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Theoretical and experimental study of the absolute configuration of helical structure of (2*R*,3*S*)-Rubiginone A_2 analog

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ABSTRACT

A novel analogue of (2*R*,3*S*)-Rubiginone A_2 was synthesized as a chiral helical model compound via an eight-step procedure (2.7% overall yield). Quantum methods, such as density functional theory (DFT) at different basis sets of 6-311+(d), 6-311++G(2d,p), were used to compute its optical rotation and electronic circular dichroism at the B3LYP/6-311++G(2d,p) level in the gas phase and in solution using PCM model, respectively. UV corrections were performed in electronic circular dichroism (ECD) simulations to match the experimental ECD well. The suitable computational methods, e.g., B3LYP/6-311++G(2d,p)//B3LYP/6-311++G(2d,p) in the gas phase using zero-point energy in Boltzmann statistics, were found and suggested for optical rotation and circular dichroism computations that can be used for absolute configuration determination of chiral helical compounds.

1. Introduction

Determination of absolute configuration has been always a big challenge in stereochemistry. Theoretical methods, such as quantum tools used in calculations of specific optical rotation (OR) and electronic circular dichroism (ECD) have been used in the determination of absolute configurations, and a great number of chiral compounds have been well investigated via the methods.[1] However, it has rarely been well utilized in examining absolute configurations of chiral helical structures, which are an important type of compounds. For example, (2*R*,3*S*)-Rubiginone A_2[2] (**1**) and its novel analog **2** can form helical conformations due to repulsive interaction between the two carbonyl O atoms in solution. Nevertheless, helical structures generally exhibit remarkable bioactivities,[2] which have attracted the many researchers' synthesis interests.[3] Thus, it is of great importance to systematically investigate the correlation of structures and their OR and ECD. In the literature, (2*R*,3*S*)-**1** was first reported with interesting antitumor activity. But for an economical and easy study, its novel analog **2** was synthesized as a model molecule in the relationship investigation. Since the repulsive force exists between the two O atoms, the two O atoms cannot locate in the same plane. One O atom must be back and another should be front of the paper. Thus, they form two major helical conformations (**2A** and **2B**) and exist in solution. The two conformations can exchange quickly due to the low transition state barrier and they cannot be detectable at room temperature, this looks like that the two major conformations of cyclohexane in solution. They have different relative energy. Therefore, the two helical conformers have different contributions to the whole OR and ECD both in theory and experiment.

2. Results and discussion

2.1. Synthesis of (2*R*,3*S*)-2

Absolute configurations of chiral centers may have partial racemization under some reaction conditions in totally synthetic procedure. Although chiral catalysts have been widely employed to construct chiral centers, it was also reported that the same ligand might lead different configuration formation when different substrates were used.[4] Thus, the best way is to use chiral building blocks whose chiral centers can be preserved during the transformation. Based on this consideration, the commercially available (2*R*,5*R*)-(+)-dihydrocarvone **3** was employed as the enantiopure starting material (Fig. 1) for the synthesis of (2*R*,3*S*)-**2**.

In an early synthetic scheme, we tried to synthesize (*R*)-6-methylcyclohex-2-enone **4** from 2-cyclohexen-1-one with assistance of chiral auxiliary reagent. In practice, **4** was synthesized from (2*R*,5*R*)-(+)-dihydrocarvone **3** directly. Ozonolysis of **3** in methanol

