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# Synthesis of symmetric HIJ-ring model of ciguatoxin

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**Abstract**—A tricyclic model ether compound comprising 6/8/6 ether rings was synthesized via a new route including conjugate addition to form a symmetric eight-membered ether-ketone with *syn*/*trans* stereochemistry in selective manner. The corresponding vinyl triflate of this ketone was allowed to convert to the vinyl methyl derivative via cross-coupling reaction. This *endo*-olefinic tetrahydro-2*H*-oxocin was selectively reduced to afford α-methyl product. The corresponding *exo*-olefinic oxocane derivative, on the other hand, provided the β-methyl isomer as the major diastereoisomer (2/1). Our previous report on the synthesis of this final product was revised due to some rearrangement and the mechanisms are discussed.

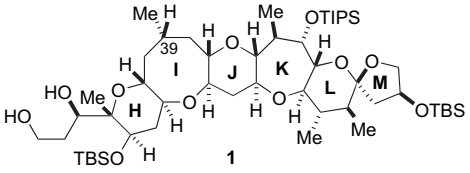

## 1. Introduction

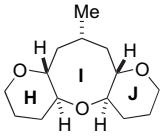
In the synthetic strategies there are many methods available for the so-called polyether marine natural products.[1] The most critical step may be the medium ring cyclization reaction, which varies to be done from seven-membered to nine-membered ring sizes for ciguatoxin,[2] for example, using acetylene–cobalt complex in our strategy.[3] We have recently reported a convergent synthesis of the HIJKLM-ring system, compound **1**, a right segment of ciguatoxin.[4] In that report, the stereocenters on the eight-membered I-ring have been achieved with an efficient stereocontrol on the basis of (1) conjugate addition of ether oxygen to enone to form the H-ring in *syn*/*trans* manner, (2) cross-coupling via the corresponding *endo*-olefinic vinyl triflate to introduce the methyl group, and (3) selective reduction of the *endo*-olefin to form the 39-α-methyl group on the basis of the conformation of oxocin moiety. We report here the synthesis of HIJ ring as a much simpler model compound **2** of ciguatoxin in order to make the stereochemical question much clearer in the construction of the eight-membered I-ring.

## 2. Results and discussion

### 2.1. Synthesis of symmetric 6/8/6-ketone rings

The acetylene compound **3**[5] was prepared from commercially available D-glucal triacetate in nine steps and subjected to iodoboration to form the vinyl iodide **4** (Scheme 1).[6] This iodide was allowed to couple with acetylene **5** under Sonogashira Pd coupling condition providing the ene–yne **6**.




The cobalt-mediated cyclization of **6** was facilitated through **7** for the formation of eight-membered ether ring **8** according to our protocol of the synthesis of the medium ring cyclization. The exocyclic olefin was once oxidized to the corresponding carbonyl compound **9** under Lemieux–Johnson condition, namely combination of $NaIO_4$ and catalytic amount of $OsO_4$ in a mixed solvent system to assist the solubility of the hydrophobic substrate and hydrophilic reagents. We further proceeded the following reductive decomplexation reaction with tri-*n*-butyltin hydride or sodium hypophosphite for such an acetylene–dicobalthexacarbonyl complex to the corresponding olefin as reported in our previous papers.[7,8a] It was, however, different from the isolated acetylene complex in the reactivity of **9**, as well as the olefin **8**; thus, they were convertible only in low yields via direct reduction to the corresponding olefins such as **10**. We found that two-step sequential reductions including hydrosilylation and desilylation afforded the enone **10** in 74% overall yield.[8] It was further used as precursor for the formation of tetrahydropyran ring under different conditions.

