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Formal Synthesis of Gracilamine Using Rh(I)-Catalyzed [3 + 2 + 1] Cycloaddition of 1-Yne−Vinylcyclopropanes and CO

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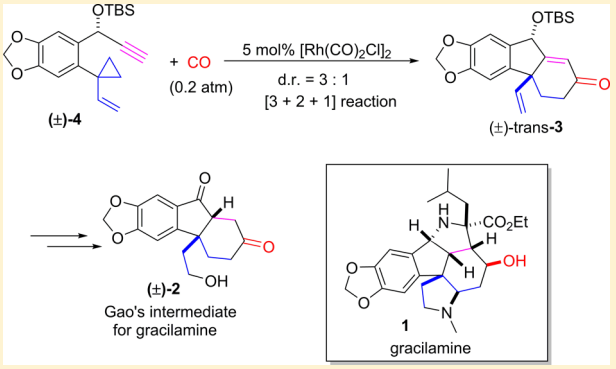
Supporting Information

ABSTRACT: Reported here is a formal synthesis of gracilamine using Rh(I)-catalyzed [3 + 2 + 1] reaction of yne-VCP (±)-**4** and CO. The key reaction gave the cycloadduct (±)-*trans*-**3** with the A−B−C core structure of gracilamine. This advanced intermediate was further transformed to Gao's intermediate (±)-**2** via regular transformations to realize the formal synthesis of gracilamine. The present strategy was used to accomplish the asymmetric formal synthesis of gracilamine using chiral substrate (+)-**4**.



Gracilamine (**1**) is a structurally novel pentacyclic ring containing alkaloid belonging to the Amaryllidaceae alkaloid family (Scheme 1). It was isolated from *Galanthus gracilis*, collected from the Turkish mountain by Ünver and Kaya in 2005.[1] Plants from the Amaryllidaceae family have long been recognized for their medicinal properties ranging from antitumor, antiviral, and anti-inflammatory activities to immunostimulatory and acetylcholinesterase inhibitory activities.[2] Owing to the limited availability of gracilamine in nature, the biological activities of this potentially important compound have not been determined yet.

The appealing structure, potential biological activity and the scarcity of this natural product have prompted the synthetic chemists to develop routes toward the total synthesis of gracilamine. Till date only two total synthesis of gracilamine have been reported. In 2012, Ma and co-workers reported the first total synthesis of gracilamine using a biomimetic intramolecular [3 + 2] cycloaddition.[3] In 2014, Gao and co-workers reported another elegant route for the total synthesis of gracilamine using a photo-Nazarov reaction as the key step to synthesize (±)-**2** with the linearly fused A−B−C ring of gracilamine.[4] The advanced intermediate (±)-**2** was ultimately converted to gracilamine after a few steps. Recently, Snyder and co-workers reported a formal synthesis of gracilamine using intramolecular Diels−Alder reaction as key step.[5] Syntheses of the above three groups are racemic. Developing new routes, especially asymmetric ones, are highly required in order to provide asymmetric gracilamine for further investigations.

Recently we developed a Rh(I)-catalyzed [3 + 2 + 1] cycloaddition of 1-ene/yne−vinylcyclopropanes (VCPs) and CO,[6] which can be used to construct 5,6- and 6,6-bicyclic systems (Scheme 2). A salient feature of this cycloaddition reaction is that the bridgehead quaternary center can be built, which is still a formidable challenge in synthesis.[7] The impact of this Rh(I)-catalyzed [3 + 2 + 1] reaction in synthesis has been demonstrated through its use as key step in the total synthesis of (±)-agarofuran[6] and the formal syntheses of (±)-galanthamine and (±)-lycoramine.[8]

Building on our previous achievements, we were keen to apply our [3 + 2 + 1] reaction to the formal synthesis of gracilamine (Scheme 1). The key step in our design is to convert yne-VCP substrate (±)-**4** via the [3 + 2 + 1] reaction to (±)-*trans*-**3**, which has the A−B−C core structure of gracilamine and can be further converted to Gao's intermediate (±)-**2**.[9] In addition to this desire of realizing the formal synthesis, we also wanted to answer a critical question related to the key [3 + 2 + 1] cycloaddition reaction which is, whether we can achieve reasonable chiral induction (or high diastereoselective ratio) of the [3 + 2 + 1] reaction and whether the diastereomers from this reaction can be separated, when a chiral substrate (+)-**4** is used. If the answer to this question is yes, then the present formal synthesis could serve as an asymmetric route to gracilamine, which has not been fulfilled so far. With the above-mentioned purposes, we began our racemic synthesis first and then tested its asymmetric version, both of which are reported here.

Our synthesis commenced from the known bromide **5**,[10] which was obtained by bromination of commercially available piperonyl cyanide (Scheme 3). Compound **5** underwent cyclopropanation by treatment with ethylene dibromide and lithium amide in DME at 80 °C,[11] giving **6** in 71% yield. The

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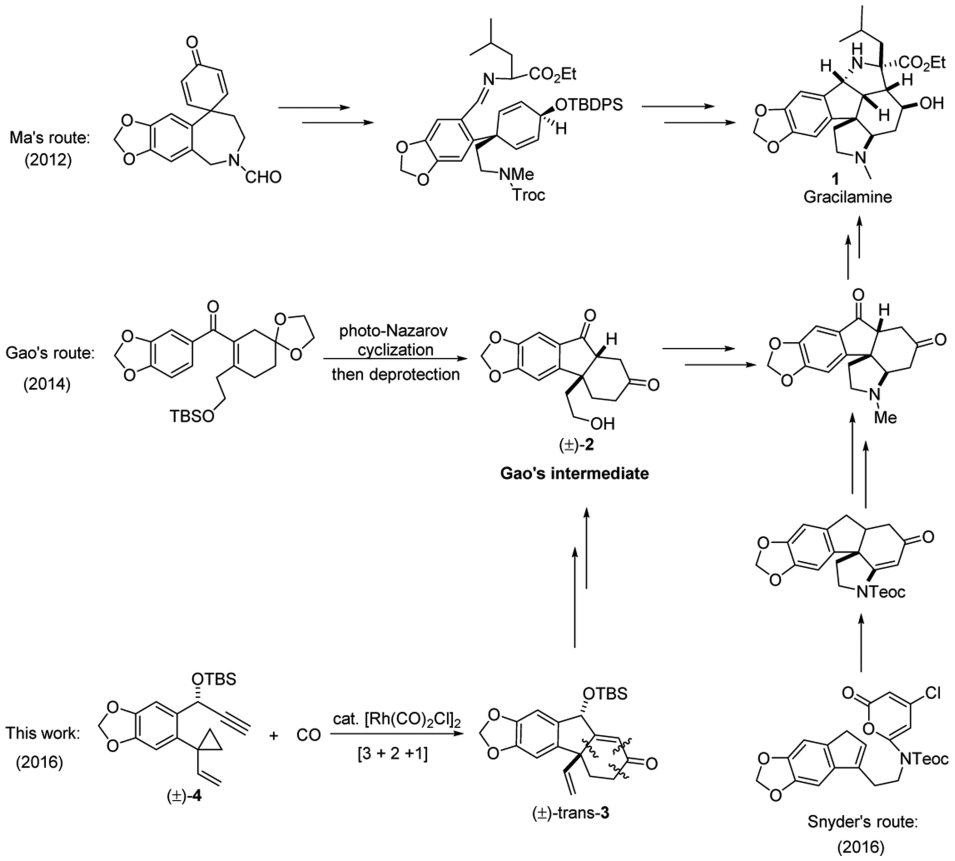
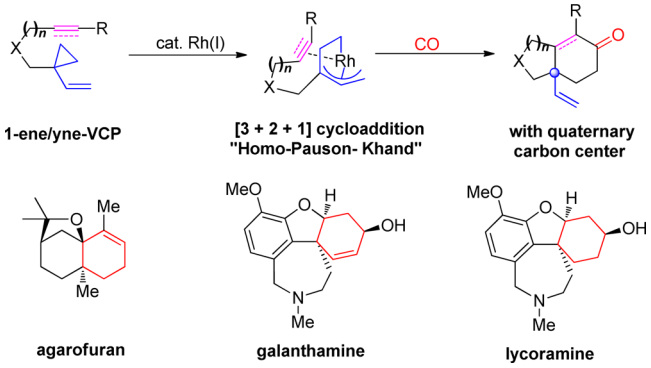
Scheme 1. Gracilamine and Its Synthesis by Ma, Gao, Snyder and Us (Present Work)

