JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

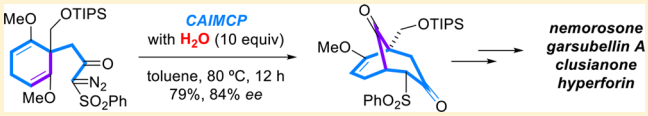
Enantioselective Approach to Polycyclic Polyprenylated Acylphloroglucinols via Catalytic Asymmetric Intramolecular Cyclopropanation

Yuta Uetake, Masahiro Uwamori, and Masahisa Nakada*

Department of Chemistry and Biochemistry, Faculty of Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan

Supporting Information

ABSTRACT: The formal enantioselective total synthesis of nemorosone, garsubellin A, clusianone, and hyperforin is described. The catalytic asymmetric intramolecular cyclopropanation (CAIMCP) of an α-diazo ketone, a common synthetic intermediate for the above four polycyclic polyprenylated acylphloroglucinols previously reported by us, exhibited low enantioselectivity. However, CAIMCP of the corresponding α-diazo β-keto sulfone afforded the desired product in 79% yield with 84% ee. Investigation of the CAIMCP of the α-diazo β-keto sulfone demonstrated the formation of a rearrangement product in the presence of molecular sieves 4 Å, whereas, in the presence of H_2O, the byproduct derived from ring-opening of the desired cyclopropane was observed. X-ray crystallographic analysis suggested that the above two products are derived from the same chiral intermediate. The product derived from ring-opening of the cyclopropane was successfully transformed to the respective synthetic intermediates for the total syntheses of nemorosone, garsubellin A, clusianone, and hyperforin, which had previously been reported by us.



INTRODUCTION

Many polycyclic polyprenylated acylphloroglucinols (PPAPs) have been reported thus far, and their numbers continue to increase with expanding structural diversity. PPAPs feature a variety of complex structural motifs, such as a highly oxygenated and densely substituted bicyclo[3.3.1]nonane-2,4,9-trione or bicyclo[3.2.1]octane-2,4,8-trione core bearing prenyl or geranyl side chains, among others.[1] The diverse biological activities as well as complex and intriguing structures of PPAPs make them attractive targets for total synthesis, and hence, many synthetic studies[2,3] have been reported to date.

We have been interested in the structure−activity relationship (SAR) studies on PPAPs because some PPAPs are structurally closely related, but their varying side chains often lead to different biological activities. For example, nemorosone exhibits anti-HIV and antitumor activities,[4] hyperforin shows antidepressant and antitumor activities,[5] garsubellin A has anti-Alzheimer activity,[6] and clusianone possesses antiviral activity against both HIV and Epstein−Barr virus in addition to antitumor activity;[7] however, the differences in their structures lie only in the substituents, as shown in Figure 1.

From the aforementioned interest in pursuing the SAR studies of PPAPs, we have developed a synthetic approach to the bicyclo[3.3.1]nonane-2,4,9-trione core and reported total syntheses of nemorosone,[3m] garsubellin A,[3p] clusianone,[3q] and hyperforin.[3r] However, because these previous total syntheses afforded racemic products, we have decided to investigate an enantioselective approach to PPAPs. We herein report the formal enantioselective total synthesis of nemorosone, garsubellin A, clusianone, and hyperforin via a common chiral intermediate that was prepared by the catalytic asymmetric intramolecular cyclopropanation (CAIMCP) of an α-diazo β-keto sulfone.

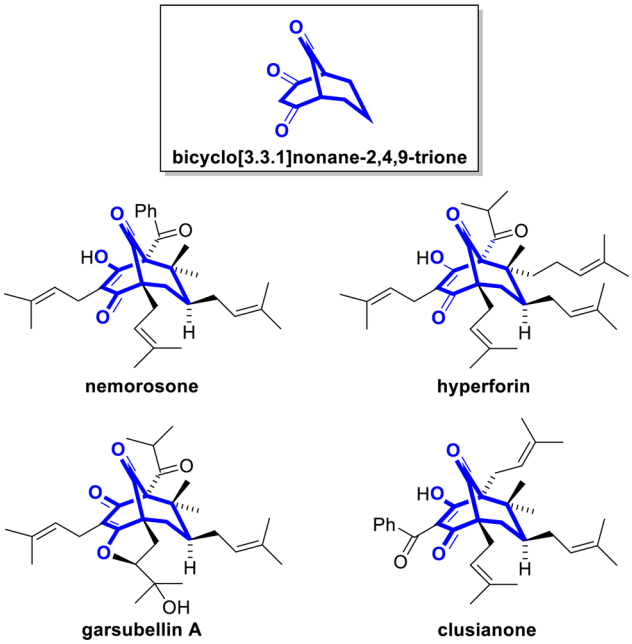


Figure 1. Structures of bicyclo[3.3.1]nonane-2,4,9-trione, nemorosone, hyperforin, garsubellin A, and clusianone.

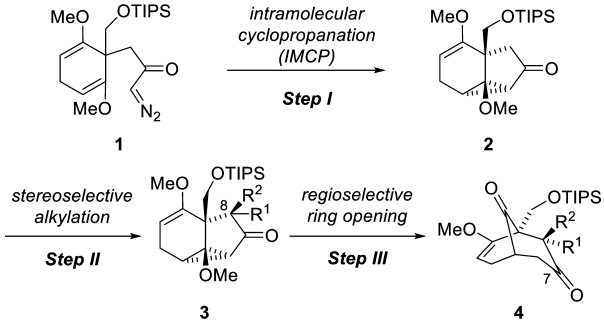
Received: November 23, 2014
Published: January 12, 2015

DOI: 10.1021/jo5026699
J. Org. Chem. 2015, 80, 1735−1745

RESULTS AND DISCUSSION

Scheme 1 shows our previously reported approach to racemic **4** via a common synthetic intermediate,[3m,p−r,8] cyclopropane **2**.

Scheme 1. Our Previously Reported Approach to Racemic 4 via Cyclopropane 2



This approach features intramolecular cyclopropanation of **1** (step I),[9] subsequent stereoselective alkylations of **2** (step II), and regioselective ring opening of the cyclopropane ring in **3** (step III). Step I proceeded smoothly at room temperature owing to the favorable intramolecular process, affording cyclopropane **2** in high yield. Step II allowed the introduction of two methyl groups at the C8 position to generate the all-carbon quaternary center, which was followed by step III to afford **4**, leading to the total synthesis of nemorosone, garsubellin A, and clusianone. Alternatively, step II could also allow the introduction of two different groups at the C8 position, making it stereogenic, because the alkylation at the C8 position proceeded from the less hindered convex side. Indeed, this approach allowed the stereoselective total synthesis of hyperforin. Step III was regioselective because the electron-donating methoxy group on the cyclopropane and the electron-withdrawing ketone cooperatively facilitated the ring-opening reaction.

As described above, we have achieved the total syntheses of the four PPAPs. However, to pursue SAR studies, the PPAPs must be synthesized enantioselectively. Because step I is the desymmetrization step, it could be pursued enantioselectively through the use of a chiral catalyst. Consequently, we began to investigate the CAIMCP of α-diazo ketone **1**.

The CAIMCP of **1** was examined using a catalytic amount of $(CuOTf)_2$·PhMe (5 mol %) and ligands **L1**−**L3** (15 mol %) in toluene (Figure 2), which are the standard reaction conditions

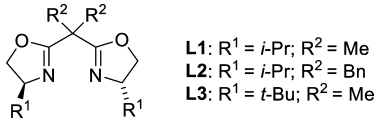
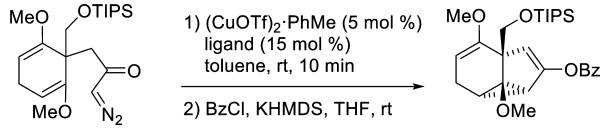


Figure 2. Structures of ligands **L1**−**L3**.

used for CAIMCP in our laboratory (Table 1).[9] Unfortunately, the enantioselectivity was low (16−42% ee) with all three ligands (entries 1−3, Table 1).

The unsuccessful CAIMCP of **1** directed us to investigate the CAIMCP of α-diazo β-keto sulfone,[9a] because a number of α-diazo β-keto sulfones were previously developed by us and successfully converted to the corresponding chiral cyclopropanes with high yield and enantioselectivity.[9]

Table 1. CAIMCP of α-Diazo Ketone 1 with CuOTf and Ligands L1−L3

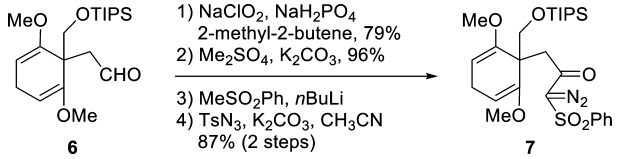


entry	ligand	yield[a] (%)	ee[b] (%)
1	**L1**	49	42
2	**L2**	48	21
3	**L3**	27	16

[a]Isolated yield (two steps). [b]Enantiomeric excess determined by HPLC (see the Experimental Section).

The α-diazo β-keto sulfone **7** was prepared from aldehyde **6** as shown in Scheme 2. The reaction of **6** with a lithiated methyl

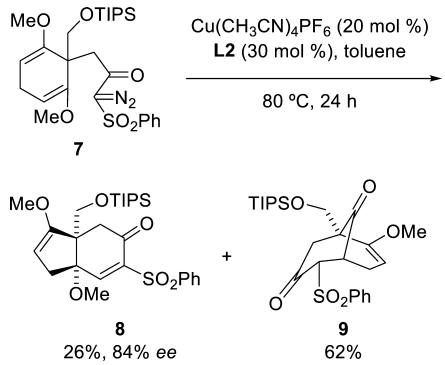
Scheme 2. Preparation of α-Diazo β-Keto Sulfone 7 from 6



phenyl sulfone afforded the desired adduct in high yield, but the resultant alcohol readily added to the enol ether. Therefore, **6** was oxidized to the corresponding carboxylic acid, followed by formation of the methyl ester, the reaction with a dianion of methyl phenyl sulfone, and finally diazo transfer, to afford **7**.

The CAIMCP of **7** was first examined using $(CuOTf)_2$·PhMe, but $Cu(CH_3CN)_4PF_6$, which was easier to handle, was used in subsequent reactions. The CAIMCP of **7** using $Cu(CH_3CN)_4PF_6$ (20 mol %) and ligand **L2** (30 mol %) in toluene at 80 °C afforded compounds **8** (26%, 84% ee) and **9** (62%) (Scheme 3). The ee of **9** was difficult to determine by

Scheme 3. Preliminary Studies on CAIMCP of α-Diazo β-Keto Sulfone 7



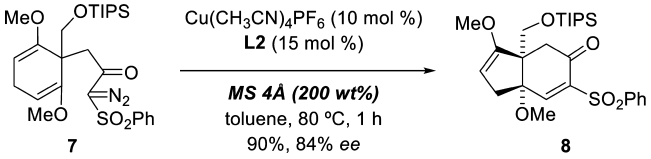
HPLC analysis because a small amount of its enol form exists in equilibrium. Interestingly, cyclopropanes were not isolated in the reaction of **7**, but the formation of **9** indicated that the ring-opening reaction followed cyclopropane formation. On the other hand, the structure of **8** was not readily elucidated by NMR studies.

Previous experience with CAIMCP in our laboratory has revealed the formation of unidentified products in the presence

DOI: 10.1021/jo5026699
J. Org. Chem. 2015, 80, 1735−1745

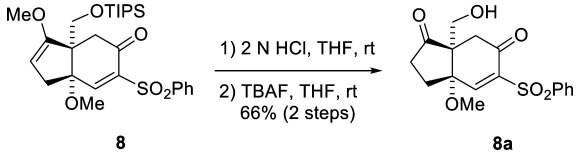
of trace amounts of H_2O; hence, the CAIMCP of **7** was carried out in the presence of molecular sieves (MS) 4 Å to remove any trace amounts of H_2O (Scheme 4). Interestingly, **8** was obtained as the sole product in the reaction using MS 4 Å.