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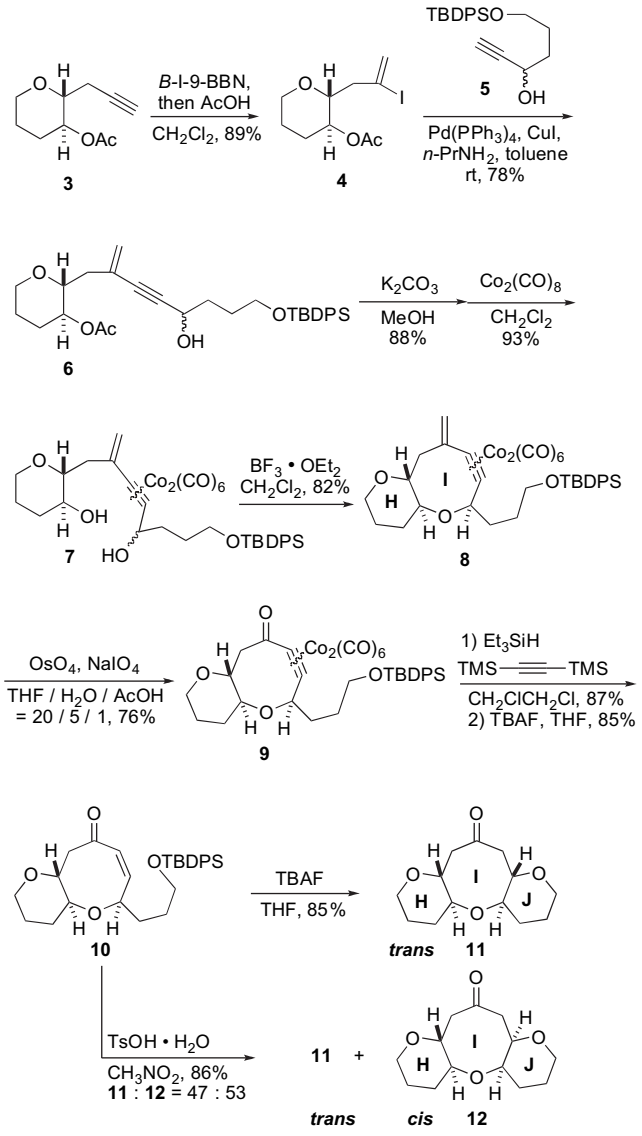



**Scheme 1**. Synthesis of the symmetric *trans*/*syn*/*trans* ketone of 6/8/6 ring system and its *trans*/*syn*/*cis* isomer.

The enone **10** having *O*-TBDPS group was first subjected to the same acidic condition for a cyclization of tetrahydropyran H-ring as our previous case in the HIJKLM-ring synthesis; thus, *p*-toluenesulfonic acid in nitromethane solvent. Surprisingly, this acidic condition allowed the reaction providing a mixture of *trans*/*cis* isomers of **11** and **12** in almost 1/1 ratio. Alternative basic condition was applied for this conjugate addition cyclization; thus, treatment with TBAF first provided a penta-coordinated fluoro silane, which might enhance the nucleophilicity of the neighboring oxygen atom under a possible milder condition rather than a corresponding alkoxide nucleophile. In fact, TBAF/THF condition afforded exclusively *trans* isomer **11** in 85% yield. Interestingly, this product showed only seven lines in its $^{13}C$ NMR to prove this molecule being symmetric.

These results demonstrated a striking difference in the selectivity for **10** to undergo the conjugate addition cyclization under different conditions and to provide a mixture of *trans*-**11** and *cis*-**12** products. The conformation of the