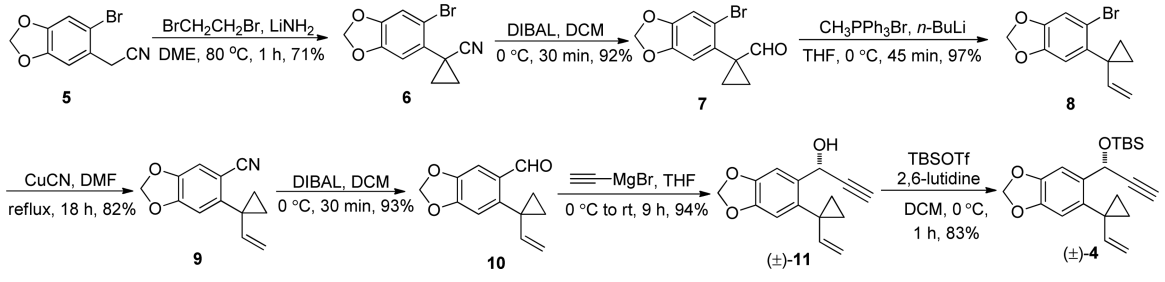


Scheme 2. [3 + 2 + 1] Reaction and the Natural Products Synthesized Employing This Reaction



cyanide group of **6** was then converted to aldehyde by treating **6** with DIBAL, followed by acidification, generating the cyclopropane aldehyde **7** in 92% yield. The aldehyde compound was subjected to 1-carbon elongation Wittig reaction to form the vinyl cyclopropane **8** in 97% yield. In order to introduce a propargyl group in place of the bromo group in **8**, we planned to convert the bromo group directly to an aldehyde group, which can then be easily transformed to a propargyl functionality. But lithium-halogen exchange with *n*-butyllithium followed by treatment with either DMF[12] or TMS-acetylene aldehyde[13] failed to give our desired product **10** or (±)-**11**, possibly because of the steric bulk of the adjacent vinyl cyclopropane moiety. Due to these reasons, we turned our attention to convert the bromo group to a cyano group via cyanation, by refluxing the compound **8** with copper cyanide in DMF,[14] which afforded the compound **9** in 82% yield. Then the cyano group in **9** was easily converted to aldehyde by treatment with DIBAL, followed by acidification, generating **10** in 93% yield. The aldehyde group in **10** then underwent Grignard reaction with ethynyl magnesium bromide, giving rise

Scheme 3. Preparation of [3 + 2 + 1] Reaction Substrate (±)-4



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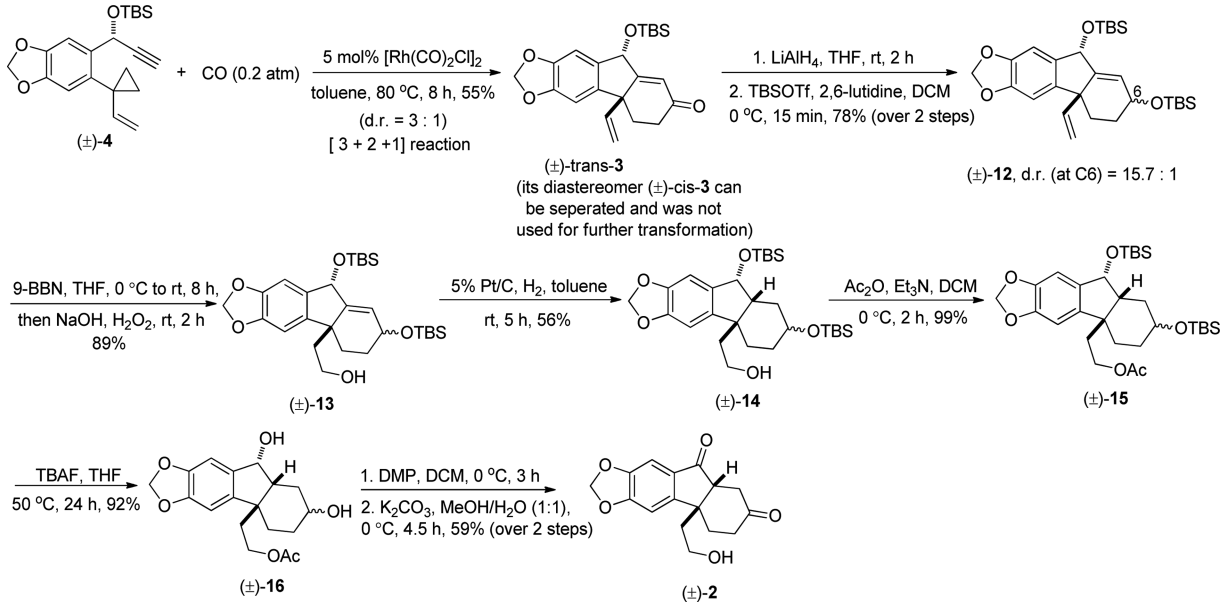
Scheme 4. Racemic Synthesis of Gracilamine through Synthesis of Gao's Intermediate (±)-2



to the desired propargylic alcohol (±)-**11** in 94% yield.[15] The hydroxyl functionality was protected with TBS group to give the desired [3 + 2 + 1] reaction substrate (±)-**4** in 83% yield.

Next, we tried the key Rh(I)-catalyzed [3 + 2 + 1] cycloaddition of (±)-**4** and CO at 80 °C with 5 mol % of the rhodium catalyst under a balloon pressured mixed gas of CO and N_2 (the ratio of CO/N_2 was 1/4, and this was usually labeled as 0.2 atm CO). To our delight, the target reaction occurred smoothly and gave the desired 5/6 ring-fused product **3** in 55% yield with a diastereomeric ratio of about 3:1, which was determined by crude ^{1}H NMR (Scheme 4). (±)-*trans*-**3** was the major product of the [3 + 2 + 1] reaction, and this can be understood by the two competing alkyne insertion transition states, which determine the stereochemistry of the final [3 + 2 + 1] reaction (Figure 1).[16−18] Both **TS-*trans* and TS-*cis*** suffer

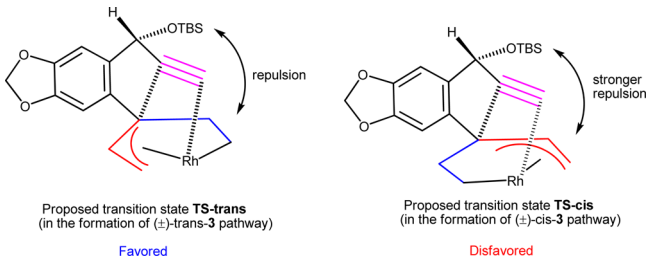


Figure 1. Two proposed alkyne insertion transition states, which determine the relative stereochemistry of the [3 + 2 + 1] reaction.

the steric repulsions (as indicated in Figure 1), but the repulsion between the OTBS group and the ethyl moiety (in blue, which comes from the original cyclopropyl group) in the former transition state is less than the repulsion between OTBS group and the vinyl moiety (in red) in the latter transition state, as judged by the experimental preference of the formation of (±)-*trans*-**3**.

The mixture of the [3 + 2 + 1] adducts (±)-*trans*-**3** and (±)-*cis*-**3** were subjected to careful column chromatography to get their single diastereomers, respectively. Attempts to reduce the ketone and the *α,β*-unsaturated double bond in major diastereomer (±)-*trans*-**3** simultaneously by refluxing with lithium aluminum hydride, or by treatment with L-Selectride[19] at low temperature failed. In both cases, only the carbonyl group in (±)-*trans*-**3** was reduced, keeping the *α,β*-unsaturated double bond intact. Moreover, treating (±)-*trans*-**3** with a combination of nickel chloride and sodium borohydride surprisingly resulted in the reduction of both *α,β*-unsaturated double bond and the vinylic double bond, leading to an undesired saturated compound, as judged by crude NMR spectrum of the reaction product. Due to these unsuccessful attempts, we decided to reduce first the carbonyl group in (±)-*trans*-**3** to give its corresponding alcohol, by treatment with lithium aluminum hydride. Then this crude alcohol was subjected to TBS protection using TBSOTf and 2,6-lutidine as base, affording compound (±)-**12** in 78% yield (over 2 steps) with a diastereomeric ratio of about 15.7:1 at C6. Next, the vinylic double bond present at the junction of the 5/6 fused ring system in (±)-**12** was subjected to hydroboration-oxidation reaction with 9-BBN[20] to afford the corresponding primary alcohol (±)-**13** in 89% yield. Then hydrogenation was carried out by using Pt/C and hydrogen gas to reduce the double bond inside the 6-membered ring, affording compound (±)-**14** in 56% yield. Acetylation of (±)-**14** with acetic anhydride, triethylamine and a catalytic amount of DMAP, afforded compound (±)-**15** in 99% yield. The secondary TBS ethers in (±)-**15** were deprotected by treatment with excess TBAF to afford the diol (±)-**16** in 92% yield.[21]

Diol (±)-**16** by treatment with Dess−Martin Periodinane underwent oxidation to afford the corresponding diketone, which was used in the next reaction after careful work up without further purification. The diketone, when treated with potassium carbonate in methanol at 0 °C, underwent deacetylation, generating our target compound (±)-**2** in 59% yield (over 2 steps). The NMR data of compound (±)-**2** obtained in this study matched with that of Gao's intermediate, indicating the success of the formal racemic synthesis of gracilamine.[4]

Then we embarked on the asymmetric formal synthesis of gracilamine by obtaining a chiral substrate (+)-**4**, considering that the diastereoselectivity of [3 + 2 + 1] reaction was an