Scheme 4. CAIMCP of 7 in the Presence of MS 4 Å



Treatment of **8** with 2 N HCl and subsequent reaction of the crude product with TBAF afforded crystalline **8a**, which was suitable for X-ray crystallographic analysis (Scheme 5). X-ray

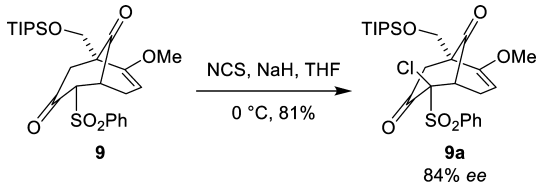
Scheme 5. Conversion of 8 to 8a for the X-ray Crystallographic Analysis



crystallographic analysis of **8a** revealed that its crystal structure was rather unexpected and indicated that a skeletal rearrangement occurred during the course of the reaction.[10] The absolute configuration of **8** was elucidated to be that shown in Scheme 5 on the basis of the X-ray crystallographic analysis of **8a**.

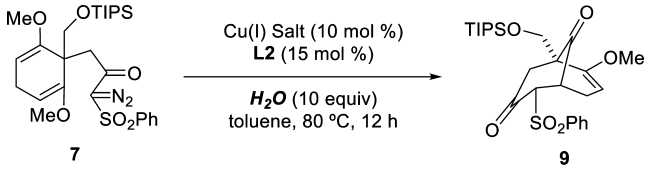
To determine the absolute configuration of **9**, its crystalline derivative was explored. After several attempts, **9a**, which was prepared by the reaction of **9** with NCS and NaH, was isolated as a single crystal suitable for X-ray crystallographic analysis. The crystal structure indicated the absolute configuration was as shown in Scheme 6.[10] HPLC analysis of **9a** indicated 84% ee, the same value as that of **8a**, which also indicates that the chiral purities of **8** and **9** were the same.

Scheme 6. Conversion of 9 to 9a for the X-ray Crystallographic Analysis



To investigate the origin of the two entirely different structures of **8** and **9**, we carried out the CAIMCP of **7** in the presence of H_2O and found that CAIMCP in the presence of H_2O (10 equiv) afforded **9** in 79% yield (84% ee) without the formation of **8** (entry 1, Table 2). Use of an excess amount of H_2O (15 equiv) resulted in the decreased yield (68%), though the ee did not change (84% ee). The yield and ee in the reaction using H_2O (5 equiv) were almost the same (80%, 84% ee) as those in entry 1, Table 2. H_2O (10 equiv) was used to ensure accurate measurement of the H_2O added to the small-scale reactions. The effects of cationic Cu(I) salts on the

Table 2. CAIMCP of 7 in the Presence of H_2O (10 equiv) and Optimization of Cu(I) Salt



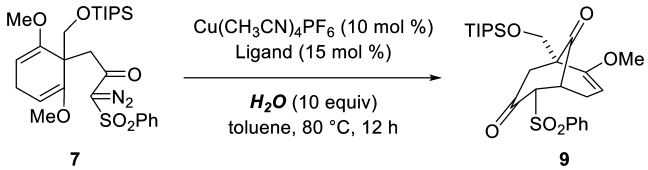
entry	Cu(I) salt	yield[a] (%)	ee[b] (%)
1	$Cu(CH_3CN)_4PF_6$	79	84
2	$Cu(CH_3CN)_4BF_4$	59	82
3	$Cu(CH_3CN)_4NTf_2$	76	84
4	CuCl + $NaBAr^F$	67	74
5	CuCl + $AgSbF_6$	79	82

[a]Isolated yield. [b]Enantiomeric excess determined by HPLC analysis of the corresponding **9a** (see the Experimental Section).

reaction were also surveyed (entries 2–5); $Cu(CH_3CN)_4PF_6$ was found to be the best choice in terms of yield and ee.

CAIMCP using other bisoxazoline ligands **L1** (entry 1, Table 3) and **L3**–**L8** (entries 3–8, Table 3) (Figures 2 and 3) was

Table 3. CAIMCP of 7 in the Presence of H_2O (10 equiv) and Optimization of the Ligand



entry	ligand	yield[a] (%)	ee[b] (%)
1	**L1**	70	84
2	**L2**	79	84
3	**L3**	75	37
4	**L4**	40	48
5	**L5**	61	84
6	**L6**	59	82
7	**L7**	61	51
8	**L8**	54	49

[a]Isolated yield. [b]Enantiomeric excess determined by HPLC analysis of the corresponding **9a** (see the Experimental Section).

also examined. The same enantioselectivity (84% ee) was achieved using **L1** or **L5**; however, the yields obtained in these reactions did not exceed that of the reaction using **L2** (entry 2,

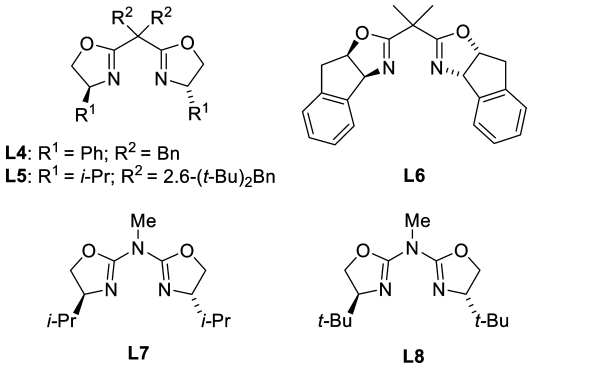
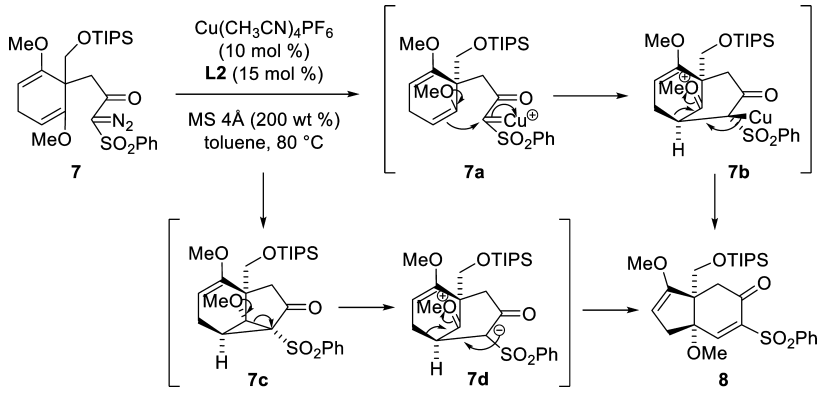


Figure 3. Structures of ligands **L4**–**L8**.

DOI: 10.1021/jo5026699
J. Org. Chem. 2015, 80, 1735–1745

Scheme 7. Proposed Reaction Pathways from 7 to 8



Scheme 8. Proposed Reaction Pathways from 7 to 9

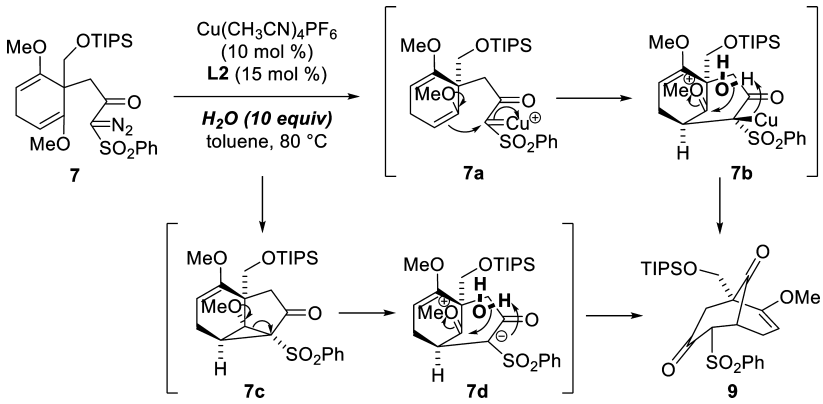


Table 3). Consequently, **L2** was selected as the best ligand for the CAIMCP of **7**.

A rearranged product such as **8** was not formed in the CAIMCP of **1**. Hence, the rearrangement must be attributed to the introduction of the $PhSO_2$ group in the substrate. Because the $PhSO_2$ group is bulky, the cyclopropane with the *cis*-substituted $PhSO_2$ and MeO groups is unstable owing to the steric strain between the two vicinal groups. Consequently, we assumed that the in situ generated Cu(I)−carbene complex **7a** (Scheme 7) underwent rearrangement to afford **8** via **7b**. Alternatively, it is also speculated that cyclopropane **7c** may be formed first but readily undergoes ring opening, because of the steric strain between the $PhSO_2$ and MeO groups as well as the cooperative effect of the electron-donating MeO group and the electron-withdrawing $PhSO_2$ group. Subsequent rearrangement then affords **8** via **7d**.

On the other hand, in the CAIMCP of **7** in the presence of H_2O, it was surmised that the reaction of H_2O with reactive synthetic intermediates such as **7b** and **7d** would occur to afford **9** via liberation of the MeO group (Scheme 8). Since the reaction of H_2O must proceed faster than the rearrangement (shown in Scheme 7) to afford **9**, one would expect H_2O to be in close proximity to the reaction intermediates and be coordinated with the Cu(I)−carbene complex.[11] The results of the X-ray crystallographic analyses are consistent with the proposed pathways (Schemes 7 and 8), which involve the same reaction intermediates.

Considering the absolute configurations of **8** and **9**, which were formed by the CAIMCP of **7**, the enantioselectivity in the reaction would be well explained by model A in Figure 4.[3a,12] The cyclopropanation of **7** was thought to occur preferentially

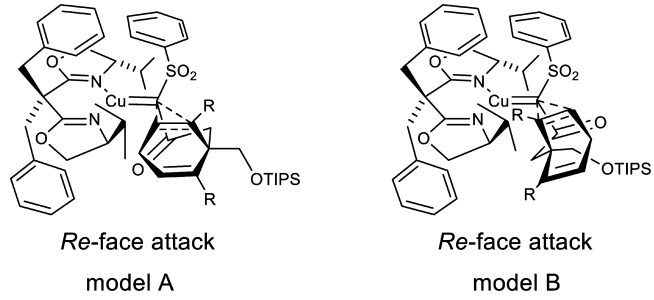


Figure 4. Proposed models A and B (R = OMe).

at the *Re*-face (defined by the Cu═C—C arrangement) of the chiral catalyst−carbene complex, because steric hindrance would be encountered during cyclopropanation at the *Si*-face. If the double bond approaches from the *Si*-face, the resulting pyramidal conformation of the carbene C atom in the transition state[12] means that the bulky phenyl sulfonyl group would interact unfavorably with the isopropyl group as well as the benzyl group of the ligand.

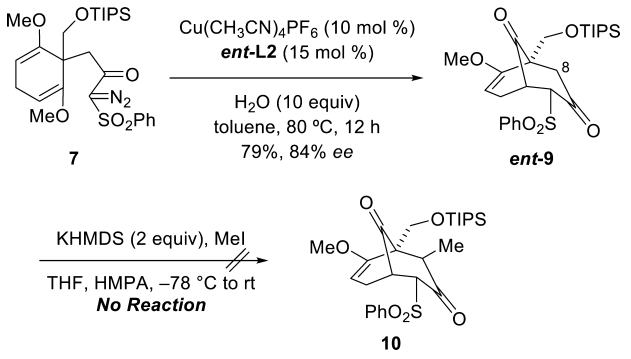
In contrast to the reaction at the *Si*-face, the reaction at the *Re*-face would be preferred because the unfavorable interactions with the phenyl sulfonyl group would be negligible in the transition states derived from models A and B. Thus, the phenyl sulfonyl group performs a crucial role in enantioselection. Model A is preferred because model B has an unfavorable steric interaction arising from the methoxy group, as shown in Figure 4.