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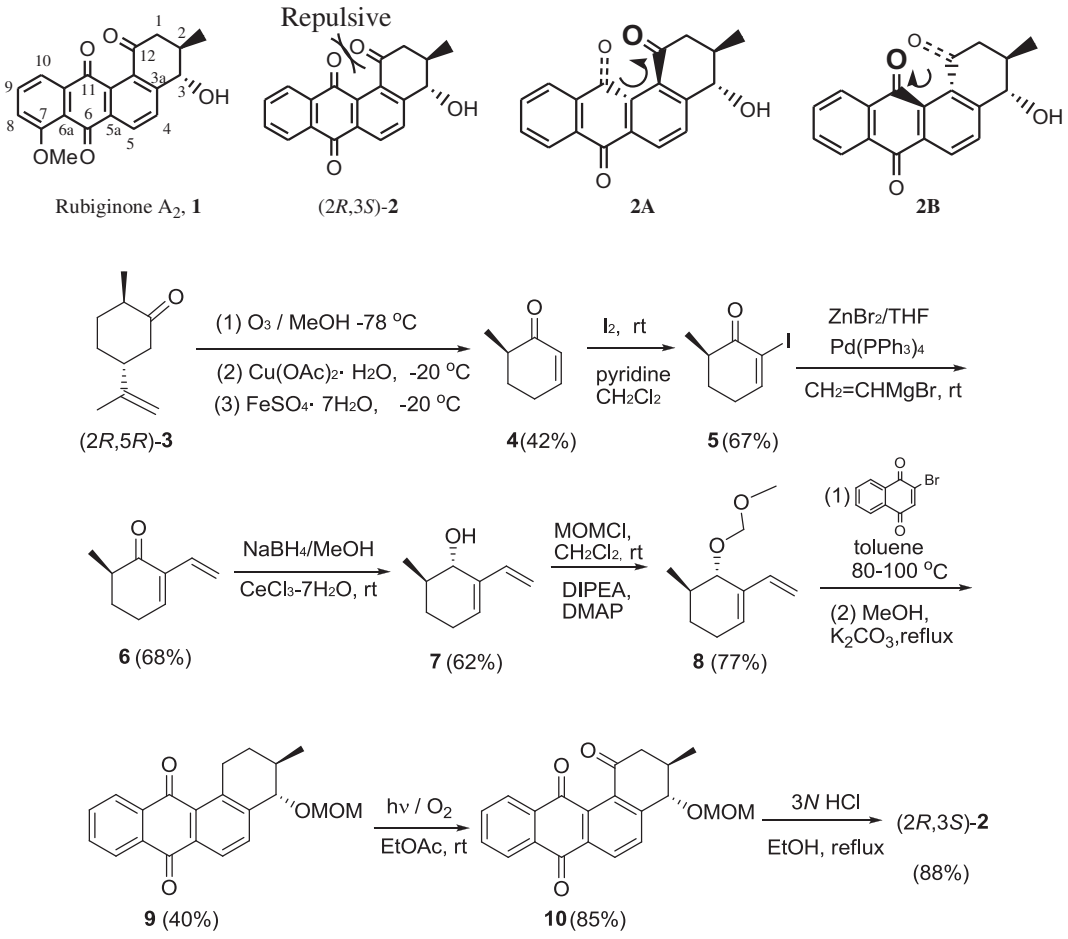

Fig. 1. The synthetic route to (2*R*,3*S*)-**2**.

and subsequent treatment with $Cu(OAc)_2/FeSO_4$ resulted in cyclic α,β-unsaturated enone **4** in 42% yield.[5] In the step, ozone should be kept in appropriate flow and flushed away at −78 °C at the end of oxidation. α-Iodination of enone **4** gave iodoenone **5** in 67% yield.[6] As the catalyst, 1.5 N pyridine was enough. Palladium-catalyzed cross coupling under Negishi conditions afforded ketodienes **6** in 68% yield.[7] $ZnBr_2$ was very useful in the step. Grignard reagent did not attack carbonyl group after reaction with $ZnBr_2$, so carbonyl group in **5** was unnecessary to be protected. However, it was very critical to dry the $ZnBr_2$ because of its humidity. Starting from ketodienes **6**, Luche reduction ($NaBH_4/CeCl_3$) afforded enol **7** in 62% yield.[8] Its absolute configuration was assigned after final product **2** was obtained and used in ROESY experiments. The methoxymethyloxy (OMOM) derivative **8** was obtained from enol **7** in 77% by reaction with methyl chloromethyl ether (MOMCl) and diisopropylethylamine (DIPEA).[9] What is more, it can endure basic reagent and oxidant in the following reaction. So it is suitable to protect the hydroxy in enol **7**. Treatment of methoxymethyloxy derivative **8** with 2-bromonaphthalene-1,4-dione at 80 °C in toluene afforded the cycloadduct, which was immediately subjected to the aromatization reaction with K_2CO_3 in MeOH to provide dione **9** in a yield of 40%. Subsequent photooxygenation of dione **9** afforded the trione **10** in 85% yield.[10] In the photo-oxidation reaction, ethyl acetate was used as a solvent. Chloroform or dichloromethane may afford halogenated by-product, and benzene is a toxic solvent. Hydrolysis of trione **10** in the presence of aqueous hydrochloric acid (3 N) in alcohol afforded **2** in 88% yield.[11] 2.7% of overall yield was achieved via the eight steps reaction. The purity of the final product was examined via HPLC using mixture of water and acetonitrile (35/65) at the flow-rate of 1 mL/min. The pure product was then used in ROESY experiments. The NOE between H-2 and H-3 was not observed and this exhibited the two protons are trans-position. Since C-2 has *R* configuration, therefore, it has an *S* configuration on C-OH (C-3). Thus, the obtained product had (2*R*,3*S*) configuration. If it has (2*R*,3*R*) absolute configuration, its OR should be negative based on the OR of −106 in chloroform for (2*R*,3*R*)-SNA-8073-B, which has the same planar structure as (2*R*,3*S*)-Rubiginone A_2 except for stereochemistry.[12]