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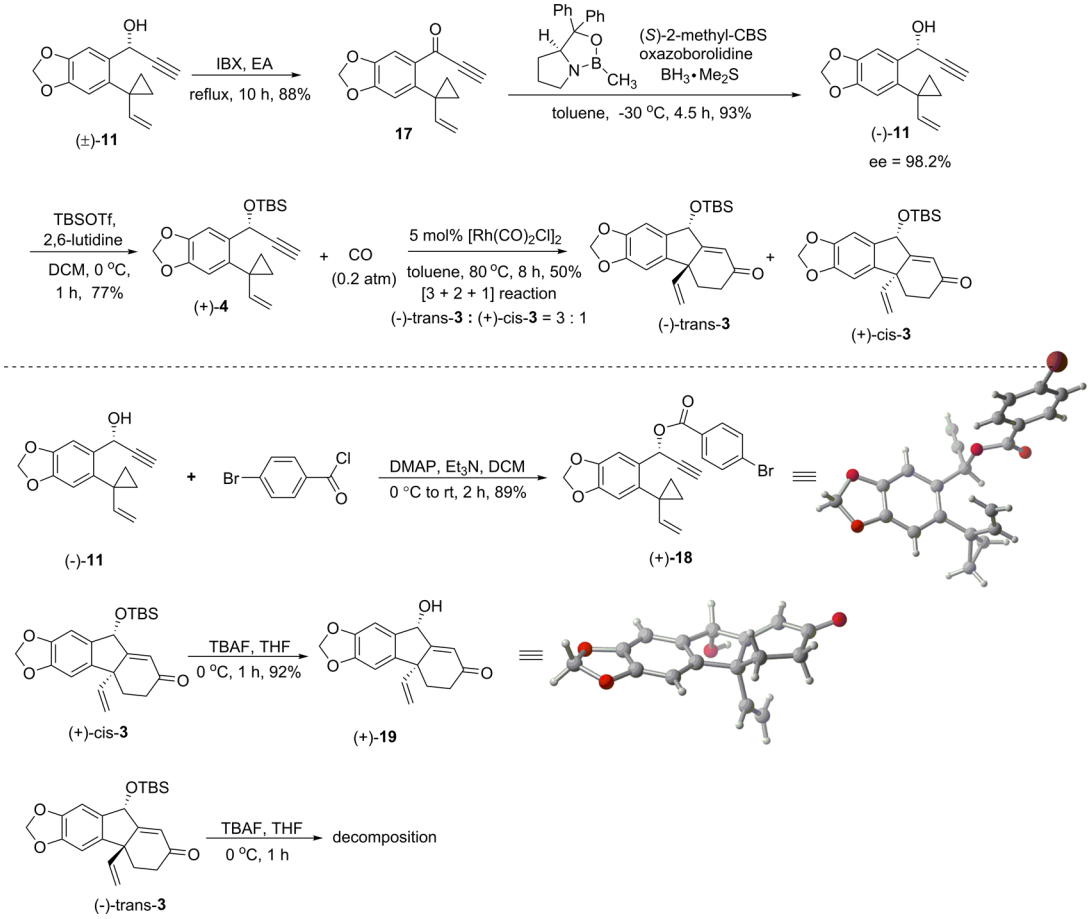
Scheme 5. Asymmetric Formal Synthesis of Gracilamine and Confirmation of Stereochemistry of Several Key Intermediates

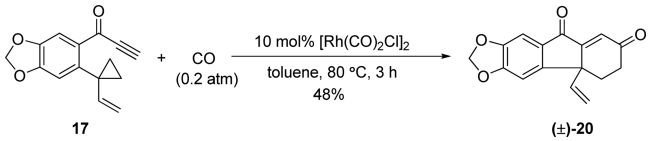


acceptable 3:1 (Scheme 5). Initially we tried to do an asymmetric alkynylation on the aldehyde **10**. Probably due to the steric hindrance caused by the adjacent vinyl cyclopropane moiety, several known methods such as Zn-promoted,[22a] Ti-catalyzed[22b−d] and In-catalyzed[22e] asymmetric alkynylation reactions failed. Hence we performed the Grignard reaction on aldehyde **10** with ethynylmagnesium bromide, as done previously, to form the propargyl alcohol (±)-**11**, which was then oxidized to ketone **17** on refluxing with IBX for 10 h in ethyl acetate.[23] This ketone was then reduced using (*S*)-CBS (Corey−Bakshi−Shibata) reagent[24] and $BH_3{\cdot}Me_2S$[25] to afford the asymmetric propargyl alcohol (−)-**11** in 98.2% ee (Scheme 5). The absolute configuration of (−)-**11** was confirmed by X-ray crystallography of its derivative, (+)-**18** (Scheme 5) . Protection of alcohol gave chiral substrate, (+)-**4**. The Rh(I)-catalyzed [3 + 2 + 1] reaction of (+)-**4** and CO gave (−)-*trans*-**3** and (+)-*cis*-**3** in a combined yield of 50%, still with diastereomeric ratio of 3:1. Both (−)-*trans*-**3** and (+)-*cis*-**3** can be respectively used for the asymmetric synthesis of gracilamine.

Scheme 5 also includes our efforts to confirm the stereochemistry of (−)-*trans*-**3** and (+)-*cis*-**3**. Deprotection of (−)-*cis*-**3** with TBAF generated (+)-**19**, and its structure was assured by X-ray analysis. Surprisingly, deprotection of (−)-*trans*-**3** with TBAF resulted in decomposition (the reason for this was unclear to us). We assigned the absolute structure of (−)-*trans*-**3** as the opposite diastereomer of (+)-*cis*-**3**.

Here, we point out that compound **17** can also undergo the [3 + 2 + 1] reaction with CO, even though its yield was only 48% when 10 mol % catalyst was used (Scheme 6).

Scheme 6. [3 + 2 + 1] Reaction of 17 with CO



In summary, we have developed an efficient approach toward the formal synthesis of gracilamine by using our [3 + 2 + 1] cycloaddition of 1-yne−vinylcyclopropane and CO. We also realized the asymmetric version of this route to gracilamine when chiral substrate (+)-**4** was used, even though the diastereoselectivity of the [3 + 2 + 1] reaction was moderate. This strategy could be used to synthesize other natural products containing 5/6 ring-fused hydrofluorenone core structures. We encourage more scientists to use this method in their target- and function-oriented synthesis.

EXPERIMENTAL SECTION

General Information. Air- and moisture-sensitive reactions were carried out in oven-dried glassware sealed with rubber septa under a positive pressure of dry argon. Similarly, sensitive liquids and solutions were transferred via syringe. Reactions were stirred using Teflon coated magnetic stir bars. Elevated temperatures were maintained using thermostat-controlled silicone oil baths. Organic solutions were

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concentrated using a rotary evaporator with a desktop vacuum pump. Tetrahydrofuran (THF), dimethoxyethane (DME) and toluene were distilled from sodium and benzophenone prior to use. Dichloromethane (DCM) was distilled from CaH_2 prior to use. *N*,*N*′-Dimethylformamide (DMF) and methanol were dried by molecular sieves prior to use. Synthetic reagents were purchased and used without further purification unless otherwise indicated. Analytical TLC was performed with 0.25 mm silica gel G plates with a 254 nm fluorescent indicator. The TLC plates were visualized by ultraviolet light and treatment with phosphomolybdic acid stain followed by gentle heating. Purification of products was accomplished by flash chromatography on silica gel, and the purified compounds showed a single spot by analytical TLC. The diastereomeric ratio was determined by ^{1}H NMR of crude reaction mixtures. NMR spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C using $CDCl_3$ (^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm) or C_6D_6 (^{1}H, 7.16 ppm; ^{13}C, 128.0 ppm) as internal standard. The following abbreviations were used to explain the multiplicities: s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, m = multiplet, coupling constant (Hz), and integration. IR spectra were recorded on Bruker Tensor 27 Fourier transform infrared spectrometer and reported in wavenumbers (cm^{-1}). HRMS were recorded on Bruker Apex IV FTMS mass spectrometer (ESI) or Micromass U.K. GCT GC-MS mass spectrometer (EI). Optical rotations were measured on a PerkinElmer 341 LC spectrometer. Enantiomer excess (ee) values were determined by analytical liquid chromatography (HPLC) analysis on a Shimadzu chromatograph (Daicel chiral columns Chiralpak IA, IC, and ID (4.6 × 250 mm). PE refers to petroleum ether and EA refers to ethyl acetate.

*1-(6-Bromobenzo[d][1,3]dioxol-5-yl)cyclopropanecarbonitrile (**6**).* 2-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)acetonitrile **5** (3.06 g, 12.7 mmol) and $LiNH_2$ (2.88 g, 125.2 mmol) were dissolved in DME (35 mL) at ambient temperature under an argon atmosphere and 1,2−dibromoethane (5.5 mL, 63.5 mmol) was added dropwise over 15 min whereupon its color changed to brown. The mixture was heated at 80 °C for 1 h and during the course of the reaction, the color of the mixture changed to black. The mixture was cooled on an ice/water bath diluted with diethyl ether (100 mL) and quenched with dropwise addition of water (30 mL). The mixture was extracted with diethyl ether (3 × 30 mL) and the combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate and the solvent was evaporated. The residue was purified through column chromatography on silica gel (PE/EA 10:1) to yield the product **6** (2.41 g, 71% yield) as a yellow solid.