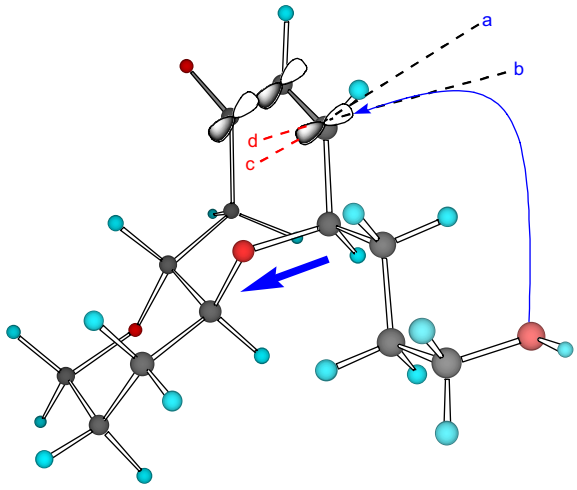



**Figure 1**. Conformation of the enone **10** on the basis of the Macromodel MM3 calculation.[9]

dihydro-oxocinone ring in **10** leading to **11** would be as illustrated in Figure 1, where the conjugated enone π-system (δ 6.85 ppm) should overlap with the polarized C–O bond. Felkin–Nguyen (Ahn) model can explain the lowest minimum approach of the nucleophile oxygen along the lines *a* and *b* shown in Figure 1. In this conformation, the nucleophile oxygen atom from the directions *c* and *d* would be obviously difficult, since it should overcome the congested concave zone; thus, it formed a single product **11**.

When the enone **10** was treated with $TsOH \cdot H_2O$, on the other hand, the protonated enone of the dihydro-oxocinone ring might have very different conformation as in Figure 2. The orbital interaction with the C–O polarization might not be significant in this case due to the even repulsive interaction between the two electronically deficient carbon atoms at the neighboring position. Therefore, the conjugate addition would happen from both sides of the enone to provide the mixture of **11** and **12**.

The α and β protons of the unsaturated carbonyl compound **10** appeared at δ 5.66 and 5.92 ppm in its $^1H$ NMR spectrum. This implied that the olefin and carbonyl groups are not strongly conjugated at the ground state, but seem to be at the transition state since it ends up with the conjugate addition with stereoselectively under basic condition, but non-selectively under acidic conditions.

This seems contradictory in comparison with our previous case in a stereoselective synthesis of **1** (giving only *trans* product by treatment with $TsOH \cdot H_2O$). The difference from the current system (from **10** to **11**) might be attributed to the fact that there is a presence of an additional stereogenic carbon atom, which might help the preferable conformation as shown in Figure 1. In fact, the protected secondary hydroxyl group did situate in an equatorial position of the *trans* product (tetrahydropyran ring). In the cis isomer, this hydroxyl group is located in a congested concave position, instead.

### 2.2. Synthesis of the symmetric HIJ ring

The *trans*/*syn*/*trans* tricyclic ketone **11** was further converted into racemic vinyl triflate **13**, which was allowed to