OR of (2*R*,3*S*)-**2** was measured in two solvents ($[\alpha]_D^{20}$, +75 (*c* 0.5, chloroform) or +82 (*c* 0.5, methanol)), and its ECD spectra were determined in methanol. The effect of methanol on its ECD used here is investigated. The ECD is illustrated in Fig. 2. To confirm that the loss of MOM group from **10** to **2** under strong acidic condition did not result in the configuration change of C-3, the OR and ECD of **10** were measured. The recorded OR of **10** was +235 (*c* 1.0, chloroform). In addition, the recorded ECD of **10** in methanol seemed the same as that of **2** (Fig. 2, superimposed CDs). Both ECDs had the positive Cotton effects at about 210, 269, and 331 nm, respectively, and a negative Cotton effect at 230 nm. These results indicated that both **2** and **10** had the same absolute configurations on C-2 and C-3, namely (2*R*,3*S*). It meant that the configurations of C-3 and C-2 were kept unchanged in the conversion of **10** to **2** under the condition of refluxing in 3 N HCl.

2.2. OR computational methods

The conformational searches were performed by using MMFF94S force field. Totally ten free conformations were found (Fig. 3). The ten conformations were then optimized at the B3LYP/6-31G(d), B3LYP/6-31+G(d,p), and B3LYP/6-311++G(2d,p) levels in the gas phase, respectively.[13] Only the geometries obtained at the B3LYP/6-311++G(2d,p) level were illustrated in Fig. 3. Their

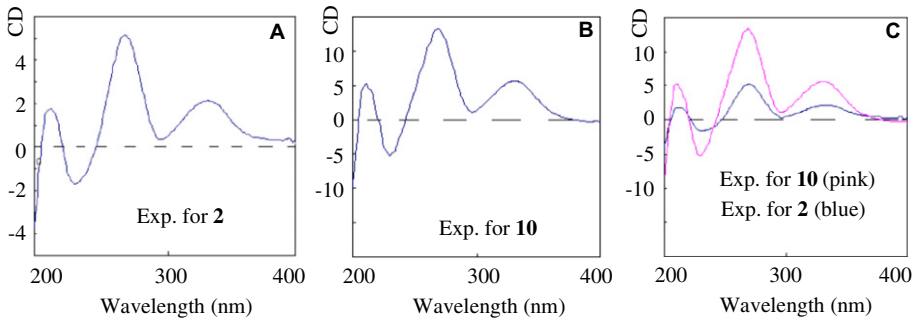

Fig. 2. The recorded ECDs for (2*R*,3*S*)-**2** (A), (2*R*,3*S*)-**10** (B) measured in MeOH and their superimpose ECD (C). Effect of MeOH on ECD was considered here.

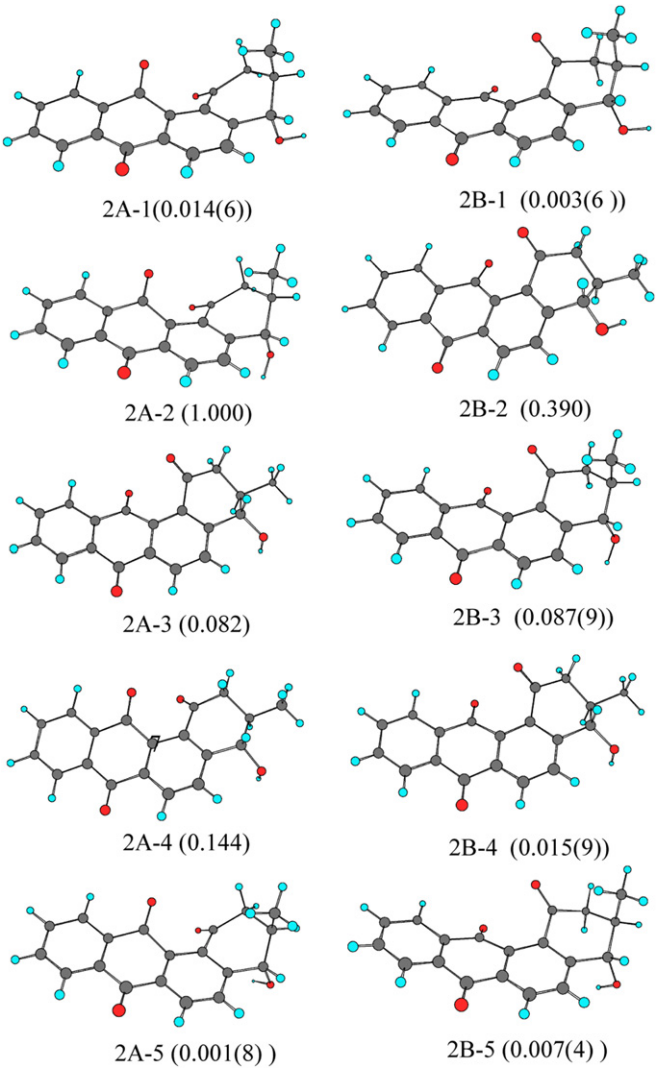

Fig. 3. The ten conformations obtained at the B3LYP/6-311++G(2d,p) level and their relative Gibbs free energy data (kcal/mol).