6. Yellow solid. mp = 110−112 °C. TLC R_f (PE/EA 5:1) = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (dd, J = 7.5, 5.3 Hz, 2H), 1.73 (dd, J = 7.5, 5.3 Hz, 2H), 6.00 (s, 2H), 6.81 (s, 1H), 7.05 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.4, 17.3, 102.2, 111.2, 113.2, 117.7, 121.6, 128.1, 147.4, 148.8. IR (neat): ν 2913, 2229, 1612, 1503, 1478, 1417, 1395, 1343, 1141, 1089 cm^{-1}. HRMS (ESI): calcd for $C_{11}H_8BrNO_2Na$ ($[M + Na]^+$) 287.9631, found 287.9626.

*1-(6-Bromobenzo[d][1,3]dioxol-5-yl)cyclopropanecarbaldehyde (**7**).* The compound **6** (1.68 g, 6.31 mmol) was dissolved in DCM (28 mL) and DIBAL (1 M) in hexane (7.0 mL, 7.0 mmol) was added to it at 0 °C. The reaction mixture was stirred at 0 °C for 30 min under an argon atmosphere, then quenched with saturated aqueous ammonium chloride solution (10 mL). After that, saturated potassium sodium tartrate tetrahydrate solution (25 mL) and diethyl ether (20 mL) were added. The mixture was stirred for 1 h. Then it was worked up with diethyl ether (2 × 30 mL) and the organic layer was washed with water (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. Purification of the residue through flash column chromatography on silica gel (PE/EA 5:1) afforded the aldehyde 7 as a white solid (1.57 g, 92% yield).

7. White solid. mp = 94−95 °C. TLC R_f (PE/EA 5:1) = 0.5. ^{1}H NMR (400 MHz, C_6D_6): δ 0.80 (dd, J = 7.3, 4.3 Hz, 2H), 1.27 (dd, J = 7.3, 4.3 Hz, 2H), 5.17 (s, 2H), 6.32 (s, 1H), 6.84 (s, 1H), 8.95 (s, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ 17.5, 37.9, 101.8, 112.3, 113.0, 118.2, 131.0, 147.5, 148.4, 198.4. IR (neat): ν 3054, 2911, 2839, 2739, 1700, 1497, 1429, 1246, 1143, 1037 cm^{-1}. HRMS (ESI): calcd for $C_{11}H_9BrO_3Na$ ($[M + Na]^+$) 290.9627, found 290.9624.

*5-Bromo-6-(1-vinylcyclopropyl)benzo[d][1,3]dioxole (**8**).* Methyltriphenylphosphonium bromide (4.19 g, 11.7 mmol) was dissolved in anhydrous THF (17 mL) and cooled to 0 °C. *N*-butyllithium (2.5 M) in THF (3.5 mL, 8.75 mmol) was added dropwise to it and the mixture was stirred at 0 °C for 30 min under an argon atmosphere, during which time it turned bright yellow. After that the aldehyde **7** (1.57 g, 5.83 mmol) dissolved in THF (20 mL) was slowly added to the ylide at 0 °C and the reaction mixture was stirred at this temperature for 45 min. The reaction mixture was diluted with diethyl ether (30 mL) and quenched with saturated aqueous ammonium chloride solution (15 mL) and water (15 mL). The mixture was extracted with diethyl ether (2 × 30 mL) and the combined organic extracts were washed with water (40 mL) and brine (40 mL), dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Purification of the residue through column chromatography on silica gel (PE/EA 10:1) afforded the vinylcyclopropane **8** as a light yellow liquid (1.51 g, 97% yield).

8. Light yellow liquid. TLC R_f (PE/EA 5:1) = 0.8. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (s, 4H), 4.52 (d, J = 17.0 Hz, 1H), 4.90 (d, J = 10.2 Hz, 1H), 5.47 (dd, J = 17.0, 10.2 Hz, 1H), 5.96 (s, 2H), 6.81 (s, 1H), 7.01 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.7, 29.9, 101.7, 111.9, 112.5, 112.9, 117.2, 134.7, 143.3, 147.0, 147.2. IR (neat): ν 3083, 3006, 2895, 1633, 1502, 1478, 1418, 1343, 1229, 1135 cm^{-1}. HRMS (EI): calcd for $C_{12}H_{11}BrO_2$ (M^+) 265.9937, found 265.9939.

*6-(1-Vinylcyclopropyl)benzo[d][1,3]dioxole-5-carbonitrile (**9**).* The compound **8** (1.42 g, 5.32 mmol) was dissolved in DMF (6 mL) and copper cyanide (956 mg, 10.7 mmol) was added to it. The reaction mixture was refluxed for 18 h at 153 °C under an argon atmosphere, then cooled to room temperature. The reaction solution was column chromatographed (PE/EA 20:1) on silica gel to afford the product **9** as a yellow solid (926.4 mg, 82% yield).

9. Yellow solid. mp = 78−80 °C. TLC R_f (PE/EA 5:1) = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (s, 4H), 4.51 (d, J = 17.0 Hz, 1H), 4.95 (d, J = 10.4 Hz, 1H), 5.55 (dd, J = 17.0, 10.4 Hz, 1H), 6.06 (s, 2H), 6.86 (s, 1H), 7.02 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.6, 28.2, 102.3, 107.3, 111.7, 112.1, 112.7, 118.1, 143.1, 143.4, 146.5, 151.3. IR (neat): ν 2986, 2913, 2221, 1622, 1495, 1430, 1378, 1260, 1170, 1124 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_{12}NO_2$ ($[M + H]^+$) 214.0863, found 214.0858.

*6-(1-Vinylcyclopropyl)benzo[d][1,3]dioxole-5-carbaldehyde (**10**).* To a solution of the compound **9** (435 mg, 2.04 mmol) in dry DCM (17 mL) was added DIBAL (1 M) in hexane (8.2 mL, 8.17 mmol) dropwise at 0 °C. The reaction mixture was stirred for 30 min at 0 °C under an argon atmosphere, then quenched with saturated aqueous ammonium chloride solution (15 mL). After that, saturated potassium sodium tartrate tetrahydrate solution (20 mL) and diethyl ether (20 mL) were added. The mixture was stirred for 20 min. Then it was worked up with diethyl ether (2 × 20 mL), water (25 mL), brine (25 mL) and dried over anhydrous sodium sulfate. The solvent was removed in vacuum and the residue was column chromatographed on silica gel (PE/EA 10:1) to afford the aldehyde **10** as a yellow solid (409.2 mg, 93%).

10. Yellow solid. mp = 68−70 °C. TLC R_f (PE/EA 10:1) = 0.5. ^{1}H NMR (400 MHz, C_6D_6): δ 0.61 (dd, J = 6.6, 4.4 Hz, 2H), 0.72 (dd, J = 6.6, 4.4 Hz, 2H), 4.51 (d, J = 17.2 Hz, 1H), 4.80 (d, J = 10.4 Hz, 1H), 5.14 (s, 2H), 5.19 (dd, J = 17.2, 10.4 Hz, 1H), 6.54 (s, 1H), 7.68 (s, 1H), 10.53 (s, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ 15.7, 26.2, 101.7, 106.6, 111.2, 113.3, 131.0, 142.0, 146.1, 147.7, 152.3, 189.6. IR (neat): ν 3080, 2910, 2889, 1671, 1610, 1503, 1482, 1370, 1253, 1126 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_{12}O_3Na$ ($[M + Na]^+$) 239.0679, found 239.0675.

*(±)-1-(6-(1-Vinylcyclopropyl)benzo[d][1,3]dioxol-5-yl)prop-2-yn-1-ol [(±)-**11**].* To a solution of the aldehyde **10** (363.6 mg, 1.68 mmol) in anhydrous THF (17 mL) was added ethynylmagnesium bromide (0.5 M) in THF (7.5 mL, 3.75 mmol) at 0 °C. The reaction mixture was stirred overnight for 9 h and the temperature was raised from 0 °C to room temperature. It was quenched with saturated aqueous ammonium chloride solution (20 mL), extracted with diethyl ether (3

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J. Org. Chem. 2016, 81, 6757−6765

× 20 mL) and washed with water (20 mL), brine (20 mL). The solution was dried over anhydrous sodium sulfate, and then solvent was evaporated and the residue was purified by column chromatography on silica gel (PE/EA 5:1) to afford the propargyl alcohol (±)-**11** as a yellow solid (382.2 mg, 94%).

(±)-11. Yellow solid. mp = 74−75 °C. TLC R_f (PE/EA 5:1) = 0.3. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97−1.09 (m, 2H), 1.10−1.16 (m, 1H), 1.16−1.21 (m, 1H), 2.21 (brs, 1H), 2.56 (d, J = 2.0 Hz, 1H), 4.53 (d, J = 17.1 Hz, 1H), 4.92 (d, J = 10.3 Hz, 1H), 5.52 (dd, J = 17.1, 10.3 Hz, 1H), 5.87 (d, J = 2.0 Hz, 1H), 5.95 (s, 2H), 6.73 (s, 1H), 7.22 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.4, 15.6, 27.1, 60.7, 73.7, 84.4, 101.2, 107.5, 110.8, 112.7, 133.2, 134.8, 145.6, 147.1, 147.6. IR (neat): ν 3418, 3287, 3083, 2997, 2916, 1631, 1506, 1493, 1400, 1246 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{14}O_3Na$ ([M + Na]$^+$) 265.0835, found 265.0832.