As described above, CAIMCP of **7** in the presence of H_2O successfully afforded **9**, which would be a key synthetic

DOI: 10.1021/jo5026699
J. Org. Chem. 2015, 80, 1735−1745

intermediate for the total synthesis of PPAPs. However, the aforementioned X-ray crystallographic analysis indicated that *ent*-**9** must be prepared to synthesize the PPAPs in their natural form. Hence, CAIMCP using *ent*-**L2** was carried out to obtain *ent*-**9** (Scheme 9). Alkylation of *ent*-**9** would be a quick

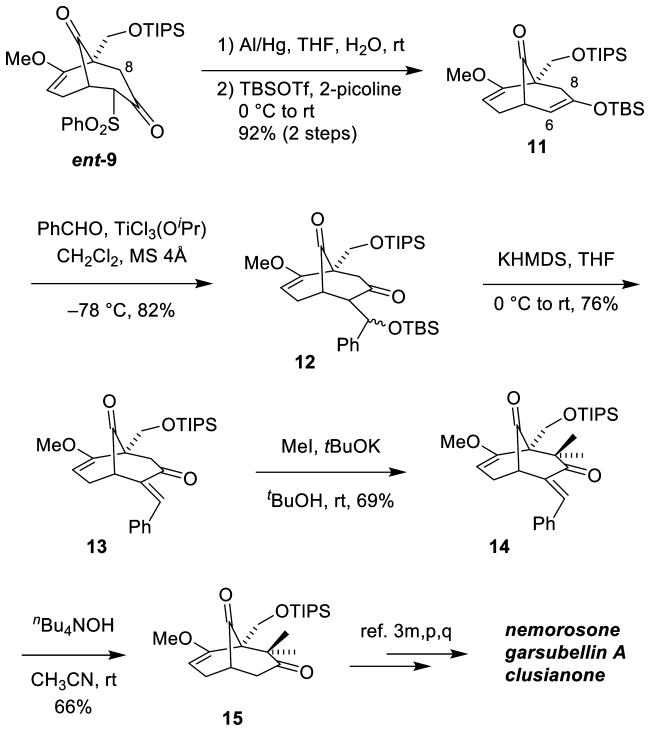
Scheme 9. CAIMCP of 7 with *ent*-L2 and Attempted Methylation of the Dianion of *ent*-9



approach to obtain intermediates for the total synthesis of PPAPs. Unfortunately, no alkylation at C8 occurred in the reaction of *ent*-**9** with KHMDS (2 equiv) or LDA (2 equiv), probably because of the steric hindrance at the C8 position by the vicinal all-carbon quaternary center. Consequently, we had to make a detour to introduce substituents at the C8 position.

The problem with C8 alkylation directed our attention to using the ketone obtained by removal of the $PhSO_2$ group of *ent*-**9**. The regioselective introduction of a benzylidene group at the C6 position of the ketone derived from *ent*-**9** to form **13** was expected to be possible owing to the steric hindrance at the C8 position (Scheme 10).[15] The reaction of *ent*-**9** with

Scheme 10. Formal Asymmetric Total Synthesis of Nemorosone, Garsubellin A, and Clusianone

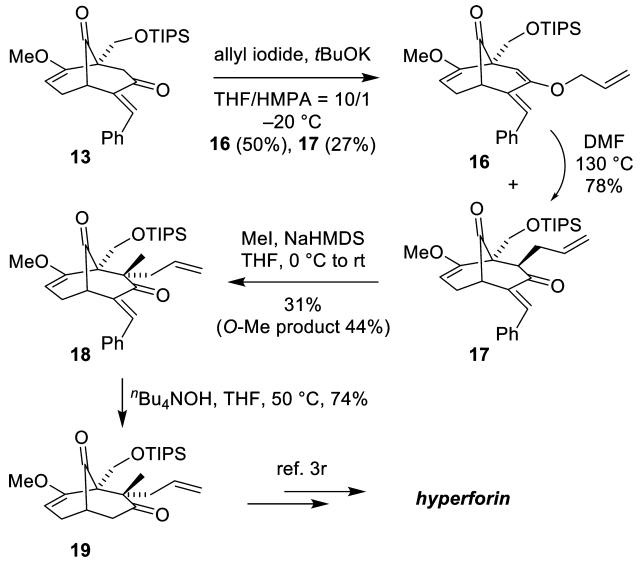


aluminum amalgam removed the $PhSO_2$ group to afford the desired ketone, which was treated with (TBS)OTf and 2-picoline to afford **11** as the sole product in 92% yield (two steps). The use of 2-picoline was key to the formation of **11**, as other more bulky and less bulky bases resulted in no reaction and reduced regioselectivity, respectively.

The Mukaiyama aldol reaction of **11** with benzaldehyde afforded **12**, which upon treatment with KHMDS in THF afforded **13**. Dimethylation of the C8 position of **13** using MeI and ^{t}BuOK in ^{t}BuOH proceeded successfully to afford **14** in 69% yield. The benzylidene group in **14** was removed using ^{n}Bu$_4$NOH in acetonitrile to afford **15**. The final product **15** proved to be identical to the racemic **15** previously reported by us (^{1}H and ^{13}C NMR, IR, and HRMS).[3m] Since we have already reported the transformations of **15** to nemorosone, garsubellin A, and clusianone, the formal enantioselective total synthesis of these three PPAPs has thus been achieved.

Next, the transformation of **13** to **19**, an intermediate for the total synthesis of hyperforin reported by us, was investigated (Scheme 11). To stereoselectively introduce the allyl and

Scheme 11. Formal Asymmetric Total Synthesis of Hyperforin



methyl groups at the C8 position, allylation of the C8 position of **13** must be performed first, since alkylation at the C8 position takes place from the less hindered convex side. The reaction of **13** with allyl iodide afforded both the *O*-allylated (**16**, 50%) and *C*-allylated (**17**, 27%) products, but **16** was successfully converted to **17** in 78% yield by heating at 130 °C in DMF. The C8 methylation was crucial, but despite much optimization, **18** was obtained in only 31% yield when using MeI and NaHMDS in THF. However, the *O*-Me byproduct, obtained in 44% yield, could be recycled upon acidification. Finally, the benzylidene group in **18** was removed using ^{n}Bu$_4$NOH in THF to afford **19**. The final product **19** proved to be identical to the racemic **19** previously reported by us (^{1}H and ^{13}C NMR, IR, and HRMS),[3m] confirming that the formal enantioselective total synthesis of hyperforin has been achieved.

■ CONCLUSION

In summary, the CAIMCP of an α-diazo ketone, a synthetic intermediate for PPAPs reported by us, exhibited low

DOI: 10.1021/jo5026699
J. Org. Chem. 2015, 80, 1735–1745

enantioselecitivy; however, CAIMCP of the corresponding α-diazo β-keto sulfone was found to afford products with 84% ee and in 79% yield. To our surprise, the products were not cyclopropanes, and characterization of the structures revealed that ring opening of the desired cyclopropane, as well as skeletal rearrangement, occurred during the course of the CAIMCP. Further investigation on the reaction conditions of the CAIMCP disclosed that the reaction in the presence of MS 4 Å afforded only the rearranged product, while the reaction in the presence of H_2O afforded the product derived from the ring opening of the desired cyclopropane as the sole product. X-ray crystallographic analysis suggested that the two products would be derived from the same chiral intermediate. The product derived from the ring opening of the cyclopropane was successfully transformed to the synthetic intermediates that were previously reported by us, accomplishing the formal enantioselective total synthesis of nemorosone, garsubellin A, clusianone, and hyperforin, which would contribute to SAR studies of PPAPs. This provides the potential for finding new artificial analogues that could exhibit significant biological activity.

EXPERIMENTAL SECTION

General Methods. ^1H and ^{13}C NMR spectra, including NOESY and DEPT spectra, were recorded on a 400 MHz spectrometer. ^1H and ^{13}C chemical shifts are reported in parts per million downfield from tetramethylsilane (TMS; δ scale) with the solvent resonances as internal standards. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; br, broad. IR spectra were recorded on an FT/IR spectrometer using an attenuated total reflectance (ATR) attachment. Optical rotations were measured using the cell (having 3.5 mm diameter, 1 dm = 10 cm length, and less than 2 mL volume) and the solution (prepared using a 2 mL mess flask) at the indicated temperature (t) and are reported as $[\alpha]_D^t$ (c (g/mL), solvent). All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel plates using UV light as the visualizing agent and phosphomolybdic acid and heat as the developing agents. Silica gel (60, particle size 0.040−0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on self-made 0.3 mm silica gel plates. THF and Et_2O were distilled from sodium/benzophenone ketyl. Toluene was distilled from sodium. CH_2Cl_2 and MeCN were distilled from CaH_2, and all commercially available reagents were used without further purification. Optical rotations were measured on a polarimeter at a wavelength of 589 nm. High-resolution mass spectra were obtained with electrospray ionization (ESI) on an orbitrap spectrometer, and theoretical monoisotopic molecular masses were typically within 5 ppm. Melting points are uncorrected. TLC R_f values of purified compounds were included.

8-(Benzoyloxy)-2,6-dimethoxy-1-[((triisopropylsilyl)oxy)-methyl]tricyclo[4.3.0.0^{5,7}]nona-2,8-diene (5) (General Procedure). To a stirred solution of $(CuOTf)_2$·PhMe (4.8 mg, 0.0093 mmol) in toluene (0.2 mL) was added bisoxazoline ligand **L1** (7.4 mg, 0.028 mmol) in toluene (0.8 mL) via a cannula, and the reaction mixture was stirred at room temperature for 1 h. The resulting solution (0.14 mL, 10 mol %, of **L1**−Cu(I) complex) was added to a stirred solution of diazoketone[3m] **1** (10.5 mg, 0.0257 mmol) in toluene (0.3 mL) via syringe at 0 °C, and the resultant solution was stirred at room temperature. After the starting material was consumed, the reaction mixture was quenched with 30% aqueous NH_4OH solution (1 mL), and the aqueous layer was extracted with Et_2O (2 mL × 3). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, and evaporated. To a solution of the crude cyclopropane in THF (0.3 mL) was added KHMDS (0.5 M in PhMe, 1 mL, 0.05 mmol, 2.0 equiv) at 0 °C, and the reaction mixture was stirred for 30 min. To the reaction mixture was added BzCl (0.015 mL, 0.13 mmol, 5.0 equiv), and the resultant solution was stirred at 0 °C for 30 min. The reaction mixture was quenched with 30% aqueous NH_4OH solution (1 mL), and the aqueous layer was extracted with Et_2O (1 mL × 3). The combined organic layer was washed with brine (2 mL), dried over Na_2SO_4, and evaporated. The residue was purified by preparative TLC (hexane/ethyl acetate = 10/1) to afford **5** (6.1 mg, 49%, 42% ee) as a clear oil: R_f = 0.26 (hexane/ethyl acetate = 10/1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.10−8.03 (m, 2H), 7.60−7.55 (m, 1H), 7.49−7.42 (m, 2H), 4.99 (d, J = 1.8 Hz, 1H), 4.70 (dd, J = 7.3, 1.8 Hz, 1H), 4.23 (d, J = 9.6 Hz, 1H), 4.14 (d, J = 9.6 Hz, 1H), 3.48 (s, 3H), 3.31 (s, 3H), 2.67 (ddd, J = 16.9, 9.2, 7.3 Hz, 1H), 2.43 (dd, J = 8.2, 1.8 Hz, 1H), 1.90 (ddd, J = 16.9, 2.3, 1.8 Hz, 1H), 1.79 (ddd, J = 9.2, 8.2, 2.3 Hz, 1H), 1.14−1.03 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0 (Cq), 159.1 (Cq), 148.4 (Cq), 133.5 (CH), 130.2 (CH), 129.7 (Cq), 128.7 (CH), 110.6 (CH), 95.0 (CH), 61.9 (CH_2), 57.3 (CH_3), 55.0 (CH_3), 53.2 (Cq), 35.4 (CH), 27.3 (CH), 19.6 (CH_2), 18.3 (CH_3), 18.2 (CH_3), 12.3 (CH); IR (ATR) ν_{max} 2940, 2865, 1741, 1642, 1451, 1263, 1110, 1065, 706 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{28}H_{40}O_5SiNa$ 507.2537, found 507.2534; $[\alpha]_D^{21}$ +6.0 (c 0.050, $CHCl_3$ (42% ee)); ee was determined by HPLC analysis (230 nm), Daicel Chiralpak IA-3 0.46 cm ⌀ × 25 cm (hexane/^{i}PrOH = 100/1, flow rate 0.5 mL/min), retention time 11.3 min (minor enantiomer), 12.6 min (major enantiomer).