relative Gibbs free energy (GFE) data were also summarized below the structures, respectively. The optical rotations were then calculated for the ten conformers at the B3LYP/6-311++G(2d,p) level in the gas phase. Total electronic energy (TEE) were used in OR computations ($[\alpha]_{\Delta E}$). GFE data were also used in OR calculations ($[\alpha]_{\Delta Gibbs}$). Zero-point energy corrections were also used in OR prediction ($[\alpha]_{\Delta z\text{-}p}$). Then, the single point energy (SPE) obtained at the B3LYP/aug-cc-pVDZ level in chloroform by using PCM model was used in OR computations ($[\alpha]_{\Delta sp}$). To further investigate the effect of chloroform on OR values, all ten conformations were further optimized at the B3LYP/6-311+G(d) level by using PCM model. The OR data were computed at the B3LYP/6-311++G(2d,p) level in the gas phase ($[\alpha]_{\Delta g}$) and in chloroform ($[\alpha]_{\Delta l}$), respectively. All of the ORs for (2*R*,3*S*)-**2** are summarized in Table 1.

Table 1
The OR values using four quantum methods

	Optimization in the gas phase				Optimization in solution	
	$[\alpha]_{\Delta E}$[e]	$[\alpha]_{\Delta z\text{-}p}$[f]	$[\alpha]_{\Delta Gibbs}$[g]	$[\alpha]_{\Delta sp}$[h]	$[\alpha]_{\Delta g}$[i]	$[\alpha]_{\Delta l}$[j]
Method 1[a]	+57.3	+55.1	+111.9	−20.2	—	—
Method 2[b]	+40.6	+97.5	+129.9	−21.5	—	—
Method 3[c]	+37.0	+91.4	+202.3	−25.6	—	—
Method 4[d]	—	—	—	—	+19.8	−9.0

[a] B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d).
[b] B3LYP/6-311++G(2d,p)//B3LYP/6-31+G(d,p).
[c] B3LYP/6-311++G(2d,p)//B3LYP/6-311++G(2d,p).
[d] B3LYP/6-311++G(2d,p)//PCM/B3LYP/6-311+G(d).
[e] Using total energy in OR in computations.
[f] Using zero-point energy.
[g] Using free energy.
[h] Using SPE.
[i] Performed in the gas phase.
[j] Performed in $CHCl_3$.

The OR data predicted in the gas phase had correct positive sign. Most of the predicted OR values were from +41 to +129. The closest predicted OR value was +91.4 by using the ZPE in method 3. Unfortunately, the ORs obtained by using the SPE in chloroform were negative (from −20.2 to −25.6) in all three methods. It seems that the use of SPE corrections in chloroform is not suitable for OR predictions for the chiral helical structures. At the same time, it was found that the method 4, PCM/B3LYP/6-311++G(2d,p)//PCM/B3LYP/6-311+G(d), could not provide correct OR predictions for the helical chiral compound, for example, the predicted OR was −9.0. Based on the results, the best method for the OR prediction on helical structures should be methods 1, 2, and 3 in the gas phase by using ZPE.

2.3. ECD computational methods

Encouraged by the close predictions with method 3 in the gas phase, the ECDs for (2*R*,3*S*)-**2** were computed at the B3LYP/6-311++G(2d,p) level by using the conformations obtained at the B3LYP/6-311++G(2d,p) level.[14] The TEE data were used in ECD simulations. Unexpectedly, it seemed that the predicted ECD curve of **2** had different configuration from the expected (2*R*,3*S*) (see the superimposed plot in Fig. 4b). Actually, the synthesized **2** should have the absolute configuration of (2*R*,3*S*). Therefore, the method used herein may not be suitable for predictions on the absolute configuration of helical structures.

Alternatively, GFE and ZPE (vibrational corrections) were used in ECD simulations again (Fig. 5). In both cases, the simulations were

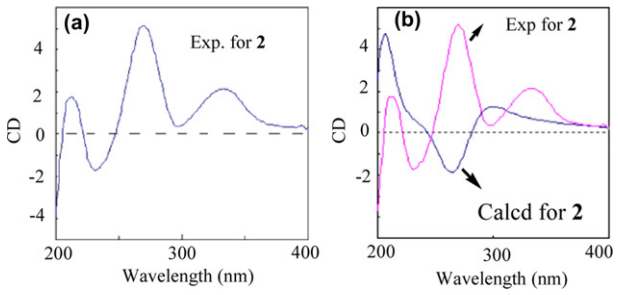

Fig. 4. Comparison of the experimental ECD with the computed ECD using total electronic energy in simulations.