*(±)-tert-Butyldimethyl(1-(6-(1-vinylcyclopropyl)benzo[d][1,3]-dioxol-5-yl)prop-2-ynyloxy)silane [(±)-**4**].* To a solution of the alcohol (±)-**11** (178.4 mg, 0.74 mmol) in dry DCM (10 mL) at 0 °C was added 2, 6-lutidine (0.17 mL, 1.47 mmol) followed by dropwise addition of TBDMSOTf (0.25 mL, 1.10 mmol). After stirring for 1 h at 0 °C, the reaction mixture was quenched with water (10 mL), then worked up with diethyl ether (3 × 15 mL) and washed with water (15 mL) and brine (15 mL). The organic phase was separated and dried over anhydrous sodium sulfate. Finally, the organic solution was concentrated and purified by column chromatography on silica gel (PE/EA 20:1) to give compound (±)-**4** (217.6 mg, 83%) as a light yellow liquid.

(±)-4. Light yellow liquid. TLC R_f (PE/EA 10:1) = 0.8. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.09 (s, 3H), 0.21 (s, 3H), 0.90 (s, 9H), 0.94−1.03 (m, 2H), 1.04−1.12 (m, 1H), 1.23−1.29 (m, 1H), 2.44 (d, J = 2.0 Hz, 1H), 4.56 (dd, J = 17.1, 1.1 Hz, 1H), 4.90 (dd, J = 10.4, 1.1 Hz, 1H), 5.48 (dd, J = 17.1, 10.4 Hz, 1H), 5.74 (d, J = 2.0 Hz, 1H), 5.93 (d, J = 1.4 Hz, 1H), 5.95 (d, J = 1.4 Hz, 1H), 6.69 (s, 1H), 7.16 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.8, −4.4, 15.2, 15.7, 18.0, 25.7, 27.1, 61.0, 72.9, 86.0, 101.0, 107.4, 110.3, 112.8, 131.5, 136.7, 144.5, 146.95, 146.99. IR (neat): ν 3304, 3084, 2931, 2891, 2857, 1631, 1484, 1379, 1236, 1126 cm^{-1}. HRMS (ESI): calcd for $C_{21}H_{28}O_3SiNa$ ([M + Na]$^+$) 379.1700, found 379.1698.

*9-(tert-Butyldimethylsilyloxy)-4b-vinyl-5,6-dihydro-4bH-fluoreno-[2,3-d][1,3]dioxol-7(9H)-one (**3**).* A solution of the compound (±)-**4** (400.3 mg, 1.12 mmol) and $[Rh(CO)_2Cl]_2$ (21.5 mg, 5 mol %) in anhydrous toluene (23 mL) was bubbled by CO (0.2 atm) for 5 min. The reaction mixture was immersed in an 80 °C oil bath and stirred under balloon pressure gas of CO (0.2 atm) for 8 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. Purification of the residue through column chromatography on silica gel (PE/EA 10:1) afforded the product **3** as yellow oil (240 mg, 55% combined yield). The diastereoselectivity of (±)-*trans*-**3** and (±)-*cis*-**3** was determined by the crude ^{1}H NMR of the final product as 3:1 (at 6.67 ppm for the major and 6.65 ppm for the minor diastereomer). The two diastereomers were columned again on silica gel (PE/DCM 2:1) to separate them thoroughly.

(±)-*trans*-3. Yellow oil. TLC R_f (PE/EA 5:1) = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$) [for the major isomer [(±)-*trans*-**3**]]: δ 0.22 (s, 3H), 0.25 (s, 3H), 1.00 (s, 9H), 2.10 (ddd, J = 14.2, 13.0, 4.4 Hz, 1H), 2.32−2.50 (m, 2H), 2.62 (ddd, J = 17.5, 14.0, 4.8 Hz, 1H), 4.96 (d, J = 17.2 Hz, 1H), 5.11 (d, J = 10.0 Hz, 1H), 5.62 (d, 1.0 Hz, 1H), 5.89 (dd, J = 17.2, 10.0 Hz, 1H), 5.96 (s, 1H), 5.97 (s, 1H), 6.14 (d, J = 1.0 Hz, 1H), 6.66 (s, 1H), 6.76 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.6, −4.5, 18.2, 25.8, 33.7, 33.9, 50.7, 74.2, 101.4, 102.9, 104.2, 114.6, 121.4, 134.5, 138.2, 139.0, 147.9, 148.5, 172.1, 198.9. IR (neat): ν 2954, 2931, 2891, 2853, 1679, 1475, 1286, 1250, 1041 cm^{-1}. HRMS (ESI): calcd for $C_{22}H_{29}O_4Si$ ([M + H]$^+$) 385.1830, found 385.1838.

(±)-*cis*-3. Yellow oil. TLC R_f (PE/EA 5:1) = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$) [for the minor isomer [(±)-*cis*-**3**]]: δ 0.17 (s, 3H), 0.20 (s, 3H), 0.86 (s, 9H), 1.88−1.99 (m, 1H), 2.40−2.51 (m, 2H), 2.72 (ddd, J = 18.2, 14.0, 4.6 Hz, 1H), 5.12 (d, J = 10.4 Hz, 1H), 5.17 (d, J = 17.2 Hz, 1H), 5.32 (s, 1H), 5.95−6.05 (m, 3H), 6.10 (s, 1H), 6.65 (s, 1H), 6.77 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.2, −4.1, 18.0, 25.7, 33.0, 34.6, 52.0, 75.3, 101.5, 102.9, 105.4, 115.0, 124.6, 134.0, 139.9, 140.7, 147.7, 149.3, 168.5, 200.1. IR (neat): ν 2955, 2931, 2892, 2858, 1679, 1473, 1282, 1258, 1042 cm^{-1}. HRMS (ESI): calcd for $C_{22}H_{29}O_4Si$ ([M + H]$^+$) 385.1830, found 385.1835.

*(±)-(4b-Vinyl-5,6,7,9-tetrahydro-4bH-fluoreno[2,3-d][1,3]dioxole-7,9-diyl)bis(oxy)bis(tert-butyldimethylsilane) [(±)-**12**].* Lithium aluminum hydride (68.6 mg, 1.81 mmol) was dissolved in anhydrous THF (10 mL) at 0 °C and a solution of the enone (±)-*trans*-**3** (278.4 mg, 0.72 mmol) in dry THF (2 mL) was added to it, and then washed with THF (3 × 2 mL). The reaction mixture was stirred for 2 h at 0 °C, quenched with saturated aqueous ammonium chloride solution (40 mL). Then saturated potassium sodium tartrate tetrahydrate solution (20 mL) and diethyl ether (20 mL) were added. The mixture was stirred for 1 h. It was worked up with diethyl ether (2 × 30 mL), water (30 mL) and brine (30 mL). The organic solution was concentrated under reduced pressure and dried in vacuum to give crude alcohol as a colorless liquid, which was directly used in the next step without further purification. The diastereoselectivity at C6 of the reduction was determined by the crude ^{1}H NMR of the product as 6:1 (at 4.35 ppm for the major and 4.26 ppm for the minor diastereomer).

To a solution of above alcohol in dry DCM (12 mL) was added 2, 6-lutidine (0.14 mL, 1.22 mmol) followed by addition of TBDMSOTf (0.21 mL, 0.92 mmol) at 0 °C. After stirring for 15 min at 0 °C, the reaction mixture was quenched with water (20 mL), then worked up with diethyl ether (2 × 20 mL) and washed with water (30 mL) and brine (30 mL). After drying over anhydrous sodium sulfate, the organic solution was concentrated and purified by column chromatography through silica gel (PE/EA 50:1) to give the compound (±)-**12** (281.1 mg, 78% yield over 2 steps) as yellow oil.

The diastereoselectivity of (±)-**12** was determined by the crude ^{1}H NMR of the final product as 7.5:1 (at 4.36 ppm for the major and 4.26 ppm for the minor diastereomer). After chromatography, the diastereoselectivity of (±)-**12** in the final was 15.7:1.

(±)-12. Yellow oil. TLC R_f (PE/EA 5:1) = 0.8. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.23 (s, 3H), 0.25 (s, 3H), 0.92 (s, 9H), 1.03 (s, 9H), 1.64−1.74 (m, 1H), 1.76−1.85 (m, 1H), 1.85−1.96 (m, 1H), 2.09 (ddd, J = 12.4, 3.6, 2.8 Hz, 1H), 4.31−4.39 (m, 1H), 4.92 (dd, J = 17.2, 1.2 Hz, 1H), 5.02 (dd, J = 10.1, 1.2 Hz, 1H), 5.43 (s, 1H), 5.77 (s, 1H), 5.88 (dd, J = 17.2, 10.1 Hz, 1H), 5.92 (d, J = 1.2 Hz, 1H), 5.94 (d, J = 1.2 Hz, 1H), 6.62 (s, 1H), 6.75 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.61, −4.58, −4.5, 1.0, 18.3, 18.4, 25.89, 25.91, 28.9, 32.8, 49.6, 68.6, 74.2, 101.0, 103.0, 104.0, 113.7, 122.9, 136.4, 140.5, 142.0, 147.0, 147.7, 148.5. IR (neat): ν 2928, 2856, 1736, 1597, 1470, 1364, 1258, 1084 cm^{-1}. HRMS (ESI): calcd for $C_{28}H_{44}O_4Si_2Na$ ([M + Na]$^+$) 523.2670, found 523.2681.