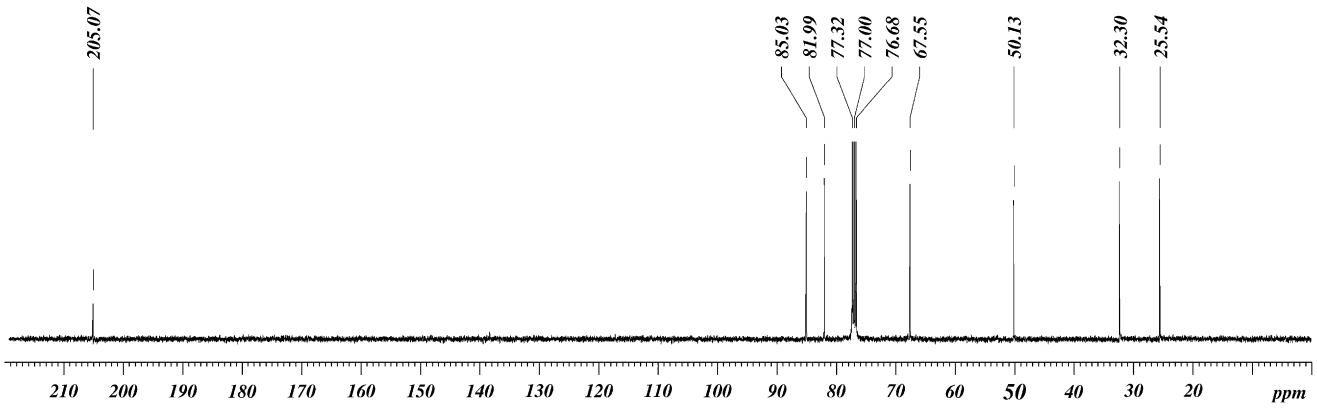



**Figure 2**. $^{13}$C NMR spectrum of symmetric ketone **11** showing only seven lines.

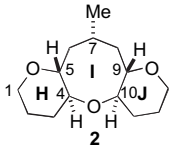
do cross-coupling with methylmagnesium bromide in the presence of Fe(acac)$_3$ catalyst to afford the *endo*-olefin **14** in good yield.[10] This *endo*-olefin product was hydrogenated stereoselectively using Crabtree's catalyst to give a single diastereoisomer HIJ-ring model **2**.[11]

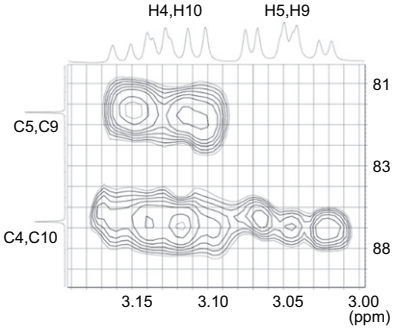
We summarized the $^1$H and $^{13}$C NMR data of HIJ-ring model **2** in Table 1. Figure 3 shows $^{13}$C NMR spectrum, which has only eight lines corresponding to the symmetry of **2**. Previously we had reported about the same compound, which we synthesized in a different route. It showed all the 14 lines in the $^{13}$C NMR spectrum.[12] There was difference between this result and previous result. In 2004, Tachibana's group (Tokyo University) reported the synthesis of the same HIJ-ring model via an alternative route and they also reported that the compound was observed with only eight lines in $^{13}$C NMR.[13] Their report prompted us to repeat this model once again. We then confirmed the previous route and compounds of our previous HIJ-ring model.

### 2.3. Reduction of *exo*-olefin

The stereochemistry of the methyl group is of interesting outcome depending on the olefin precursor. As shown in Scheme 2, the *endo*-olefin (**14**) afforded the α-methyl product (**2**) with high stereoselectivity. The corresponding *exo*-olefin precursor **15** was prepared via Wittig methylenation from the ketone **11**, and reduction with $PtO_2$ in EtOH solvent afforded a mixture of the stereoisomer in 2/1 ratio; thus, major β-methyl derivative **16** and minor α-methyl derivative **2** in total 86% yield (Scheme 3). The products were inseparable from each other, so this ratio was estimated from the NMR data; 1.06 (d, 7.5 Hz) and 1.05 (d, 7.5 Hz), respectively. Although the data are not shown, the platinum or

**Table 1**. Comparison of $^1$H and $^{13}$C spectra of **2** with previous work (now assigned as **21**)[12] and Tachibana's work[13]




| Position | $^1$H (ppm) | | | | $^{13}$C (ppm) | | | |
|---|---|---|---|---|---|---|---|---|
| | Previous work | | Tachibana's work | *This work* | Previous work | | Tachibana's work | *This work* |
| 1,13 | 3.40 | 3.74 | 3.25 | *3.25* | 67.5 | 67.8 | 67.4 | *67.4* |
| | 3.86–3.93 | 3.84 | 3.80 | *3.80* | — | — | — | — |
| 2,12 | 1.66–1.73 | 1.86–1.92 | 1.60 | *1.61* | 25.6 | 25.7 | 25.9 | *25.9* |
| | 1.66–1.73 | 1.86–1.92 | 1.60 | *1.61* | — | — | — | — |
| 3,11 | 1.36 | 1.42–1.48 | 1.41 | *1.41* | 29.4 | 31.9 | 33.0 | *33.0* |
| | 2.02 | 1.80 | 2.02 | *2.02* | — | — | — | — |
| 4,10 | 3.02 | 4.08 | 3.13 | *3.13* | 75.8 | 77.8 | 81.7 | *84.4* |
| 5,9 | 2.98 | 3.19 | 3.05 | *3.05* | 78.4 | 80.6 | 84.3 | *81.7* |
| 6,8 | 1.20 | 1.26 | 1.56 | *1.56* | 36.0 | 38.6 | 46.4 | *46.4* |
| | 1.96 | 1.40–1.49 | 1.79 | *1.79* | — | — | — | — |
| 7 | 1.46–1.52 | | 1.88 | *1.88* | 39.1 | | 27.9 | *28.0* |
| 7-Me | 0.89 | | 1.02 | *1.02* | 17.1 | | 28.1 | *28.1* |