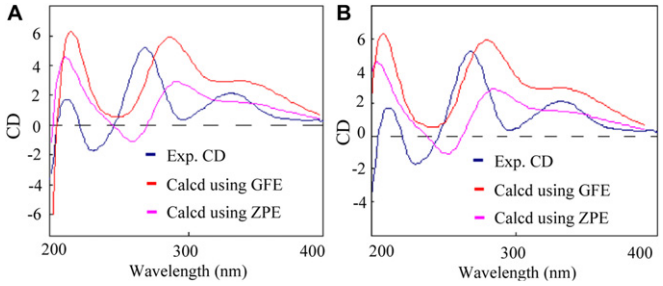

Fig. 5. The simulated ECD for (2*R*,3*S*)-**2** using zero-point energy and Gibbs free energy without UV corrections (A) and with UV corrections (B).

close to the experimental results. Red-shifts were observed in the simulated ECDs. For example, the positive Cotton effects at 210, 269, and 331 nm in experiments moved to 212, 294, and near 340 nm in simulations with ZPE, and 216, 288, and 338 nm with GFE, respectively. After UV correction, the simulated ECD was closer to the experimental ECD (Fig. 5B). The results revealed that more reasonable predictions on ECD of chiral helical structures could be obtained by using GFE in its ECD simulations.

Finally, the B3LYP/6-31+G(d,p)-optimized in the gas phase and the B3LYP/6-311+G(d)-optimized geometries in chloroform were employed further in ECD computations at the B3LYP/6-311++G(2d,p) level, respectively. The simulated ECD spectra were illustrated in Fig. 6. It was found that both of the simulated ECDs did not match the experimental results well. Large red-shifts were found, especially when the B3LYP/6-31+G(d,p)-optimized geometries were used in ECD computations (Fig. 6(A)), even if the UV corrections were performed, the differences are still large and they were not illustrated here.

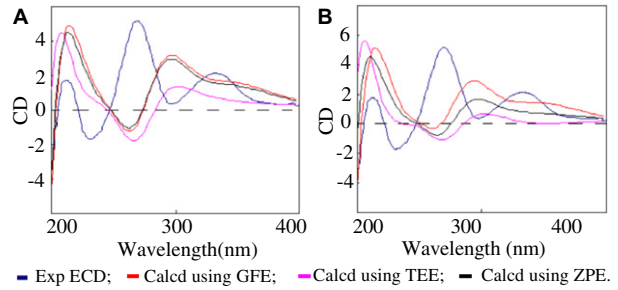

Fig. 6. The computed ECD spectra at the B3LYP/6-311++G(2d,p) level using B3LYP/6-31+G(d,p)-optimized geometries in the gas phase (A) and B3LYP/6-311+G(d)-optimized conformers in $CHCl_3$ using PCM model (B).

2.4. Conclusion

Based on the comparison of the three methods, it was found that the method of B3LYP/6-311++G(2d,p)//B3LYP/6-311++G(2d,p) could predict the relatively correct OR values by using TEE and ZPE data. This method can predict ECD well, especially using GFE after UV corrections. However, using SPE to predict OR magnitudes may lead wrong conclusion. Wrong ECD prediction may happen if using TEE.

3. Experimental section

3.1. General methods

Experiments, which required an inert atmosphere were carried out under argon. Melting points were obtained on a micro melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were determined in $CDCl_3$ at 400 MHz for ^1H and 100 MHz for ^{13}C or 500 MHz for ^1H and 125 MHz for ^{13}C. IR spectra were recorded with KBr pellets. Optical rotations were determined on a polarimeter. High resolution mass (HRMS) data were recorded via a positive ion electrospray or electron impact mass spectrometry using a time-of-flight analyzer.

Silica gel (200–300 mesh) was used for flash column chromatography. Tetrahydrofuran and toluene were dried over sodium metal under argon. Other reagents and solvents were used directly if not otherwise specifics.

3.2. Synthetic details and characterization

*3.2.1. (R)-6-Methylcyclohex-2-enone (**4**).* To a solution of (2*R*,5*R*)-(+)-dihydrocarvone **3** (2.0 g, 13.6 mmol) in methanol (40 mL), cooled at −78 °C, was introduced a steam of ozone till a blue color persisted. Then the solution was flushed with oxygen till the color disappeared. The reaction mixture was then allowed to warm to −20 °C, and copper (II) acetate monohydrate (3.3 g, 16.5 mmol, 1.2 equiv) was added. $FeSO_4 \cdot 7H_2O$ (4.6 g, 16.5 mmol, 1.2 equiv) was added 10 min later. The green solution was maintained at −20 °C for 3 h and then at room temperature for 3 h. After the addition of water (80 mL), the solution was extracted with ether (5×25 mL). The combined organic layers were then washed with an aqueous saturated Na_2CO_3 solution (5×12 mL) and brine (3×10 mL), and finally dried over anhydrous Na_2SO_4. After filtration the solvent was removed by rotatory evaporation and the crude product was purified by flash column chromatography with acetone/petroleum ether (1:40 v/v) to give compound **4** as a light yellow oil (0.62 g, 42%). R_f=0.38 (1:10, ethyl acetate/petroleum ether); $[\alpha]_D^{20}$ +103 (*c* 1.0, CH_2Cl_2); IR (KBr) ν_{max} 3070, 2960, 2873, 1729 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.13 (3H, d, *J*=6.8 Hz, CH_3), 1.69–1.79 (1H, m, H-5), 2.04–2.08 (1H, m, H-5), 2.36–2.42 (3H, m, 2 H-4 and H-6), 5.98 (1H, td, $J_{2,3}$=10 Hz, $^4J_{2,4}$=1.9 Hz, H-2), 6.92 (1H, m, $J_{2,3}$=10 Hz, $J_{3,4}$=3.8 Hz, H-3). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.0, 25.5, 30.8, 41.6, 129.3, 149.7, 202.4; HRMS (ESI) *m*/*z* calcd for $C_7H_{10}ONa$ $[M+Na]^+$ 133.0624, found 133.0635.