*(±)-2-(7,9-Bis((tert-butyldimethylsilyl)oxy)-5,6,7,9-tetrahydro-4bH-fluoreno[2,3-d][1,3]dioxol-4b-yl)ethanol [(±)-**13**].* A solution of the compound (±)-**12** (162.9 mg, 0.33 mmol) in THF (6.5 mL), 9-BBN (0.5 M) in THF (3.4 mL, 1.70 mmol) was added at 0 °C. The ice bath was removed after 5 min and the reaction mixture was stirred at room temperature for 8 h. Then NaOH (3.4 mL, 3 M) and 30% H_2O_2 (5.0 mL) were added sequentially to the solution at 0 °C. The reaction mixture was stirred for 2 h, then diluted with diethyl ether (100 mL), and washed with water (2 × 30 mL), brine (2 × 30 mL) and dried over anhydrous sodium sulfate. The solvent was removed under vacuo. Column chromatography over silica gel (PE/EA 5:1) afforded the product (±)-**13** (149.8 mg, 89% yield) as a light yellow oil.

After chromatography, the diastereoselectivity of (±)-**12** in the final was 10:1. (at 5.67 ppm for the major and 5.71 ppm for the minor diastereomer).

(±)-13. Light yellow oil. TLC R_f (PE/EA 5:1) = 0.2. ^{1}H NMR (400 MHz, C_6D_6): δ 0.13 (s, 3H), 0.16 (s, 6H), 0.23 (s, 3H), 1.02 (s, 9H), 1.05 (s, 9H), 1.34−1.44 (m, 1H), 1.72−1.84 (m, 3H), 1.88−2.00 (m, 2H), 3.22−3.36 (m, 2H), 4.25−4.32 (m, 1H), 5.36 (d, J = 1.2 Hz, 1H), 5.38 (d, J = 1.2 Hz, 1H), 5.67 (s, 1H), 5.89 (brs, 1H), 6.56 (s, 1H), 7.02 (s, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ −4.5, −4.4, −4.3, 18.43, 18.45, 26.07, 26.13, 29.9, 33.3, 41.9, 45.1, 59.9, 68.9, 74.6, 101.1, 103.8, 104.5, 121.9, 137.3, 141.9, 147.6, 148.1, 152.8. IR (neat): ν 3425, 2954, 2932, 2889, 2858, 2279, 1690, 1617, 1472, 1255 cm^{-1}.

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J. Org. Chem. 2016, 81, 6757−6765

HRMS (ESI): calcd for $C_{28}H_{46}O_5Si_2Na$ ([M + Na]$^+$) 541.2776, found 541.2781.

*(±)-2-(7,9-Bis(tert-butyldimethylsilyloxy)-5,6,7,8,8a,9-hexahydro-4bH-fluoreno[2,3-d][1,3]dioxol-4b-yl)ethanol [(±)-**14**].* The alcohol (±)-**13** (27.0 mg) was dissolved in toluene (3.5 mL) and Pt/C (5%, 101.3 mg, 0.026 mmol) was added to it and the reaction mixture was stirred at room temperature under a balloon pressure of hydrogen gas for 5 h. The mixture was filtered through Celite by washing with EA and followed by removal of the solvent and column chromatography through silica gel (PE/EA 10:1) to afford the product (±)-**14** (15.1 mg, 56% yield) as a yellow oil.

(±)-**14.** Yellow oil. TLC R_f (PE/EA 3:1) = 0.7. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.13 (s, 3H), 0.17 (s, 3H), 0.91 (s, 9H), 0.95 (s, 9H), 1.03−1.12 (m, 1H), 1.13−1.22 (m, 1H), 1.41−1.49 (m, 2H), 1.58−1.67 (m, 1H), 1.74 (dd, J = 7.6, 7.6 Hz, 2H), 1.79 (ddd, J = 14.1, 4.1, 4.1 Hz, 1H), 1.97 (ddd, J = 13.4, 13.4, 4.0 Hz, 1H), 2.60 (ddd, J = 11.2, 5.6, 5.6 Hz, 1H), 3.53−3.64 (m, 1H), 3.68−3.80 (m, 1H), 3.94 (brs, 1H), 5.32 (d, J = 5.6 Hz, 1H), 5.92 (d, J = 1.2 Hz, 1H), 5.94 (d, J = 1.2 Hz, 1H), 6.59 (s, 1H), 6.74 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.88, −4.86, −4.8, −4.6, −3.6, 18.1, 18.3, 25.6, 25.81, 25.83, 25.9, 29.3, 30.1, 44.3, 45.8, 47.9, 59.9, 65.9, 75.9, 101.0, 103.3, 105.4, 138.4, 139.0, 146.7, 147.1. IR (neat): ν 3360, 2928, 1671, 1471, 1359, 1287, 1254, 1044 cm^{-1}. HRMS (ESI): calcd for $C_{28}H_{48}O_5Si_2Na$ ([M + Na]$^+$) 543.2933, found 543.2946.

*(±)-2-(7,9-Bis(tert-butyldimethylsilyloxy)-5,6,7,8,8a,9-hexahydro-4bH-fluoreno[2,3-d][1,3]dioxol-4b-yl)ethyl acetate [(±)-**15**].* A solution of the alcohol (±)-**14** (45.8 mg, 0.088 mmol) in anhydrous DCM (2.2 mL) was cooled to 0 °C. Then triethyl amine (18.3 mg, 0.18 mmol), acetic anhydride (19.6 mg, 0.19 mmol) and catalytic amount of DMAP sequentially. The reaction mixture was stirred at 0 °C for 2 h, then quenched with water (10 mL). It was worked up with diethyl ether (3 × 10 mL) and washed with water (10 mL) and brine (10 mL). It was dried over anhydrous sodium sulfate and the solvent was removed under vacuo. Column chromatography over silica gel (PE/EA 20:1) afforded the product (±)-**15** (48.4 mg, 99% yield) as a viscous liquid.

(±)-**15.** Viscous liquid. TLC R_f (PE/EA 20:1) = 0.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.14 (s, 3H), 0.17 (s, 3H), 0.90 (s, 9H), 0.95 (s, 9H), 1.09 (ddd, J = 14.2, 11.4, 2.6 Hz, 1H), 1.15−1.23 (m, 1H), 1.46−1.53 (m, 1H), 1.58−1.66 (m, 1H), 1.77 (dd, J = 7.4, 7.4 Hz, 2H), 1.73−1.83 (m, 1H), 1.91−2.02 (m, 1H), 1.99 (s, 3H), 2.60 (ddd, J = 11.2, 5.6, 5.6 Hz, 1H), 3.90−4.00 (m, 2H), 4.11−4.21 (m, 1H), 5.29 (d, J = 5.6 Hz, 1H), 5.91 (d, J = 1.2 Hz, 1H), 5.94 (d, J = 1.2 Hz, 1H), 6.60 (s, 1H), 6.73 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.9, −4.84, −4.80, −4.5, 18.0, 18.3, 21.0, 25.7, 25.8, 25.9, 29.2, 30.1, 39.7, 45.8, 47.7, 61.8, 65.8, 75.8, 101.0, 103.5, 105.4, 138.3, 138.6, 146.8, 147.1, 171.0. IR (neat): ν 2930, 2857, 1742, 1472, 1365, 1287, 1252, 1163, 1097, 1042 cm^{-1}. HRMS (ESI): calcd for $C_{30}H_{50}O_6Si_2Na$ ([M + Na]$^+$) 585.3038, found 585.3050.

*(±)-2-(7,9-Dihydroxy-5,6,7,8,8a,9-hexahydro-4bH-fluoreno[2,3-d][1,3]dioxol-4b-yl)ethyl acetate [(±)-**16**].* To a solution of the compound (±)-**15** (37.1 mg, 0.066 mmol) in THF (1.7 mL), TBAF (1.0 M) in THF (0.83 mL, 0.83 mmol) was added and the reaction mixture was stirred at 50 °C for 24 h. The reaction mixture was quenched with water (10 mL) and the organic layer was extracted with diethyl ether (3 × 10 mL) and washed with water (10 mL) and brine (10 mL). After drying over anhydrous sodium sulfate, the solvent was removed under vacuum followed by silica gel column chromatography (EA) of the residue to yield the diol (±)-**16** (20.7 mg, 92% yield) as a light yellow oil.