2-[2,6-Dimethoxy-1-[((triisopropylsilyl)oxy)methyl]-cyclohexa-2,5-dienyl]acetic Acid (6a) and Methyl 2-[2,6-Dimethoxy-1-[((triisopropylsilyl)oxy)methyl]cyclohexa-2,5-dienyl]acetate (6b). To a stirred solution of $NaClO_2$ (2.97 g, 32.8 mmol, 1.5 equiv) and NaH_2PO_4 (5.25 g, 43.7 mmol, 2.0 equiv) in H_2O (145 mL), THF (70 mL), and 2-methyl-2-butene (70 mL) were added ^{t}BuOH (145 mL) and 2-[2,6-dimethoxy-1-[((triisopropylsilyl)-oxy)methyl]cyclohexa-2,5-dienyl]acetaldehyde[3m] (8.06 g, 21.87 mmol) at room temperature, and the reaction mixture was stirred for 12 h. The reaction mixture was diluted with Et_2O (200 mL) and quenched with saturated aqueous NH_4Cl solution (100 mL), and the aqueous layer was extracted with Et_2O (100 mL × 3). The combined organic layer was washed with brine (200 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 2/1 to 1/1) to afford **6a** (6.64 g, 79%) as a white solid: R_f = 0.10 (hexane/ethyl acetate = 4/1); mp 109.3 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 4.82 (t, J = 3.7 Hz, 2H), 3.77 (s, 2H), 3.51 (s, 6H), 2.77 (t, J = 3.7 Hz, 2H), 2.56 (s, 2H), 0.99 (br s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9 (Cq), 152.4 (Cq), 94.4 (CH), 65.2 (CH_2), 54.5 (CH_3), 48.4 (Cq), 36.7 (CH_2), 24.2 (CH_2), 17.9 (CH_3), 12.2(CH); IR (ATR) ν_{max} 2940, 2864, 1698, 1462, 1203, 1158, 1125, 780, 680 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{20}H_{36}O_5SiNa$ 407.2224, found 407.2226.

To a stirred suspension of **6a** (5.75 g, 15.0 mmol) and K_2CO_3 (4.13 g, 29.9 mmol, 2.0 equiv) in acetone (50 mL) was added Me_2SO_4 (2.13 mL, 22.4 mmol, 1.5 equiv) at 0 °C, and the resulting reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (30 mL), and the aqueous layer was extracted with EtOAc (40 mL × 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 50/1) to afford **6b** (5.73 g, 96%) as a colorless oil: R_f = 0.55 (hexane/ethyl acetate = 4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 4.80 (t, J = 3.7 Hz, 2H), 3.77 (s, 2H), 3.56 (s, 3H), 3.50 (s, 6H), 2.77 (t, J = 3.7 Hz, 2H), 2.52 (s, 2H), 0.99 (br s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (Cq), 152.6 (Cq), 94.0 (CH), 65.1 (CH_2), 54.5 (CH_3), 51.3 (CH_3), 48.5 (Cq), 36.6 (CH_2), 24.2 (CH_2), 18.0 (CH_3), 12.2 (CH); IR (ATR) ν_{max} 2943, 2865, 1741, 1699, 1464, 1200, 1153, 1126, 883 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{21}H_{38}O_5SiNa$ 421.2381, found 421.2378.

1-[2,6-Dimethoxy-1-[((triisopropylsilyl)oxy)methyl]-cyclohexa-2,5-dienyl]-3-(phenylsulfonyl)propan-2-one (6c). To a stirred solution of methyl phenyl sulfone (631.0 mg, 4.02 mmol, 1.3 equiv) in THF (20 mL) was added ^{n}BuLi (4.93 mL, 1.63 M in hexane, 2.6 equiv) at 0 °C. After the resulting yellow suspension was stirred for

DOI: 10.1021/jo5026699
J. Org. Chem. 2015, 80, 1735−1745

30 min, a solution of **6b** (1.23 g, 3.09 mmol) and HMPA (2,6 mL, 15.5 mmol, 5.0 equiv) in THF (5 mL) was added at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (20 mL), and the aqueous layer was extracted with EtOAc (15 mL × 3). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, and evaporated. The residue was sufficiently pure and was used without purification: R_f = 0.27 (hexane/ethyl acetate = 4/1); mp 113.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87−7.83 (m, 2H), 7.67−7.61 (m, 1H), 7.56−7.50 (m, 2H), 4.78 (t, J = 3.7 Hz, 2H), 4.11 (s, 2H), 3.71 (s, 2H), 3.48 (s, 6H), 2.77 (s, 2H), 2.61 (dt, J = 21.5, 3.7 Hz, 1H), 2.44 (dt, J = 21.5, 3.7 Hz, 1H), 0.96 (br s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8 (Cq), 151.9 (Cq), 139.0 (Cq), 134.1 (CH), 129.2 (CH), 128.6 (CH), 94.8 (CH), 67.1 (CH_2), 65.1 (CH_2), 54.5 (CH_3), 48.8 (Cq), 45.1 (CH_2), 24.1 (CH_2), 17.9 (CH_3), 12.1 (CH); IR (ATR) ν_{max} 2940, 2864, 1709, 1697, 1309, 1164, 1130, 780 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{27}H_{42}O_6SiSNa$ 545.2364, found 545.2364.

3-Diazo-1-[2,6-dimethoxy-1-[((triisopropylsilyl)oxy)methyl]-cyclohexa-2,5-dienyl]-3-(phenylsulfonyl)propan-2-one (7). To a stirred solution of crude **6c** and TsN_3 (792.2 mg, 4.02 mmol, 1.3 equiv) in acetonitrile (20 mL) was added K_2CO_3 (1.11 g, 8.04 mmol, 2.6 equiv), and the reaction mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with Et_2O (20 mL), the organic layer was washed with aqueous 2 N KOH solution (two times), and the aqueous layer was extracted with Et_2O (20 mL × 3). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 15/1 to 6/1) to afford **7** (1.44 g, 87%, two steps) as a pale yellow solid: R_f = 0.44 (hexane/ethyl acetate = 4/1); mp 112.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03−7.99 (m, 2H), 7.65−7.59 (m, 1H), 7.55−7.49 (m, 2H), 4.65 (t, J = 3.7 Hz, 2H), 3.69 (s, 2H), 3.42 (s, 6H), 2.64 (s, 2H), 2.61 (dt, J = 21.1, 3.7 Hz, 1H), 2.44 (dt, J = 21.1, 3.7 Hz, 1H), 0.96 (br s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.2 (Cq), 151.5 (Cq), 142.1 (Cq), 133.9 (CH), 129.1 (CH), 128.1 (CH), 94.7 (CH), 65.1 (CH_2), 54.3 (CH_3), 49.4 (Cq), 40.3 (CH_2), 24.0 (CH_2), 17.9 (CH_3), 12.1 (CH); IR (ATR) ν_{max} 2941, 2864, 2129, 2118, 1697, 1662, 1332, 1146, 725 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{27}H_{40}O_6N_2SiSNa$ 571.2269, found 571.2268.

(1*S*,6*S*)-1,7-Dimethoxy-3-(phenylsulfonyl)-6-[((triisopropropylsilyl)oxy)methyl]bicyclo[4.3.0]nona-2,6-dien-4-one (8). A mixture of **L2** (3.1 mg, 0.0077 mmol, 15 mol %) and $Cu(MeCN)_4PF_6$ (1.9 mg, 0.0051 mmol, 10 mol %) in toluene (1.0 mL) was stirred at room temperature for 1 h. To the resulting blue suspension were added activated MS 4 Å (54 mg, 200%, w/w) and **7** (27.3 mg, 0.0511 mmol), and the reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was filtrated through a Celite pad and quenched with saturated aqueous $NaHCO_3$ (1 mL). The aqueous layer was extracted with EtOAc (1 mL × 3), and the combined organic layer was washed with brine (3 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 10/1) to afford **8** (25.6 mg, 90%, 84% ee) as a white solid. Racemic **8** was prepared from **7** by the same procedure as above using an achiral bisoxazoline ligand, bis(4,5-dihydrooxazol-2-yl)methane: R_f = 0.38 (hexane/ethyl acetate = 3/1); mp 97.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98−7.94 (m, 2H), 7.89 (s, 1H), 7.62−7.56 (m, 1H), 7.53−7.47 (m, 2H), 4.35 (dd, J = 3.2, 1.8 Hz, 1H), 3.75 (d, J = 10.1 Hz, 1H), 3.72 (d, J = 10.1 Hz, 1H), 3.47 (s, 3H), 3.41 (s, 3H), 2.93 (dd, J = 15.1, 1.8 Hz, 1H), 2.60 (d, J = 16.5 Hz, 1H), 2.46 (d, J = 16.5 Hz, 1H), 2.42 (dd, J = 15.1, 3.2 Hz, 1H), 1.02 (br s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9 (Cq), 158.0 (Cq), 155.0 (CH), 140.7 (Cq), 139.9 (Cq), 133.8 (CH), 129.0 (CH), 128.9 (CH), 90.7 (CH), 81.8 (Cq), 64.1 (CH_2), 56.4 (CH_3), 54.0 (Cq), 53.7 (CH_3), 39.8 (CH_2), 38.6 (CH_2), 18.1 (CH_3), 18.0 (CH_3), 12.1 (CH); IR (ATR) ν_{max} 2940, 2865, 1699, 1655, 1447, 1321, 1153, 1121, 1070, 686 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{27}H_{40}O_6SiSNa$ 543.2207, found 543.2208; $[\alpha]_D^{20}$ +75 (c 0.36, $CHCl_3$); ee was determined by HPLC analysis (254 nm), Daicel Chiralpak IA-3 0.46 cm ⌀ × 25 cm (hexane/^{i}PrOH = 34/1, flow rate 0.5 mL/min), retention time 33.6 min (**8**), 38.1 min (*ent*-**8**).