*3.2.2. (R)-2-Iodo-6-methylcyclohex-2-enone (**5**).* To an ice-cold solution of enone **4** (1.0 g, 9.1 mmol) in CH_2Cl_2 (25 mL) and pyridine (2 mL) was added solid I_2 (3.0 g, 11.8 mmol) gradually. Upon completion, the mixture was stirred 3 h at room temperature. Then it was diluted with Et_2O and H_2O. The organic layer was separated, and the aqueous layer was extracted with Et_2O twice. The combined organic layers were washed with an aqueous saturated $Na_2S_2O_3$ solution, 2 M HCl (4×12 mL), brine (3×10 mL), and then dried (Na_2SO_4). The solution was concentrated and the crude product was purified by flash column chromatography with ethyl acetate/petroleum ether (1:40, v/v) to give compound **5** as a yellow viscous oil (1.44 g, 67%). R_f=0.46 (1:10 ethyl acetate/petroleum ether); $[\alpha]_D^{20}$ +54.3 (*c* 1.0, ethyl acetate); IR (KBr) ν_{max} 2928, 1725, 1687, 513 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.21 (3H, d, *J*=6.8 Hz, CH_3), 1.78–1.88 (1H, m, H-5), 2.10–2.15 (1H, m, H-5), 2.45–2.63 (3H, m, 2 H-4 and H-6), 7.70–7.73 (1H, m, H-3); ^{13}C NMR ($CDCl_3$,

125 MHz) δ 15.9, 29.5, 30.6, 41.5, 103.7, 158.5, 195.0; HRMS (EI) *m*/*z* calcd for C_7H_9IO $[M]^+$ 235.9698, found 235.9704.

*3.2.3. (R)-6-Methyl-2-vinylcyclohex-2-enone (**6**).* $ZnBr_2$ was heated at 150 °C in vacuum for half an hour. The dried $ZnBr_2$ (3.6 g, 15.8 mmol, 2.2 equiv) was dissolved in distilled THF (15 mL) under argon. The solution was cooled to −30 °C, then vinylmagnesium bromide (15.8 mL, 2.2 equiv 1.0 M in THF) was added and the reaction temperature was raised to room temperature about 15 min. In other flask, a mixture of enone **5** (1.7 g, 7.2 mmol) and tetrakis (triphenylphosphine) palladium (0.35 mol %) was dissolved in distilled THF (8 mL) under argon. The mixture of Grignard solution and $ZnBr_2$ was added to it at room temperature. Upon completion, an aqueous saturated NH_4Cl solution was added to quench the reaction at 0 °C. Ether (40 mL) was added to the mixture, and the organic layer was washed with an aqueous saturated NH_4Cl solution (3×10 mL), brine (3×10 mL), and then dried (Na_2SO_4). The crude product was purified by flash column chromatography with acetone/petroleum ether (1:50 v/v) to give compound **6** as a light yellow oil (0.66 g, 68%). R_f=0.58 (1:10 ethyl acetate/petroleum ether); $[\alpha]_D^{20}$ +48.0 (*c* 1.0, CH_2Cl_2); IR (KBr) ν_{max} 2925, 2854, 1630, 1549, 588 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.15 (3H, d, *J*=6.8 Hz, CH_3), 1.69–1.79 (1H, m, H-5), 2.04–2.10 (1H, m, H-5), 2.38–2.48 (3H, m, 2H-4 and H-6), 5.14 (1H, d, *J*=11.3 Hz, H-2′), 5.64 (1H, d, *J*=17.6 Hz, H-2′), 6.51–6.56 (1H, dd, *J*=11.3 and 17.7 Hz, H-1′), 6.97 (1H, t, *J*=4.5 Hz, H-3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.6, 27.0, 32.1, 43.4, 117.0, 130.8, 133.0, 145.8, 151.2; HRMS (EI) *m*/*z* calcd for $C_9H_{12}O$ $[M]^+$ 136.0888, found 136.0877.