(±)-**16**. Light yellow oil. TLC R_f (EA) = 0.3. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48−1.63 (m, 2H), 1.66−1.76 (m, 3H), 1.78−1.93 (m, 4H), 1.98 (s, 3H), 2.05−2.15 (m, 1H), 2.54 (dd, J = 12.4, 6.0 Hz, 1H), 3.85−3.95 (m, 1H), 3.97−4.06 (m, 1H), 4.06−4.16 (m, 1H), 5.13 (d, J = 6.0 Hz, 1H), 5.95 (d, J = 0.8 Hz, 2H), 6.62 (s, 1H), 6.84 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 29.9, 30.7, 32.6, 35.9, 45.9, 46.7, 61.7, 67.0, 76.5, 101.2, 103.4, 105.4, 136.5, 141.9, 147.1, 148.2, 171.1. IR (neat): ν 3457, 2390, 2857, 1740, 1501, 1474, 1364, 1252, 1162, 1041 cm^{-1}. HRMS (ESI): calcd for $C_{18}H_{22}O_6Na$ ([M + Na]$^+$) 357.1309, found 357.1313.

*(±)-4b-(2-Hydroxyethyl)-5,6,8,8a-tetrahydro-4bH-fluoreno[2,3-d][1,3]dioxole-7,9-dione [(±)-**2**].* A solution of the diol (±)-**16** (14.8 mg, 0.044 mmol) in dry DCM (3 mL) was cooled to 0 °C and Dess−Martin Periodinane (94.1 mg, 0.22 mmol) was added to it. The ice bath was removed and the mixture was stirred at room temperature for 3 h. Then it was cooled to 0 °C, and quenched with 1:1 mixture of saturated aqueous sodium bicarbonate and sodium thiosulfate solution (6 mL). The organic layer was extracted with diethyl ether (3 × 10 mL) and washed with water (10 mL) and brine (10 mL). After drying over anhydrous sodium sulfate, the solvent was removed under vacuum and the crude compound obtained was used in the next reaction without further purification.

The crude diketone was dissolved in a 1:1 mixture of methanol (2 mL) and water (2 mL) and potassium carbonate (24.5 mg, 0.18 mmol) was added to it at 0 °C. The reaction mixture was stirred at 0 °C for 4.5 h. then the methanol was removed in vacuum. The mixture was filtered through anhydrous magnesium sulfate by washing with DCM and followed by removal of the solvent and column chromatography through silica gel (EA) to afford Gao's intermediate (±)-**2** (7.5 mg, 59% yield over two steps) as a white solid.

(±)-**2.** White solid. mp = 121−123 °C. TLC R_f (EA) = 0.6. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (brs, 1H), 1.60−1.75 (m, 1H), 1.97−2.13 (m, 2H), 2.13−2.28 (m, 3H), 2.69 (dd, J = 16.9, 7.6 Hz, 1H), 2.89 (dd, J = 16.9, 3.5 Hz, 1H), 3.09 (dd, J = 7.6, 3.5 Hz, 1H), 3.56−3.72 (m, 2H), 6.10 (d, J = 3.5 Hz, 2H), 6.86 (s, 1H), 7.08 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.5, 35.5, 38.7, 42.1, 43.7, 50.2, 59.3, 102.1, 102.6, 103.3, 131.2, 149.1, 155.3, 156.2, 203.7, 209.9. IR (neat): ν 3359, 2922, 2852, 1658, 1633, 1467 cm^{-1}. HRMS (ESI): calcd for $C_{16}H_{16}O_5Na$ ([M + Na]$^+$) 311.0890, found 311.0890.

*1-(6-(1-Vinylcyclopropyl)benzo[d][1,3]dioxol-5-yl)prop-2-yn-1-one (**17**).* To a solution of the alcohol (±)-**11** (243.8 mg, 1.0 mmol) in EA (15 mL), IBX (560.8 mg, 2.0 mmol) was added and the reaction mixture was refluxed for 10 h. After completion, the mixture was filtered through Celite and solvent was removed under vacuum. The residue was column chromatographed over silica gel (PE/EA 20:1) to afford the product **17** (212.7 mg, 88% yield) as a white solid.

17. White solid. mp = 125−127 °C. TLC R_f (PE/EA 3:1) = 0.7. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (dd, J = 6.7, 4.7 Hz, 2H), 1.10 (dd, J = 6.7, 4.7 Hz, 2H), 3.31 (s, 1H), 4.47 (d, J = 17.0 Hz, 1H), 4.84 (d, J = 10.4 Hz, 1H), 5.64 (dd, J = 17.0, 10.4 Hz, 1H), 6.06 (s, 2H), 6.94 (s, 1H), 7.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.4, 28.4, 79.0, 82.0, 102.1, 111.1, 112.2, 113.2, 130.9, 141.3, 145.0, 146.3, 151.4, 175.4. IR (neat): ν 3380, 3062, 3029, 2923, 1953, 1600, 1492, 1451, 1384, 1238 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{13}O_3$ ([M + H]$^+$) 241.0859, found 241.0860.

*(−)-(R)-1-(6-(1-Vinylcyclopropyl)benzo[d][1,3]dioxol-5-yl)prop-2-yn-1-ol [(−)-**11**].* A solution of ketone **17** (120.7 mg, 0.50 mmol) in 12.5 mL of toluene was subsequently added by syringe to a dry flask charged with 0.60 mL (0.60 mmol, 1 M in toluene) of (*S*)-CBS reagent. The solution was cooled to −30 °C. Then 1.0 mL (2.0 mmol, 2 M) of boron methyl sulfide complex was added over 30 min. The reaction mixture was stirred for 4.5 h. Then it was quenched by slow dropwise addition of 0.5 mL of methanol at −30 °C. The solution was diluted with 40 mL ether and washed with water (30 mL), 5% $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried over anhydrous sodium sulfate, then filtered through silica gel, and concentrated. Column chromatography (PE/EA 10:1) afforded 113.1 mg (0.47 mmol, 93%) of a colorless liquid (−)-**11**. ee = 98.2% (hexanes:isopropanol = 90:10, 1.0 mL/min, 254 nm) (see the Supporting Information). It was important to note that when using 20 mol % (*S*)-CBS, we found that the reaction was much slower than using equivalent catalyst.

(−)-**11.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98−1.09 (m, 2H), 1.10−1.16 (m, 1H), 1.16−1.22 (m, 1H), 2.17 (d, J = 3.2 Hz, 1H), 2.56 (d, J = 2.4 Hz, 1H), 4.53 (dd, J = 16.9, 0.9 Hz, 1H), 4.92 (dd, J = 10.2, 0.9 Hz, 1H), 5.53 (dd, J = 16.9, 10.2 Hz, 1H), 5.88 (s, 1H), 5.96 (s, 2H), 6.74 (s, 1H), 7.22 (s, 1H). $[\alpha]_D^{20}$: −26.5° (c 1.35, $CHCl_3$).

*(+)-(R)-tert-Butyldimethyl((1-(6-(1-vinylcyclopropyl)benzo[d][1,3]dioxol-5-yl)prop-2-yn-1-yl)oxy)silane [(+)-**4**].* To a solution of the alcohol (−)-**11** (230.6 mg, 0.97 mmol) in dry DCM (15 mL) at 0

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J. Org. Chem. 2016, 81, 6757−6765

°C was added 2, 6-lutidine (0.22 mL, 1.95 mmol) followed by dropwise addition of TBDMSOTf (0.34 mL, 1.46 mmol). After stirring for 1 h at 0 °C, the reaction mixture was quenched with water (20 mL), then worked up with diethyl ether (3 × 20 mL) and washed with water (20 mL) and brine (20 mL). The organic phase was separated and dried over anhydrous sodium sulfate. Finally, the organic solution was concentrated and purified by column chromatography on silica gel (PE/EA 20:1) to give compound (+)-**4** (266.9 mg, 77% yield) as a light yellow liquid.

(+)-**4.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.09 (s, 3H), 0.21 (s, 3H), 0.90 (s, 9H), 0.96−1.02 (m, 2H), 1.06−1.12 (m, 1H), 1.23−1.28 (m, 1H), 2.44 (d, J = 2.0 Hz, 1H), 4.55 (d, J = 17.1 Hz, 1H), 4.90 (d, J = 10.3 Hz, 1H), 5.48 (dd, J = 17.1, 10.3 Hz, 1H), 5.73 (d, J = 2.0 Hz, 1H), 5.93 (s, 1H), 5.96 (s, 1H), 6.69 (s, 1H), 7.16 (s, 1H). $[\alpha]_D^{20}$: + 7.8° (c 0.87, $CHCl_3$).

*(−)-(4bS,9S)-9-((tert-Butyldimethylsilyl)oxy)-4b-vinyl-5,6-dihydro-4bH-fluoreno[2,3-d][1,3]dioxol-7(9H)-one [(−)-trans-**3**].* A solution of the compound (+)-**4** (266.9 mg, 0.75 mmol) and $[Rh(CO)_2Cl]_2$ (14.9 mg, 5 mol %) in anhydrous toluene (19 mL) was bubbled by CO (0.2 atm) for 5 min. The reaction mixture was immersed in an 80 °C oil bath and stirred under balloon pressure gas of CO (0.2 atm) for 8 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. Purification of the residue through column chromatography on silica gel (PE/EA 10:1) afforded the diastereoisomers (142.7 mg, 50% yield) as yellow oil. The two diastereomers were columned again on silica gel (PE/DCM 2:1) to separate them thoroughly.