The $^{13}$C signals of C-4(10) and C-5(9) of this work was correctly assigned on the basis of HMBC.

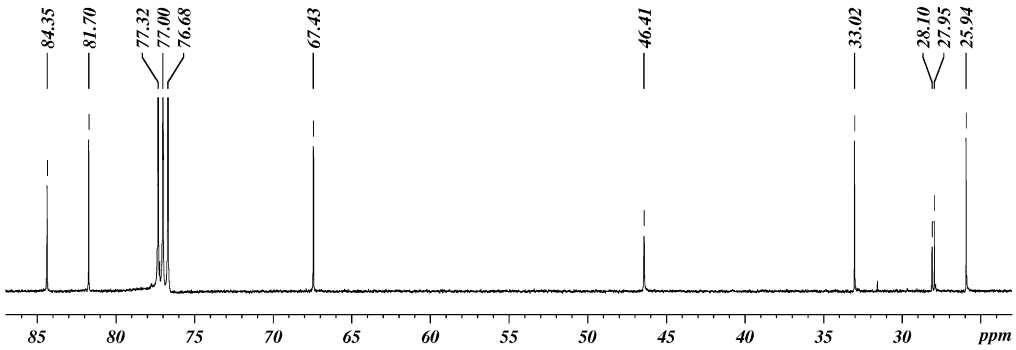
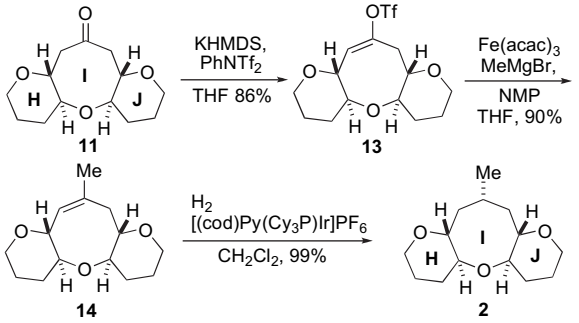
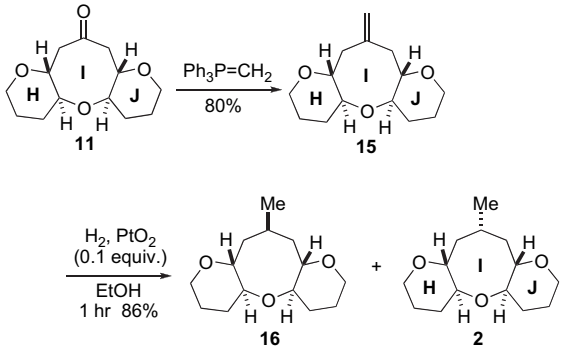