*3.2.4. (1S,6R)-6-Methyl-2-vinylcyclohex-2-enol (**7**).* To an ice-cold solution of enone **6** (0.55 g, 4.0 mmol) and $CeCl_3 \cdot 7H_2O$ (15 mg, 0.04 mmol) in 12 mL of MeOH solid $NaBH_4$ (167 mg, 4.4 mmol) were added in small portions over 10 min. After the mixture was stirred at room temperature for 5 min, Et_2O and H_2O were added to it. The organic layer was separated, and the aqueous layer was extracted with Et_2O three times. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The crude product was purified by flash column chromatography with ethyl acetate/petroleum ether (1:30, v/v) to give compound **7** as a light yellow oil (0.35 g, 62%). R_f=0.39 (1:10 ethyl acetate/petroleum ether); $[\alpha]_D^{20}$ +138 (*c* 1.0, ethyl acetate); IR (KBr) ν_{max} 3426, 3073, 3028, 2926, 1640, 1629 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.10 (3H, d, *J*=6.8 Hz, CH_3), 1.43–1.53 (4H, m), 2.15–2.21 (2H, m), 4.25 (1H, s, H-1), 5.03 (1H, d, *J*=10.9 Hz, H-2′), 5.39 (1H, d, *J*=17.6 Hz, H-2′), 5.85 (1H, t, *J*=4.1 Hz, H-3) 6.27–6.34 (1H, dd, *J*=10.9 and 17.7 Hz, H-1′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.4, 23.9, 26.5, 34.0, 66.3, 111.2, 132.3, 137.9, 138.2; HRMS (EI) *m*/*z* calcd for $C_9H_{14}O$ $[M]^+$ 138.1045, found 138.1041.

*3.2.5. (5R,6S)-6-(Methoxymethoxy)-5-methyl-1-vinylcyclohex-1-ene (**8**).* To a solution of the enol **7** (0.33 g, 2.4 mmol) and a catalytic amount of DMAP in 10 mL of CH_2Cl_2, were added 0.83 mL (4.8 mmol) of DIPEA and 0.55 mL (7.2 mmol) of MOMCl. The mixture was stirred at room temperature for 4 h. A cold aqueous saturated $NaHCO_3$ solution was added to quench the reaction. Then, it was diluted with Et_2O and H_2O. The organic layer was separated, and the aqueous layer was extracted with Et_2O three times. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The crude product was purified by flash column chromatography with ethyl acetate/petroleum ether (1:50, v/v) to give compound **8** as a light yellow oil (0.33 g, 77%). R_f=0.55 (1:30 ethyl acetate/petroleum ether); $[\alpha]_D^{20}$ +94.3 (*c* 1.0, ethyl acetate); IR (KBr) ν_{max} 2925, 1639, 1629, 1037 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.08 (3H, d, *J*=6.1 Hz, CH_3), 1.26–1.69 (3H, m), 2.18–2.31 (2H, m), 3.36 (3H, s, CH_3O), 4.21 (1H, s, H-6), 4.70–4.76 (2H, dd, *J*=6.8 and 17.5 Hz), 4.99 (1H, d, *J*=11.1 Hz, H-2′), 5.44 (1H, d, *J*=17.6 Hz, H-2′), 5.91 (1H, t, *J*=3.8 Hz, H-2), 6.31–6.38 (1H, dd, *J*=11.1 and 17.6 Hz, H-1′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.2, 24.2, 26.1, 34.0, 55.6, 71.8, 96.4, 111.2, 132.2, 138.5; HRMS (EI) *m*/*z* calcd for $C_{11}H_{18}O_2$ $[M]^+$ 182.1307, found 182.1302.

*3.2.6. (3R,4S)-4-(Methoxymethoxy)-3-methyl-1,2,3,4-tetrahydrotetraphene-7,12-dione (**9**).* A solution of 2-bromonaphthalene-1,4-dione (0.16 g, 0.66 mmol) and diene **8** (0.10 g, 0.55 mmol) in freshly distilled toluene (8 mL) was stirred under argon at 80 °C for 12 h followed at 100 °C for 2 h. After the solvent was removed in vacuo, the crude Diels–Alder adduct was dissolved in MeOH (10 mL), treated with solid K_2CO_3 (0.23 g, 1.7 mmol), and stirred at 64 °C for 1 h. The solvent was removed in vacuo, treated with water, and extracted with $CHCl_3$. The organic layer was washed with brine, dried (Na_2SO_4), concentrated, and purified by flash column chromatography with ethyl acetate/petroleum ether (1:30, v/v) to give compound **9** as a yellow solid (74 mg, 40%). R_f=0.53 (1:10 ethyl acetate/petroleum ether); $[\alpha]_D^{20}$ +79.5 (*c* 1.0, ethyl acetate); mp: 175–177 °C; IR (KBr) ν_{max} 3071, 2927, 2854, 1707, 1671, 1588, 1306, 1272, 1037, 717 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.11 (3H, d, *J*=6.8 Hz, CH_3), 1.85–1.86 (1H, m, H-2), 1.92–1.96 (1H, m, H-2), 2.11–2.15 (1H, m, H-3), 3.31–3.38 (1H, m, H-1), 3.42 (3H, s, CH_3O), 3.58–3.65 (1H, m, H-1), 4.65 (1H, d, *J*=3.3 Hz, H-4), 4.75–4.83 (2H, dd, *J*=6.9 and 25.6 Hz), 7.73–7.85 (3H, m), 8.23–8.27 (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.9, 25.4, 28.0, 31.7, 56.0, 60.7, 95.8, 125.4, 126.7, 127.5, 131.3, 132.7, 133.6, 134.4, 134.8, 135.3, 135.4, 141.9, 144.3, 183.9, 185.7; HRMS (EI) *m*/*z* calcd for $C_{21}H_{20}O_4$ $[M]^+$ 336.1362, found 336.1357.