(−)-*trans*-**3.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.22 (s, 3H), 0.25 (s, 3H), 1.00 (s, 9H), 2.10 (ddd, J = 14.2, 13.0, 4.4 Hz, 1H), 2.33−2.50 (m, 2H), 2.61 (ddd, J = 17.4, 14.4, 4.8 Hz, 1H), 4.96 (d, J = 17.1 Hz, 1H), 5.10 (d, J = 10.3 Hz, 1H), 5.62 (d, J = 1.4 Hz, 1H), 5.89 (dd, J = 17.1, 10.3 Hz, 1H), 5.95 (d, J = 1.4 Hz, 1H), 5.96 (d, J = 1.4 Hz, 1H), 6.14 (d, J = 1.4 Hz, 1H), 6.66 (s, 1H), 6.76 (s, 1H). $[\alpha]_D^{20}$: −31.2° (c 0.45, $CHCl_3$).

*(+)-(4bR,9S)-9-((tert-Butyldimethylsilyl)oxy)-4b-vinyl-5,6-dihydro-4bH-fluoreno[2,3-d][1,3]dioxol-7(9H)-one [(+)-cis-**3**].* (+)-*cis*-**3.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.17 (s, 3H), 0.26 (s, 3H), 0.86 (s, 9H), 1.89−2.00 (m, 1H), 2.40−2.51 (m, 2H), 2.72 (ddd, J = 18.1, 13.9, 4.5 Hz, 1H), 5.12 (d, J = 10.4 Hz, 1H), 5.17 (d, J = 17.2 Hz, 1H), 5.32 (s, 1H), 5.93−6.05 (m, 3H), 6.10 (s, 1H), 6.65 (s, 1H), 6.77 (s, 1H). $[\alpha]_D^{20}$: + 13.0° (c 1.03, $CHCl_3$).

*(+)-(R)-1-(6-(1-vinylcyclopropyl)benzo[d][1,3]dioxol-5-yl)prop-2-yn-1-yl 4-bromobenzoate [(+)-**18**].* To a solution of the compound (−)-**11** (24.7 mg, 0.10 mmol) in DCM (2 mL) was added DMAP (1.4 mg, 0.011 mmol) and Et_3N (29.7 mg, 23.4 mmol) at 0 °C. Then 4-bromobenzoyl chloride (44.8 mg, 0.20 mmol) was added. The resulting solution was warmed up to room temperature and stirred for 2 h. Then the mixture was quenched with water (2 mL), and the organic layer was extracted with diethyl ether (3 × 15 mL), and then washed with water (20 mL) and brine (20 mL). After drying over anhydrous sodium sulfate, the solvent was removed under vacuum followed by silica gel (PE/EA 50:1) to afford (+)-**18** (38.7 mg, 89% yield) as a white solid. The absolute configuration was confirmed by X-ray (see the Supporting Information).

(+)-**18.** White solid. mp = 135−136 °C. TLC R_f (PE/EA 5:1) = 0.6. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96−1.05 (m, 2H), 1.05−1.12 (m, 1H), 1.12−1.20 (m, 1H), 2.60 (d, J = 2.0 Hz, 1H), 4.49 (d, J = 17.0 Hz, 1H), 4.82 (d, J = 10.4 Hz, 1H), 5.47 (dd, J = 17.0, 10.4 Hz, 1H), 6.01 (s, 2H), 6.78 (s, 1H), 6.95 (d, J = 2.0 Hz, 1H), 7.32 (s, 1H), 7.56 (d, J = 8.6 Hz, 2H), 7.88 (d, J = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.37, 15.41, 27.1, 63.2, 74.8, 81.1, 101.5, 108.7, 111.0, 112.9, 128.3, 128.6, 130.3, 131.3, 131.7, 134.5, 144.4, 147.1, 148.2, 164.5. IR (neat): ν 3293, 3080, 3002, 2898, 1630, 1590, 1504, 1487, 1431, 1262 cm^{-1}. HRMS (ESI): calcd for $C_{22}H_{17}O_4BrNa$ ($[M + Na]^+$) 447.0202, found 447.0198. $[\alpha]_D^{20}$: + 19.5° (c 3.0, $CHCl_3$).

*(+)-(4bR,9S)-9-hydroxy-4b-vinyl-5,6-dihydro-4bH-fluoreno[3,2-d][1,3]dioxol-7(9H)-one [(+)-**19**].* To a solution of the compound (+)-*cis*-**3** (27.3 mg, 0.071 mmol) in THF (6 mL), TBAF·$3H_2O$ (44.7 mg, 0.14 mmol) dissolved in THF (2 mL) was added dropwise and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (3 mL) and water (10 mL). The organic layer was extracted with diethyl ether (3 × 15 mL) and washed with water (15 mL) and brine (15 mL). After drying over anhydrous sodium sulfate, the solvent was removed under vacuum followed by silica gel (PE/EA 5:1) to afford alcohol (+)-**19** (17.6 mg, 92% yield) as a yellow solid. The structure of (+)-**19** was confirmed by X-ray and its absolute configuration was then consequently assigned from (+)-**18** (see the Supporting Information).

(+)-**19.** Yellow solid. mp = 109−111 °C. TLC R_f (PE/EA 1:1) = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99 (ddd, J = 13.6, 13.6, 4.5 Hz, 1H), 2.16 (d, J = 8.2 Hz, 1H), 2.37 (ddd, J = 12.8, 4.8, 2.0 Hz, 1H), 2.42−2.53 (m, 1H), 2.70 (ddd, J = 18.3, 13.9, 4.8 Hz, 1H), 5.14 (d, J = 17.4 Hz, 1H), 5.15 (d, J = 10.2 Hz, 1H), 5.25 (d, J = 8.2 Hz, 1H), 5.99 (d, J = 2.0 Hz, 2H), 6.10 (dd, J = 17.4, 10.2 Hz, 1H), 6.23 (s, 1H), 6.70 (s, 1H), 6.92 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.0, 34.2, 52.0, 75.3, 101.6, 103.0, 105.9, 115.3, 125.3, 133.4, 140.4, 141.6, 148.1, 149.7, 166.9, 199.6. IR (neat): ν 3363, 3195, 2921, 2852, 1666, 1501, 1474, 1272, 1036, 1006 cm^{-1}. HRMS (ESI): calcd for $C_{16}H_{14}O_4Na$ ($[M + Na]^+$) 293.0784, found 293.0787. $[\alpha]_D^{20}$: + 51.9° (c 0.5, $CHCl_3$).

*(±)-4b-Vinyl-5,6-dihydro-4bH-fluoreno[2,3-d][1,3]dioxole-7,9-dione [(±)-**20**].* A solution of the compound **17** (24.0 mg, 0.1 mmol) and $[Rh(CO)_2Cl]_2$ (3.8 mg, 10 mol %) in anhydrous toluene (2 mL) was bubbled by CO (0.2 atm) for 5 min. The reaction mixture was immersed in an 80 °C oil bath and stirred under balloon pressure gas of CO (0.2 atm) for 3 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. Purification of the residue through column chromatography on silica gel (PE/EA 3:1) afforded the product (±)-**20** as a yellow solid (12.8 mg, 48% yield).

(±)-**20.** Yellow solid. mp = 162−163 °C. TLC R_f (PE/EA 3:1) = 0.3. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10−2.20 (m, 1H), 2.48−2.61 (m, 2H), 2.77 (ddd, J = 19.0, 13.6, 4.8 Hz, 1H), 4.99 (d, J = 17.2 Hz, 1H), 5.11 (d, J = 10.4 Hz, 1H), 5.94 (dd, J = 17.2, 10.4 Hz, 1H), 6.10 (d, J = 1.2 Hz, 1H), 6.11 (d, J = 1.2 Hz, 1H), 6.50 (s, 1H), 6.86 (s, 1H), 7.16 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.8, 34.9, 47.9, 102.7, 103.3, 116.0, 123.5, 130.8, 139.2, 149.2, 153.0, 155.4, 158.4, 190.0, 199.3. IR (neat): ν 3340, 3083, 2977, 2752, 2662, 2252, 1683, 1605, 1502, 1474 cm^{-1}. HRMS (ESI): calcd for $C_{16}H_{13}O_4$ ($[M + H]^+$) 269.0808, found 269.0806.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00608.

Spectra for all new compounds, HPLC chromatograms. (PDF)

X-ray crystallography data of compound (+)-**18**. (CIF)

X-ray crystallography data of compound (+)-**19**. (CIF)

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Notes

The authors declare no competing financial interest.

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NOTE ADDED AFTER ASAP PUBLICATION

There were errors in the version published ASAP July 8, 2016, where the two alkyl transition states in Figure 1 were drawn incorrectly and the explanation of their energy difference was not correct either. In the present version, Figure 1 with the correct alkyl insertion transition state model and the corresponding words describing the energy difference of these two transition states have been revised. The correct version reposted on July 20, 2016.

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