(1*S*,6*R*)-1,7-Dimethoxy-3-(phenylsulfonyl)-6-[((triisopropropylsilyl)oxy)methyl]bicyclo[4.3.0]nona-2,6-dien-4-one (8a). To a stirred solution of **8** (95.8 mg, 0.184 mmol) in THF (4 mL) was added aqueous 2 N HCl solution (1 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 2.5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution until gas evolution stopped, and the aqueous phase was extracted with Et_2O (3 mL × 3). The combined organic phase was washed with brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was dissolved in THF (4 mL), and to the solution was added TBAF (1.0 M in THF, 0.36 mL, 2.0 equiv) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (1 mL), and the aqueous phase was extracted with EtOAc (3 mL × 3). The combined organic phase was washed with brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 3/2 to 2/3) to afford **8a** (42.3 mg, 66%) as a white solid: R_f = 0.11 (hexane/ethyl acetate = 1/1); mp 164.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.99−7.94 (m, 2H), 7.65−7.58 (m, 1H), 7.55−7.49 (m, 2H), 3.83 (d, J = 11.5 Hz, 1H), 3.66 (d, J = 11.5 Hz, 1H), 3.54 (s, 3H), 2.69 (ddd, J = 13.1, 8.7, 5.5 Hz, 1H), 2.63 (d, J = 17.0 Hz, 1H), 2.57 (d, J = 17.0 Hz, 1H), 2.56−2.46 (m, 1H), 2.41−2.21 (m, 2H), 2.17 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ213.8 (Cq), 188.0 (Cq), 151.4 (CH), 141.1 (Cq), 139.1 (Cq), 134.2 (CH), 129.2 (CH), 129.0 (CH), 81.9 (Cq), 63.2 (CH_2), 59.7 (Cq), 51.9 (CH_3), 40.3 (CH_2), 35.1 (CH_2), 29.0 (CH_2); IR (ATR) ν_{max} 3517, 2949, 1742, 1698, 1308, 1152, 724 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{17}H_{18}O_6SNa$ 373.0716, found 373.0714; $[\alpha]_D^{21}$ +88 (c 0.12, $CHCl_3$).

(1*S*,5*S*,6*R*)-2-Methoxy-6-(phenylsulfonyl)-1-[((triisopropropylsilyl)oxy)methyl]bicyclo[3.3.1]non-2-ene-7,9-dione (9). A mixture of **L2** (24.4 mg, 0.0584 mmol, 15 mol %) and $Cu(MeCN)_4PF_6$ (14.5 mg, 0.0389 mmol, 10 mol %) in toluene (7.6 mL) was stirred at room temperature for 1 h. To the resulting blue suspension were added H_2O (0.075 mL, 10 equiv) and **7** (199.8 mg, 0.374 mmol, 1.0 equiv), and the reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the aqueous layer was extracted with EtOAc (5 mL × 3). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 10/1 to 6/1) to afford **9** (149.5 mg, 79%) as a pale yellow foam. Racemic **9** was prepared from **7** by the same procedure as above using an achiral bisoxazoline ligand, bis(4,5-dihydrooxazol-2-yl)methane: R_f = 0.24 (hexane/ethyl acetate = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86−7.80 (m, 2H), 7.73−7.67 (m, 1H), 7.61−7.51 (m, 2H), 4.61 (dd, J = 5.5, 1.8 Hz, 1H), 4.06 (d, J = 9.2 Hz, 1H), 3.89 (d, J = 9.2 Hz, 1H), 3.87 (br d, J = 1.8 Hz, 1H), 3.47 (s, 3H), 3.45 (m, 1H), 3.25 (d, J = 15.1 Hz, 1H), 2.79 (dd, J = 15.1, 2.3 Hz, 1H), 2.73 (ddd, J = 16.9, 5.7, 1.8 Hz, 1H), 2.27 (ddd, J = 16.9, 5.5, 1.4 Hz, 1H), 1.12−0.97 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4 (Cq), 196.9 (Cq), 155.3 (Cq), 136.7 (Cq), 134.9 (CH), 129.6 (CH), 129.2 (CH), 91.7 (CH), 81.1 (CH), 60.8 (CH_2), 55.6 (Cq), 55.5 (CH_3), 47.1 (CH_2), 45.0 (CH), 30.9 (CH_2), 18.1 (CH_3), 12.2 (CH); IR (ATR) ν_{max} 2941, 2865, 1741, 1721, 1661, 1448, 11491122, 686 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{26}H_{38}O_6SiSNa$ 529.2051, found 529.2051; $[\alpha]_D^{19}$ −55 (c 0.51, $CHCl_3$).

(1*S*,5*R*,6*R*)-6-Chloro-2-methoxy-6-(phenylsulfonyl)-1-[((triisopropropylsilyl)oxy)methyl]bicyclo[3.3.1]non-2-ene-7,9-dione (9a). To a stirred solution of **9** (39.0 mg, 0.077 mmol) in THF (1 mL) was added NaH (60% in oil, 3.7 mg, 0.092 mmol, 1.2 equiv) at 0 °C. After the reaction mixture was stirred for 5 min, *N*-chlorosuccinimide (13.3 mg, 0.10 mmol, 1.3 equiv) was added, and the stirring was continued at 0 °C for 5 min. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (1 mL), and the aqueous layer was extracted with Et_2O (1 mL × 3). The combined organic layer was washed with brine (3 mL), dried over Na_2SO_4, and evaporated. The residue was purified by preparative TLC (hexane/

DOI: 10.1021/jo5026699
J. Org. Chem. 2015, 80, 1735−1745

ethyl acetate = 3/1) to afford **9a** (33.6 mg, 81%, 84% ee) as a white solid. Racemic **9a** was prepared from racemic **9**: R_f = 0.56 (hexane/ethyl acetate = 3/1); mp 139.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20−8.14 (m, 2H), 7.70−7.64 (m, 1H), 7.58−7.51 (m, 2H), 4.81 (dd, J = 5.7, 1.8 Hz, 1H), 4.00 (d, J = 9.6 Hz, 1H), 3.93 (d, J = 9.6 Hz, 1H), 3.67−3.59 (m, 2H), 3.55 (s, 3H), 3.40 (d, J = 15.1 Hz, 1H), 2.71 (d, J = 15.1 Hz, 1H), 2.64 (ddd, J = 17.9, 6.0, 1.8 Hz, 1H), 1.11−0.99 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3 (Cq), 193.6 (Cq), 154.0 (Cq), 135.9 (Cq), 134.9 (CH), 132.5 (CH), 128.6 (CH), 92.5 (CH), 83.5 (Cq), 60.3 (CH_2), 56.2 (Cq), 55.6 (CH), 55.4 (CH), 43.6 (CH_2), 26.2 (CH_2), 18.1 (CH_3), 18.0 (CH_3), 12.1 (CH); IR (ATR) ν_{max} 2941, 2864, 2142, 2040, 1962, 1745, 1153 cm^{-1}; HRMS (ESI) [M + Na]$^+$ calcd for $C_{26}H_{37}O_6SiSClNa$ 563.1661, found 563.1662; $[\alpha]_D^{19}$ −16 (c 0.77, $CHCl_3$); ee was determined by HPLC analysis (230 nm), Daicel Chiralpak IA-3 0.46 cm ⌀ × 25 cm (hexane/^{i}PrOH = 29/1, flow rate 0.5 mL/min), retention time 14.4 min (**9a**), 16.6 min (*ent*-**9a**).

(1*R*,5*S*)-2-Methoxy-1-[((triisopropropylsilyl)oxy)methyl]-bicyclo[3.3.1]non-2-ene-7,9-dione (*ent*-9b). To a stirred 2% aqueous $HgCl_2$ solution (10 mL) was added aluminum powder (1033 mg, 27 equiv) at room temperature, and the resulting suspension was stirred for 2 min and then cooled to 0 °C. The aqueous layer was decanted, and the residue was washed with deionized water. The freshly prepared Al/Hg was suspended with THF/H_2O = 10/1 (15 mL), then *ent*-**9** (718.6 mg, 1.42 mmol, 1.0 equiv) in THF (2 mL) was added to this suspension at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. *Caution! This reaction is highly exothermic, so the reaction temperature has to be maintained below 35 °C with a water bath.* The reaction mixture was filtrated through a Celite pad, and the filtrate was evaporated. The residue (crude *ent*-**9b**) was used for the next step without further purification: R_f = 0.19 (hexane/ethyl acetate = 4/1); mp 46.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (dd, J = 6.0, 1.8 Hz, 1H), 4.02 (d, J = 9.2 Hz, 1H), 3.85 (d, J = 9.2 Hz, 1H), 3.51 (s, 3H), 2.94−2.83 (m, 2H), 2.69−2.60 (m, 3H), 2.53 (dd, J = 15.3, 2.8 Hz, 1H), 2.31 (br d, J = 16.6, 6.0 Hz, 1H), 1.11−1.00 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1 (Cq), 205.5 (Cq), 154.3 (Cq), 92.4 (CH), 60.8 (CH_2), 55.3 (CH_3), 55.0 (Cq), 48.7 (CH_2), 47.5 (CH_2), 44.8 (CH), 31.0 (CH_2), 18.1 (CH_3), 12.2 (CH); IR (ATR) ν_{max} 2942, 2865, 1722, 1663, 1463, 1244, 1153, 1107, 883 cm^{-1}; HRMS (ESI) [M + Na]$^+$ calcd for $C_{20}H_{34}O_4SiNa$ 389.2119, found 389.2119; $[\alpha]_D^{24}$ +22 (c 0.58, $CHCl_3$).

(1*R*,5*S*)-7-(*tert*-Butyldimethylsiloxy)-2-methoxy-1-[((triisopropropylsilyl)oxy)methyl]bicyclo[3.3.1]nona-2,6-dien-9-one (11). To a stirred solution of the crude *ent*-**9b** and 2-picoline (0.21 mL, 2.13 mmol, 1.5 equiv) in CH_2Cl_2 (7 mL) was added (TBS)OTf (0.39 mL, 1.70 mmol, 1.2 equiv) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (5 mL × 3). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 100/1 to 70/1) to afford **11** (625.2 mg, 92%, two steps) as a clear oil: R_f = 0.69 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (m, 1H), 4.68 (d, J = 5.2 Hz, 1H), 4.05 (d, J = 8.9 Hz, 1H), 3.54 (s, 3H), 2.83 (dd, J = 5.2, 5.2 Hz, 1H), 2.51 (dd, J = 16.3, 5.0 Hz, 1H), 2.43 (d, J = 16.9 Hz, 1H), 2.29−2.19 (m, 2H), 1.04 (br s, 21H), 0.89 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.9 (Cq), 155.5 (Cq), 150.8 (Cq), 107.6 (CH), 92.2 (CH), 61.2 (CH_2), 54.8 (CH_3), 54.6 (Cq), 44.0 (CH), 39.2 (CH_2), 30.6 (CH_2), 25.8 (CH_3), 18.2 (Cq), 18.1 (CH_3), 12.2 (CH), − 4.3 (CH_3), −4.4 (CH_3); IR (ATR) ν_{max} 2930, 2864, 1741, 1661, 1463, 1210, 1106. 859. 840, 778 cm^{-1}; HRMS (ESI) [M + Na]$^+$ calcd for $C_{26}H_{48}O_4Si_2Na$ 503.2983, found 503.2983; $[\alpha]_D^{25}$ −5.2 (c 0.61, $CHCl_3$).

