-3a,6,7,7a-tetrahydroisobenzofuran-1(3H)-one (**7g**).* Pale yellow oil, 272 mg, 100% yield. $[\alpha]^{26}_D$: −107.3 (*c* 0.96, MeOH). $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.37−7.17 (m, 5H), 5.39 (s, 1H), 4.49 (s, 2H), 4.34 (dd, *J* = 8.9, 6.7 Hz, 1H), 4.01 (dd, *J* = 8.9, 2.4 Hz, 1H), 3.57−3.48 (m, 2H), 3.07 (br, 1H), 2.81 (m, 1H), 2.30 (t, 2H), 2.13−1.89 (m, 3H), 1.82−1.73 (m, 1H). $^{13}C$ NMR (400 MHz, $CDCl_3$): δ 178.6, 138.9, 128.3, 128.1, 127.5, 127.5, 120.6, 72.9, 72.3, 68.2, 38.0, 37.6, 35.6, 24.5, 20.2. IR (neat): 2914, 1777, 1444, 1372, 1291, 1113, 1027, 743 $cm^{-1}$. MS (EI): *m*/*z* 43, 61, 88, 91, 105, 135, 151, 166, 181, 196, 226, 242, 254, 272. HRMS (EI): *m*/*z* calcd for $C_{17}H_{20}O_3$ ($M^+$) 272.1413, found 272.1416.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Copies of $^1H$ and $^{13}C$ NMR spectra and copies of chiral HPLC charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.



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