*3.2.7. (2R,3S)-**10**.* Following the procedure for photooxygenation, a solution of dione **9** (36 mg, 0.11 mmol) in ethyl acetate (10 mL) was irradiated with a 150 W halogen lamp under an atmosphere of oxygen for 48 h. Solvent was removed in vacuo and then the residue was purified by flash column chromatography with ethyl acetate/petroleum ether (1:10 v/v) to give compound **10** as a yellow solid (32 mg, 85%). R_f=0.38 (1:3 ethyl acetate/petroleum ether); mp: 181–183 °C; $[\alpha]_D^{20}$ +215 (*c* 1.0, ethyl acetate), or +235 (*c* 1.0, chloroform); IR (KBr) ν_{max} 3072, 2927, 1777, 1706, 1675, 1640, 1591, 1324, 1281, 1031, 713 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.28 (3H, d, *J*=6.7 Hz, CH_3), 2.58–2.63 (1H, m), 2.71–2.77 (1H, dd, *J*=9.4 and 17.4 Hz), 3.00–3.07 (1H, dd, *J*=7.7 and 17.4 Hz), 3.39 (3H, s, CH_3O), 4.55 (1H, d, *J*=6.9 Hz), 4.61 (2H, d, *J*=8.1 Hz), 7.74 (1H, d, *J*=7.9 Hz), 7.79–7.83 (2H, m), 8.20 (1H, d, *J*=8.3 Hz), 8.26 (1H, d, *J*=8.6 Hz), 8.39 (1H, d, *J*=7.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.1, 33.8, 42.0, 55.6, 75.3, 94.5, 126.9, 127.4, 129.1, 132.6, 133.8, 134.5, 134.9, 136.6, 148.2, 182.2, 198.9, 204.3; HRMS (EI) *m*/*z* calcd for $C_{21}H_{18}O_5$ $[M]^+$ 350.1154, found 350.1153.

*3.2.8. (2R,3S)-**2**.* A solution of trione **10** (30 mg, 0.1 mmol) in 4 mL of alcohol was added 3 N HCl solution, then it was refluxed until reactant disappeared (TLC monitoring). Solvent was removed in vacuo and then residue was purified by flash column chromatography to afford compound **2** as a yellow solid (23 mg, 88%). R_f=0.10 (1:3 ethyl acetate/petroleum ether). Its purity was checked by HPLC as 98%. Mp: 172–174 °C; $[\alpha]_D^{20}$ +75.3 (*c* 0.5, chloroform); IR (KBr) ν_{max} 3678, 3440, 3073, 2925, 1699, 1673, 1640, 1591, 1326, 1285, 714 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.23 (3H, d, *J*=6.9 Hz, CH_3), 2.13 (1H, d, *J*=3.0 Hz, OH), 2.55–2.63 (1H, m), 2.79–2.85 (1H, dd, *J*=8.6 and 16.8 Hz), 2.94–3.00 (1H, dd, *J*=6.8 and 16.8 Hz), 4.83 (1H, s), 7.77 (1H, d, *J*=8.1 Hz), 7.79–7.81 (2H, m), 8.18 (1H, d, *J*=6.8 Hz), 8.25 (1H, d, *J*=8.8 Hz), 8.39 (1H, d, *J*=8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.6, 35.1, 42.5, 71.8, 127.2, 127.6, 130.2, 132.0, 132.7, 134.1, 134.8, 135.1, 135.2, 135.6, 135.9, 150.1, 182.5, 183.7, 198.8; HRMS (EI) *m*/*z* calcd for $C_{19}H_{14}O_4$ $[M]^+$ 306.0892, found 306.0894.

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Supplementary data

NMR spectra for all compounds, computed OR, ECD for (2*R*,3*S*)-**2** and ECD for (2*R*,3*S*)-**10**. This material is available free of charge. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.11.050.

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