(1*R*,5*S*,6*R*)-6-[(*tert*-Butyldimethylsiloxy)phenylmethyl]-2-methoxy-1-[((triisopropropylsilyl)oxy)methyl]bicyclo[3.3.1]non-2-ene-7,9-dione (12). To a two-necked round-bottom flask containing activated MS 4 Å (3.20 g, 200%, w/w) and CH_2Cl_2 (30 mL) were successively added $Ti(O^iPr)_4$ (0.31 mL, 1.04 mmol, 0.3 equiv) and $TiCl_4$ (1.0 M in CH_2Cl_2, 3.1 mL, 3.1 mmol, 0.9 equiv) at 0 °C, and the reaction mixture was stirred at room temperature for 15 min. To the reaction mixture were added PhCHO (0.52 mL, 5.18 mmol, 1.5 equiv) at −78 °C and then **11** (1656.9 mg, 3.45 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) slowly via cannula. The reaction mixture was stirred at −78 °C for 1 h. After the reaction was completed, Et_3N (0.96 mL, 6.90 mmol, 2.0 equiv) was added to the reaction mixture, and the resulting mixture was stirred for 5 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) at −78 °C and was warmed to room temperature. The aqueous layer was extracted with CH_2Cl_2 (15 mL × 3). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 60/1 to 50/1) to afford **12** (major diastereomer, 1526.8 mg, 75%; minor diastereomer, 143.5 mg, 7%) as a clear oil. Data for the major diastereomer: R_f = 0.50 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.21 (m, 5H), 5.02 (d, J = 3.2 Hz, 1H), 4.64 (d, J = 5.7, 1.8 Hz, 1H), 4.05 (d, J = 9.2 Hz, 1H), 3.80 (d, J = 9.2 Hz, 1H), 3.48 (s, 3H), 2.98 (d, J = 4.6 Hz, 1H), 2.78 (dd, J = 15.6, 2.3 Hz, 1H), 2.63 (d, J = 15.6, 1H), 2.61 (m, 1H), 2.44 (ddd, J = 16.5, 5.5, 1.8 Hz, 1H), 1.86 (ddd, J = 16.5, 5.7, 1.8 Hz, 1H), 1.09−1.01 (s, 21H), 0.89 (s, 9H), − 0.07 (s, 3H), − 0.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2 (Cq), 206.7 (Cq), 155.4 (Cq), 141.8 (Cq), 128.4 (CH), 127.8 (CH), 126.6 (CH), 92.4 (CH), 77.2 (CH), 68.0 (CH), 61.1 (CH_2), 55.2 (CH_3), 54.8 (Cq), 48.1 (CH_2), 43.7 (CH), 31.7 (CH_2), 26.0 (CH_3), 18.2 (Cq), 18.1 (CH_3), 12.2 (CH), −4.6 (CH_3), −5.2 (CH_3); IR (ATR) 2928, 2864, 1739, 1712, 1463, 1248, 1104, 1057, 835, 777 cm^{-1}; HRMS (ESI) [M + Na]$^+$ calcd for $C_{33}H_{54}O_5Si_2Na$ 609.3402, found 609.3400; $[\alpha]_D^{26}$ +57 (c 2.4, $CHCl_3$). Data for the minor diastereomer: R_f = 0.44 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 4.70 (d, J = 9.2 Hz, 1H), 4.63 (dd, J = 5.5, 2.3 Hz, 1H), 3.94 (s, 2H), 3.47 (s, 3H), 2.89 (d, J = 14.2 Hz, 1H), 2.74 (br d, J = 9.2 Hz, 1H), 2.62 (dd, J = 14.2, 2.3, 1H), 2.55 (br d, J = 6.4 Hz, 1H), 2.49 (ddd, J = 16.5, 6.4, 2.3 Hz, 1H), 2.15 (dd, J = 16.5, 5.5 Hz, 1H), 1.14 (m, 21H), 0.79 (s, 9H), −0.04 (s, 3H), −0.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2 (Cq), 206.0 (Cq), 154.3 (Cq), 141.5 (Cq), 128.6 (CH), 128.5 (CH), 127.5 (CH), 92.8 (CH), 76.3 (CH), 68.0 (CH), 61.0 (CH_2), 56.0 (Cq), 55.3 (CH_3), 47.3 (CH), 45.4 (CH_2), 30.8 (CH_2), 25.8 (CH_3), 18.1 (CH_3), 18.1 (CH_3), 12.2 (CH), −4.3 (CH_3), −5.3 (CH_3); IR (ATR) ν_{max} 2928, 2863, 1729, 1254, 1091, 1068, 838, 776 cm^{-1}; HRMS (ESI) [M + Na]$^+$ calcd for $C_{33}H_{54}O_5Si_2Na$ 609.3402, found 609.3400; $[\alpha]_D^{21}$ +19 (c 0.43, $CHCl_3$).

(1*R*,5*S*)-6-Benzylidene-2-methoxy-1-[((triisopropropylsilyl)-oxy)methyl]bicyclo[3.3.1]non-2-ene-7,9-dione (13). To a solution of **12** (1305.0 mg, 2.22 mmol, 1.0 equiv) in THF (10 mL) was added KHMDS (0.5 M in toluene, 5.7 mL, 2.89 mmol, 1.3 equiv) at 0 °C, and the reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (15 mL), and the aqueous layer was extracted with Et_2O (5 mL × 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 100/1 to 70/1) to afford **13** (767.9 mg, 76%) as a clear oil: R_f = 0.44 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.44−7.33 (m, 5H), 4.79 (d, J = 5.2 Hz, 1H), 4.08 (d, J = 9.2 Hz, 1H), 4.05 (d, J = 4.1 Hz, 1H), 3.89 (d, J = 9.2 Hz, 1H), 3.55 (s, 3H), 2.98 (d, J = 16.9 Hz, 1H), 2.80 (dd, J = 16.0, 5.2 Hz, 1H), 2.59 (d, J = 16.9 Hz, 1H), 2.62−2.55 (m, 1H), 1.11−1.01 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0 (Cq), 196.5 (Cq), 155.0 (Cq), 139.4 (Cq), 138.7 (CH), 134.4 (Cq), 130.2 (CH), 129.6 (CH), 129.0 (CH), 92.7 (CH), 60.8 (CH_2), 55.3 (CH_3), 55.0 (Cq), 48.6 (CH), 46.2 (CH_2), 32.2 (CH_2), 18.1 (CH_3), 12.2 (CH); IR (ATR) ν_{max} 2942, 2865, 1738, 1690, 1665, 1245, 1153, 1130, 818, 690 cm^{-1}; HRMS (ESI) [M + Na]$^+$ calcd for $C_{27}H_{38}O_4SiNa$ 477.2431, found 477.2432; $[\alpha]_D^{26}$ −28 (c 0.46, $CHCl_3$).

(1*R*,5*S*)-6-Benzylidene-2-methoxy-8,8-dimethyl-1-[((triisopropropylsilyl)oxy)methyl]bicyclo[3.3.1]non-2-ene-7,9-dione (14). To a solution of **13** (278.0 mg, 0.61 mmol, 1.0 equiv) in ^{t}BuOH (6 mL) was added ^{t}BuOK (342.2 mg, 3.05 mmol, 5.0 equiv) at

DOI: 10.1021/jo5026699
J. Org. Chem. 2015, 80, 1735−1745

room temperature, and the reaction mixture was stirred for 30 min. To the reaction mixture was added MeI (0.23 mL, 3.66 mmol, 6.0 equiv), and after 12 h, the reaction mixture was diluted with Et_2O (15 mL) and quenched with saturated aqueous NH_4Cl solution (20 mL). The aqueous layer was extracted with Et_2O (10 mL × 3). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 70/1) to afford **14** (202.2 mg, 69%) as a clear oil: R_f = 0.54 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.31 (m, 6H), 4.81 (dd, J = 5.0, 1.8 Hz, 1H), 4.30 (d, J = 8.2 Hz, 1H), 4.05 (br d, J = 4.5 Hz, 1H), 4.03 (d, J = 8.2 Hz, 1H), 3.52 (s, 3H), 2.76 (ddd, J = 15.7, 5.0, 2.3 Hz, 1H), 2.54 (ddd, J = 15.7, 5.5, 1.8 Hz, 1H), 1.35 (s, 3H), 1.09−0.99 (m, 21H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3 (Cq), 202.5 (Cq), 155.6 (Cq), 139.2 (Cq), 137.5 (CH), 134.7 (Cq), 129.9 (CH), 129.3 (CH), 128.9 (CH), 93.9 (CH), 61.2 (Cq), 58.0 (CH_2), 54.9 (CH_3), 52.6 (Cq), 49.3 (CH), 32.1 (CH_2), 24.1 (CH_3), 20.0 (CH_3), 18.1 (CH_3), 12.3 (CH); IR (ATR) ν_{max} 2942, 2865, 1736, 1692, 1658, 1463, 1243, 1154, 1095, 998, 685 cm^{-1}; HRMS (ESI) [M + Na]$^+$ calcd for $C_{29}H_{42}O_4SiNa$ 505.2745, found 505.2745; $[\alpha]_D^{26}$ −42 (c 1.4, $CHCl_3$).

(1*R*,5*S*)-2-Methoxy-8,8-dimethyl-1-[((triisopropylsilyl)oxy)methyl]bicyclo[3.3.1]non-2-ene-7,9-dione (15). To a solution of **14** (20.2 mg, 0.0418 mmol) in MeCN (1.0 mL) was added 40% aqueous ^{n}Bu$_4$NOH solution (>50 equiv), and the reaction mixture was stirred at 50 °C. After 12 h, the reaction mixture was diluted with Et_2O (3 mL) and quenched with saturated aqueous NH_4Cl solution (3 mL). The aqueous layer was extracted with Et_2O (3 mL × 3). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 50/1 to 30/1) to afford **15** (10.9 mg, 66%) as a white solid: R_f = 0.38 (hexane/ethyl acetate = 4/1); mp 55.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (dd, J = 5.5, 1.5 Hz, 1H), 4.25 (d, J = 8.5 Hz, 1H), 3.95 (d, J = 8.5 Hz, 1H), 3.46 (s, 3H), 3.02 (dd, J = 16.5, 7.5 Hz, 1H), 2.94−2.85 (br s, 1H), 2.56 (ddd, J = 16.5, 5.5, 2.0 Hz, 1H), 2.42 (d, J = 16.5 Hz, 1H), 2.27 (ddd, J = 16.5, 5.5, 1.5 Hz, 1H), 1.19 (s, 3H), 1.04 (br s, 21H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9 (Cq), 207.6 (Cq), 154.8 (Cq), 93.6 (CH), 61.1 (Cq), 57.7 (CH_2), 54.7 (CH_3), 53.9 (Cq), 45.3 (CH_2), 44.9 (CH), 30.9 (CH_2), 23.6 (CH_3), 19.6 (CH_3), 18.1 (CH_3), 12.2 (CH); IR (ATR) ν_{max} 2940, 2864, 1708, 1656, 1458, 1122, 1105, 793, 679 cm^{-1}; HRMS (ESI) [M + Na]$^+$ calcd for $C_{22}H_{38}O_4SiNa$ 417.2432, found 417.2431; $[\alpha]_D^{25}$ +3.3 (c 0.060, $CHCl_3$).

(1*R*,5*S*,8*R*)-8-Allyl-6-benzylidene-2-methoxy-1-[((triisopropylsilyl)oxy)methyl]bicyclo[3.3.1]non-2-ene-7,9-dione (16) and (1*R*,5*S*)-7-(Allyloxy)-6-benzylidene-2-methoxy-1-[((triisopropylsilyl)oxy)methyl]bicyclo[3.3.1]nona-2,7-dien-9-one (17). To a solution of **13** (329.3 mg, 0.724 mmol) in THF (6 mL) and HMPA (0.6 mL) was added ^{t}BuOK (113.8 mg, 1.01 mmol, 1.4 equiv) at −20 °C, and the reaction mixture was stirred for 30 min. To the reaction mixture was added allyl iodide (0.086 mL, 0.941 mmol, 1.3 equiv), and the resulting mixture was stirred at the same temperature for 1.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (6 mL), and the aqueous layer was extracted with Et_2O (5 mL × 3). The combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 70/1) to afford *C*-allylated product **16** (99.6 mg, 27%) as a clear oil and *O*-allylated product **17** (177.9 mg, 50%) as a clear oil.

A solution of **17** (103.6 mg, 0.209 mmol, 1.0 equiv) in DMF (7 mL) was stirred at 130 °C for 1.5 h. The reaction mixture was partitioned between Et_2O (10 mL) and water (10 mL), and the aqueous layer was extracted with Et_2O (5 mL × 3). The combined organic layer was washed with water (15 mL) and brine (15 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 60/1) to afford **16** (80.8 mg, 78%) as a clear oil. Data for *C*-allylated product **16**: R_f = 0.26 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.28 (m, 6H), 5.63 (ddt, J = 16.9, 10.1, 6.0 Hz, 1H), 4.99 (br d, J = 10.1 Hz, 1H), 4.94 (dd, J = 16.9, 1.4 Hz, 1H), 4.80 (dd, J = 6.2, 1.8 Hz, 1H), 4.33 (d, J = 9.2 Hz, 1H), 4.03 (dd J = 4.6, 1.8 Hz, 1H), 3.81 (d, J = 9.2 Hz, 1H), 3.55 (s, 3H), 3.15 (dd, J = 11.0, 5.0 Hz, 1H), 2.78 (ddd, J = 16.0, 4.6, 1.8 Hz, 1H), 2.57 (ddd, J = 16.0, 6.2, 1.8 Hz, 1H), 2.21 (m, 1H), 1.85 (m, 1H), 1.10−1.00 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4 (Cq), 198.5 (Cq), 156.2 (Cq), 139.4 (Cq), 138.3 (CH), 134.6 (CH), 130.0 (CH), 129.4 (CH), 128.9 (CH), 117.4 (CH_2), 92.6 (CH), 59.8 (CH_2), 58.6 (Cq), 55.9 (CH), 55.3 (CH_3), 49.4 (CH), 32.5 (CH_2), 32.0 (CH_2), 18.1 (CH_3), 12.2 (CH); IR (ATR) ν_{max} 2940, 2864, 1736, 1691, 1661, 1235, 1147, 1114, 882, 683 cm^{-1}; HRMS (ESI) [M + Na]$^+$ calcd for $C_{30}H_{42}O_4SiNa$ 517.2745, found 517.2746; $[\alpha]_D^{22}$ −33 (c 0.66, $CHCl_3$). Data for *O*-allylated product **17**: R_f = 0.46 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.41(m, 6H), 6.23 (ddt, J = 17.2, 10.5, 5.0 Hz, 1H), 5.58 (dd, J = 17.2, 1.4 Hz, 1H), 5.45 (dd, J = 10.5, 1.4 Hz, 1H), 5.38 (s, 1H), 4.72 (dd, J = 5.0, 2.3 Hz, 1H), 4.59 (ddd, J = 12.6, 5.0, 1.4 Hz, 1H), 4.48 (ddd, J = 12.6, 5.0, 1.4 Hz, 1H), 4.30 (d, J = 9.2 Hz, 1H), 4.24 (d, J = 9.2 Hz, 1H), 4.12 (br d, J = 6.4 Hz, 1H), 3.69 (s, 3H), 2.89 (ddd, J = 16.2, 6.4, 2.8 Hz, 1H), 2.69 (ddd. J = 16.2, 5.0, 1.4 Hz, 1H), 1.30−1.21 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6 (Cq), 159.4 (Cq), 154.3 (Cq), 136.5 (Cq), 136.4 (Cq), 133.2 (CH), 129.1 (CH), 128.7 (CH), 127.4 (CH), 125.8 (CH), 117.6 (CH_2), 105.9 (CH), 90.7 (CH), 68.8 (CH_2), 61.1 (CH_2), 55.1 (CH_3), 53.7 (Cq), 46.0 (CH), 31.0 (CH_2), 18.1 (CH_3), 12.3 (CH); IR (ATR) ν_{max} 2940, 2863, 1738, 1463, 1150, 1116, 1068, 882, 761, 688 cm^{-1}; HRMS (ESI) [M + Na]$^+$ calcd for $C_{30}H_{42}O_4SiNa$ 517.2745, found 517.2747; $[\alpha]_D^{22}$ +42 (c 1.3, $CHCl_3$).

(1*R*,5*S*,8*S*)-8-Allyl-6-benzylidene-2-methoxy-8-methyl-1-[((triisopropylsilyl)oxy)methyl]bicyclo[3.3.1]non-2-ene-7,9-dione (18) and (1*R*,5*S*)-8-Allyl-6-benzylidene-2,7-dimethoxy-1-[((triisopropylsilyl)oxy)methyl]bicyclo[3.3.1]nona-2,7-dien-9-one (18a). To a solution of **17** (52.3 mg, 0.106 mmol) in THF (2.0 mL) was added NaHMDS (1.09 M in THF, 0.2 mL, 0.22 mmol, 2.0 equiv) at 0 °C, and the reaction mixture was stirred for 20 min. To the reaction mixture was added MeI (0.1 mL, 1.6 mmol, 15 equiv), and the resulting mixture was stirred at room temperature for 15 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (2 mL). The aqueous layer was extracted with Et_2O (3 mL × 3). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 150/1 to 100/1) to afford *C*-methylated product **18** (16.7 mg, 31%) as a clear oil and *O*-methylated product **18a** (23.5 mg, 44%) as a clear oil. Data for *C*-methylated product **18**: R_f = 0.36 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.29 (m, 6H), 6.02 (dddd, J = 16.9, 9.6, 9.6, 5.5 Hz, 1H), 5.11−5.03 (m, 2H), 4.83 (dd, J = 5.7, 1.8 Hz, 1H), 4.22 (d, J = 8.7 Hz, 1H), 4.18 (d, J = 8.7 Hz, 1H), 4.05 (m, 1H), 3.54 (s, 3H), 2.96 (dd, J = 14.2, 5.5 Hz, 1H), 2.75 (ddd, J = 15.8, 5.0, 1.8 Hz, 1H), 2.54 (ddd, J = 15.8, 5.7, 1.8 Hz, 1H), 2.42 (dd, J = 14.2, 9.6 Hz, 1H), 1.09−1.01 (m, 21H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8 (Cq), 202.7 (Cq), 155.4 (Cq), 139.4 (Cq), 137.2 (CH), 136.7 (CH), 134.7 (Cq), 129.9 (CH), 129.2 (CH), 128.9 (CH), 117.5 (CH_2), 94.2 (CH), 62.1 (Cq), 58.0 (CH_2), 54.9 (CH_3), 54.8 (Cq), 49.4 (CH), 37.9 (CH_2), 32.1 (CH_2), 20.4 (CH_3), 18.1 (CH_3), 12.2 (CH); IR (ATR) ν_{max} 941, 2864, 1736, 1691, 1658, 1463, 1231, 1161, 1113, 1007, 999, 883, 689 cm^{-1}; HRMS (ESI) [M + Na]$^+$ calcd for $C_{31}H_{44}O_4SiNa$ 531.2901, found 531.2903; $[\alpha]_D^{23}$ −57 (c 0.21, $CHCl_3$). Data for *O*-methylated product **18a**: R_f = 0.46 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.21 (m, 5H), 6.74 (s, 1H), 5.83 (dddd, J = 16.8, 10.5, 6.4, 6.4 Hz, 1H), 5.05 (dd, J = 16.8, 1.8 Hz, 1H), 5.01 (dd, J = 10.5, 1.8 Hz, 1H), 4.52 (dd, J = 5.3, 2.8 Hz, 1H), 4.29 (d, J = 9.2 Hz, 1H), 4.23 (d, J = 9.2 Hz, 1H), 3.96 (m, 1H), 3.58 (s, 3H), 3.46 (s, 3H), 3.20−3.05 (m, 2H), 2.64 (ddd, J = 16.1, 6.2, 2.8 Hz, 1H), 2.45 (ddd, J = 16.1, 5.3, 1.4 Hz, 1H), 1.10−0.99 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7 (Cq), 158.2 (Cq), 154.4 (Cq), 136.5 (Cq), 136.5 (CH), 135.3 (Cq), 131.6 (Cq), 129.0 (CH), 128.7 (CH), 127.3 (CH), 124.9 (CH), 115.5 (CH_2), 91.2 (CH), 60.5 (CH_3), 59.2 (CH_2), 57.4 (Cq), 54.9 (CH_3), 45.7 (CH), 32.2 (CH_2), 30.1 (CH_2), 18.1 (CH_3), 18.1 (CH_3), 12.3 (CH); IR

DOI: 10.1021/jo5026699
J. Org. Chem. 2015, 80, 1735−1745

(ATR) 2939, 2864, 1739, 1463, 1215, 1116, 1088, 1008, 883, 688 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{31}H_{44}O_4SiNa$ 531.2901, found 531.2902; $[\alpha]_D^{23}$ +25 (*c* 0.38, $CHCl_3$).

(1*R*,5*S*,8*S*)-8-Allyl-6-benzylidene-2-methoxy-8-methyl-1-[((triisopropropylsilyl)oxy)methyl]bicyclo[3.3.1]non-2-ene-7,9-dione (19). To a solution of **18** (3.7 mg, 0.0073 mmol) in THF (1.0 mL) was added aqueous $^nBu_4NOH$ solution (1.0 M, 0.015 mL, 2.0 equiv), and the reaction mixture was stirred at 50 °C for 3 h. The reaction mixture was diluted with Et_2O (1 mL) and quenched with saturated aqueous NH_4Cl solution (1 mL). The aqueous layer was extracted with Et_2O (1 mL × 3). The combined organic layer was washed with brine (3 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 50/1 to 30/1) to afford **19** (2.3 mg, 74%) as a clear oil: R_f = 0.25 (hexane/ethyl acetate = 10/1); ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (dddd, *J* = 17.0, 9.9, 9.6, 5.1 Hz, 1H), 5.03−4.97 (m, 2H), 4.77 (dd, *J* = 5.6, 2.3 Hz, 1H), 4.20 (d, *J* = 8.5 Hz, 1H), 4.08 (dd, *J* = 8.5 Hz, 1H), 3.49 (s, 3H), 3.02 (dd, *J* = 15.3, 6.8 Hz, 1H), 2.90 (t, *J* = 6.8 Hz, 1H), 2.86−2.80 (m, 1H), 2.61 (ddd, *J* = 16.7, 5.1, 2.3 Hz, 1H), 2.38 (dd, *J* = 15.3, 1.1 Hz, 1H), 2.30 (ddd, *J* = 16.7, 5.1, 1.1 Hz, 1H), 2.12 (dd, *J* = 14.7, 9.6 Hz, 1H), 1.10−0.99 (m, 21H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2 (Cq), 207.0 (Cq), 154.5 (Cq), 136.3 (CH), 117.5 (CH_2), 94.0 (CH), 62.1 (Cq), 57.8 (CH_2), 55.8 (CH_3), 54.7 (Cq), 45.3 (CH), 45.1 (CH_3), 37.6 (CH_2), 30.7 (CH_2), 19.9 (CH_3), 18.1 (CH_3), 12.2 (CH); IR (ATR) ν_{max} 2941, 2865, 1715, 1659, 1463, 1109, 883, 681 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{24}H_{40}O_4SiNa$ 443.2588, found 443.2589; $[\alpha]_D^{23}$ +20 (*c* 0.15, $CHCl_3$).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C spectra for new compounds, HPLC data for **5** and **9a**, and CIF data for compounds **8a** and **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mnakada@waseda.jp. Phone and fax: +813-5286-3240.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the Materials Characterization Central Laboratory, Waseda University, for characterization of new compounds. This work was financially supported in part by a Grant-in-Aid for Scientific Research on Innovative Areas (2105) and for Scientific Research (B) (25293003) by MEXT and a Waseda University Grant for Special Research Projects. We thank Dr. Motoo Shiro of Rigaku X-ray Research Laboratory for the X-ray crystal structure determination of compound **8**.

■ REFERENCES

(1) The numbering of compounds corresponds to Grossman's review. Reviews: (a) Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963. (b) Singh, I. P.; Sidana, J.; Bharate, S. B.; Foley, W. J. *Nat. Prod. Rep.* **2010**, *27*, 393. (c) Njardarson, J. T. *Tetrahedron* **2011**, *67*, 7631. (d) Richard, J.-A.; Pouwer, R. H.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2012**, *51*, 4536. (e) Simpkins, N. S. *Chem. Commun.* **2013**, *49*, 1042. (f) Richard, J.-A. *Eur. J. Org. Chem.* **2014**, 273. See also: (g) Verotta, L. *Phytochem. Rev.* **2002**, *1*, 389. (h) Tsukano, C.; Siegel, D. R.; Danishefsky, S. J. *J. Synth. Org. Chem. Jpn.* **2010**, *68*, 592.

(2) Synthetic and related studies: (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc.* **1999**, *121*, 4724. (b) Usuda, H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2002**, *4*, 859. (c) Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943. (d) Young, D. G. J.; Zeng, D. *J. Org. Chem.* **2002**, *67*, 3134. (e) Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 3621. (f) Kraus, G. A.; Nguyen, T. H.; Jeon, I. *Tetrahedron Lett.* **2003**, *44*, 659. (g) Ciochina, R.; Grossman, R. B. *Org. Lett.* **2003**, *5*, 4619. (h) Klein, A.; Miesch, M. *Tetrahedron Lett.* **2003**, *44*, 4483. (i) Kraus, G. A.; Dneprovskaia, E.; Nguyen, T. H.; Jeon, I. *Tetrahedron* **2003**, *59*, 8975. (j) Mehta, G.; Bera, M. K. *Tetrahedron Lett.* **2004**, *45*, 1113. (k) Nicolaou, K. C.; Carenzi, G. E. A.; Jeso, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 3895. (l) Mehta, G.; Bera, M. K. *Tetrahedron Lett.* **2006**, *47*, 689. (m) Ahmad, N. M.; Rodeschini, V.; Simpkins, N. S.; Ward, S. E.; Wilson, C. *Org. Biomol. Chem.* **2007**, *5*, 1924. (n) Shimizu, Y.; Kuramochi, A.; Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2007**, *48*, 4173. (o) Rodeschini, V.; Simpkins, N. S.; Wilson, C. *J. Org. Chem.* **2007**, *72*, 4265. (p) Ahmad, N. M.; Rodeschini, V.; Simpkins, N. S.; Ward, S. E.; Blake, A. J. *J. Org. Chem.* **2007**, *72*, 4803. (q) Mehta, G.; Bera, M. K.; Chatterje, S. *Tetrahedron Lett.* **2008**, *49*, 1121. (r) Raikar, S. B.; Nuhant, P.; Delpech, B.; Marazano, C. *Eur. J. Org. Chem.* **2008**, *7*, 1358. (s) Mehta, G.; Bera, M. K. *Tetrahedron Lett.* **2008**, *49*, 1417. (t) Takagi, R.; Inoue, Y.; Ohkata, K. *J. Org. Chem.* **2008**, *73*, 9320. (u) Tolon, B.; Delpech, B.; Marazano, C. *ARKIVOC* **2009**, 452. (v) Mehta, G.; Bera, M. K. *Tetrahedron Lett.* **2009**, *50*, 3519. (w) Couladouros, E. A.; Dakanali, M.; Demadis, K. D.; Vidali, V. P. *Org. Lett.* **2009**, *11*, 4430. (x) Mehta, G.; Dhanbal, T.; Bera, M. K. *Tetrahedron Lett.* **2010**, *51*, 5302. (y) Richard, J.-A.; Chen, D. Y.-K. *Eur. J. Org. Chem.* **2012**, 484. (z) Mehta, G.; Das, M.; Kundu, U. K. *Tetrahedron Lett.* **2012**, *53*, 4538. (aa) Simpkins, N. S.; Holtrup, F.; Rodeschini, V.; Taylor, J. D.; Wolf, R. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6144. (bb) Hayes, C. J.; Simpkins, N. S. *Org. Biomol. Chem.* **2013**, *11*, 8458. (cc) Mehta, G.; Bera, M. K. *Tetrahedron* **2013**, *69*, 1815. (dd) Grenning, A. J.; Boyce, J. H.; Porco, J. A. *J. Am. Chem. Soc.* **2014**, *136*, 11799. (ee) Schmitt, S.; Feidt, E.; Hartmann, D.; Huch, V.; Jauch, J. *Synlett* **2014**, *25*, 2025.

(3) Total synthesis: (a) Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200. (b) Siegel, D. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 1048. (c) Tsukano, C.; Siegel, D. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8840. (d) Qi, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 12682. (e) Simpkins, N. S.; Taylor, J. D.; Weller, M. D.; Hayes, C. J. *Synlett* **2010**, *4*, 639. (f) Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1103. (g) George, J. H.; Hesse, M. D.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2010**, *12*, 3532. (h) Garnsey, M. R.; Lim, D.; Yost, J. M.; Coltart, D. M. *Org. Lett.* **2010**, *12*, 5234. (i) Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2010**, *66*, 6569. (j) Qi, J.; Beeler, A. B.; Zhang, Q.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2010**, *132*, 13642. (k) Zhang, Q.; Mitasev, B.; Qi, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2010**, *132*, 14212. (l) Biber, N.; Möws, K.; Plietker, B. *Nat. Chem.* **2011**, *3*, 938. (m) Zhang, Q.; Porco, J. A., Jr. *Org. Lett.* **2012**, *14*, 1796. (n) Uwamori, M.; Saito, A.; Nakada, M. *J. Org. Chem.* **2012**, *77*, 5098. (o) Pepper, H. P.; Lam, H. C.; Bloch, W. M.; George, J. H. *Org. Lett.* **2012**, *14*, 5162. (p) Sparling, B. A.; Moebius, D. C.; Shair, M. D. *J. Am. Chem. Soc.* **2013**, *135*, 644. (q) Uwamori, M.; Nakada, M. *J. Antibiot.* **2013**, *66*, 141. (r) Uwamori, M.; Nakada, M. *Nat. Prod. Commun.* **2013**, *8*, 955. (s) Uwamori, M.; Nakada, M. *Tetrahedron. Lett.* **2013**, *54*, 2022. (t) Lindermayr, K.; Plietker, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 12183. (u) Horeischi, F.; Biber, N.; Plietker, B. *J. Am. Chem. Soc.* **2014**, *136*, 4026. (v) Bellavance, G.; Barriault, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 6701. (w) Boyce, J. H.; Porco, J. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 7832.

(4) (a) de Oliveira, C. M. A.; Porto, A. L. M.; Bittrichc, V.; Marsaioli, A. J. *Phytochemistry* **1999**, *50*, 1073. (b) Lokvama, J.; Braddocka, J. F.; Reichardtb, P. B.; Clausenc, T. P. *Phytochemistry* **2000**, *55*, 29. (c) Cuesta-Rubio, O.; Velez-Castro, H.; Frontana-Uribe, B. A.; Cárdenas, J. *Phytochemistry* **2001**, *57*, 279. (d) Cuesta-Rubio, O.; Frontana-Uribe, B. A.; Ramírez-Apan, T.; Cárdenas, J. *Z. Naturforsch., C: Biosci.* **2002**, *57*, 372. (e) Pardo-Andreu, G. L.; Nunez-Figueredo, Y.; Tudella, V. G.; Cuesta-Rubio, O.; Rodrigues, F. P.; Pestana, C. R.; Uyemura, S. A.; Leopoldino, A. M.; Alberici, L. C.; Curti, C. *Mitochondrion* **2011**, *11*, 255.

DOI: 10.1021/jo5026699
J. Org. Chem. 2015, 80, 1735−1745

(5) (a) Gurevich, A. I.; Dobrynin, V. N.; Kolosov, M. N.; Popravko, S. A.; Ryabova, I. D.; Chennov, B. K.; Derbentseva, N. A.; Aizenman, B. E.; Garagulya, A. D. *Antibiotiki* **1971**, *6*, 510. (b) Bystrov, N. S.; Chernov, B. K.; Dobrynin, V. N.; Kolosov, M. N. *Tetrahedron Lett.* **1975**, *16*, 2791. (c) Medina, M. A.; Martinez-Poveda, B.; Amores-Sanchez, M. I.; Quesada, A. R. *Life Sci.* **2006**, *79*, 105. (d) Quiney, C.; Billard, C.; Salanoubat, C.; Fourneron, J. D.; Kolb, J. P. *Leukemia* **2006**, *20*, 1519. (e) Beerhues, L. *Phytochemistry* **2006**, *67*, 2201. (f) Gharge, D.; Pavan, T.; Sunil, B.; Dhabale, P. *J. Pharm. Res.* **2009**, *2*, 1373.

(6) (a) Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull.* **1997**, *45*, 947. (b) Fukuyama, Y.; Minami, H.; Kuwayama, A. *Phytochemistry* **1998**, *49*, 853.

(7) (a) Ito, C.; Itoigawa, M.; Miyamoto, Y.; Onoda, S.; Rao, K. S.; Mukainaka, T.; Tokuda, H.; Nishino, H.; Furukawa, H. *J. Nat. Prod.* **2003**, *66*, 206. (b) Piccinelli, A. L.; Cuesta-Rubio, O.; Chica, M. B.; Mahmood, N.; Pagano, B.; Pavone, M.; Barone, V.; Rastrelli, L. *Tetrahedron* **2005**, *61*, 8206. (c) Reis, F. H. Z.; Pardo-Andreu, G. L.; Nunez-Figueredo, Y.; Cuesta-Rubio, O.; Marin-Prida, J.; Uyemura, S. A.; Curti, C.; Alberici, L. C. *Chem.-Biol. Interact.* **2014**, *212*, 20.

(8) (a) Abe, M.; Nakada, M. *Tetrahedron Lett.* **2006**, *47*, 6347. (b) Abe, M.; Nakada, M. *Tetrahedron Lett.* **2007**, *48*, 4873. (c) Abe, M.; Saito, A.; Nakada, M. *Tetrahedron Lett.* **2010**, *51*, 1298.

(9) (a) Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Takano, M.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 2860. (b) Takano, M.; Umino, A.; Nakada, M. *Org. Lett.* **2004**, *6*, 4897. (c) Sawada, T.; Nakada, M. *Adv. Synth. Catal.* **2005**, *347*, 1527. (d) Takeda, H.; Nakada, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2896. (e) Takeda, H.; Honma, M.; Ida, R.; Sawada, T.; Nakada, M. *Synlett* **2007**, 579. (f) Honma, M.; Takeda, H.; Takano, M.; Nakada, M. *Synlett* **2009**, 1695. (g) Hirai, S.; Nakada, M. *Tetrahedron Lett.* **2010**, *51*, 5076. (h) Hirai, S.; Nakada, M. *Tetrahedron* **2011**, *67*, 518. (i) Sawada, T.; Nakada, M. *Tetrahedron: Asymmetry* **2012**, *23*, 350. (j) Sawada, T.; Nakada, M. *Org. Lett.* **2013**, *15*, 1004.

(10) See the Supporting Information for ORTEP drawings of the crystal structures of **8a** and **9a** with 50% probability ellipsoids. CCDC 1035044 (**8a**) and CCDC 1035205 (**9a**) contain 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.

(11) Bisoxazoline−Cu(II)−aqua complex; see: Jaschinski, T.; Hiersemann, M. *Org. Lett.* **2012**, *14*, 4114.

(12) Models A and B are depicted on the basis of Pfaltz's model[13] and the theoretical analysis.[14]

(13) (a) Fritschi, H.; Leutenegger, U.; Phaltz, A. *Helv. Chim. Acta* **1988**, *71*, 1553. (b) Phaltz, A. In *Modern Synthetic Methods 1989*; Scheffold, R., Ed.; Springer: Berlin, Heidelberg, 1989; p 199.

(14) Fraile, J. M.; García, J. I.; Martínes-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **2001**, *123*, 7616.

(15) Johnson, W. S. *J. Am. Chem. Soc.* **1943**, *65*, 1317.

DOI: 10.1021/jo5026699
J. Org. Chem. 2015, 80, 1735−1745