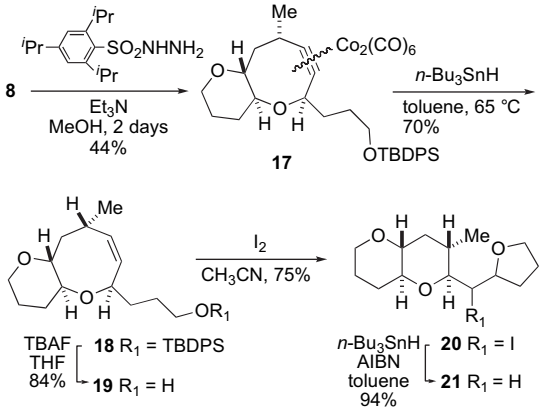

**Figure 3**. $^{13}C$ NMR spectrum of symmetric HIJ-ring model **2** showing only eight lines.




**Scheme 2**. Synthesis of the symmetric 6/8/6-oxocane, as a model of HIJ-ring of ciguatoxin.




**Scheme 3**. Stereochemistry of 7-methyl group from the *exo*-olefinic precursor.




**Scheme 4**. Previous synthetic route, which led us **21**.

palladium catalysts seem to isomerize the double bond between **14** and **15** under the reduction condition and the stereochemistry of the product may be depended on the relative reduction rate versus isomerization.

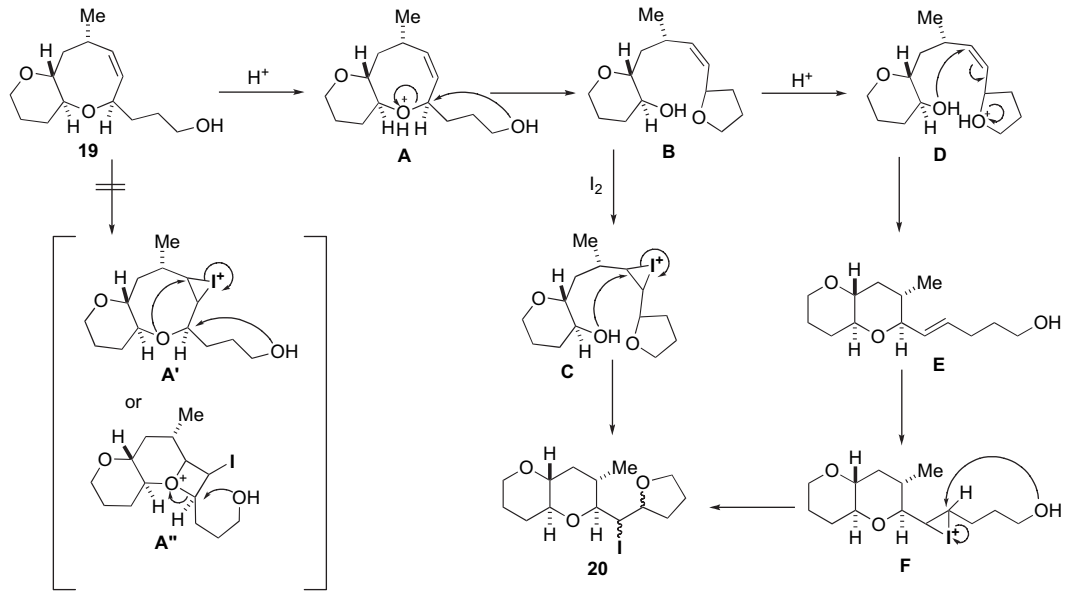
## 2.4. Revision of previous structure and rearrangement mechanism

We have re-examined our synthesis from compound **8** according to our previous route, which is indicated in Scheme 4. Diimide reduction afforded **17** having α-methyl group, which was decomplexed with tri-*n*-butyltin hydride to olefin **18**. After removal of the silyl protecting group, the alcohol **19** was subjected to the critical condition with iodine in acetonitrile solvent. It afforded a condensed cyclic compound **20** carrying an iodine atom, which was identical with the previous HIJ-ring model compound on the basis of $^{1}H$ and $^{13}C$ NMR spectra. Then reductive de-iodination from **20** with tri-*n*-butyltin hydride in the presence of AIBN gave **21**, which was also identical with the previous reduction product. Here we have to revise the structure, which was reported to be as **2** in the previous paper, to be **21**.

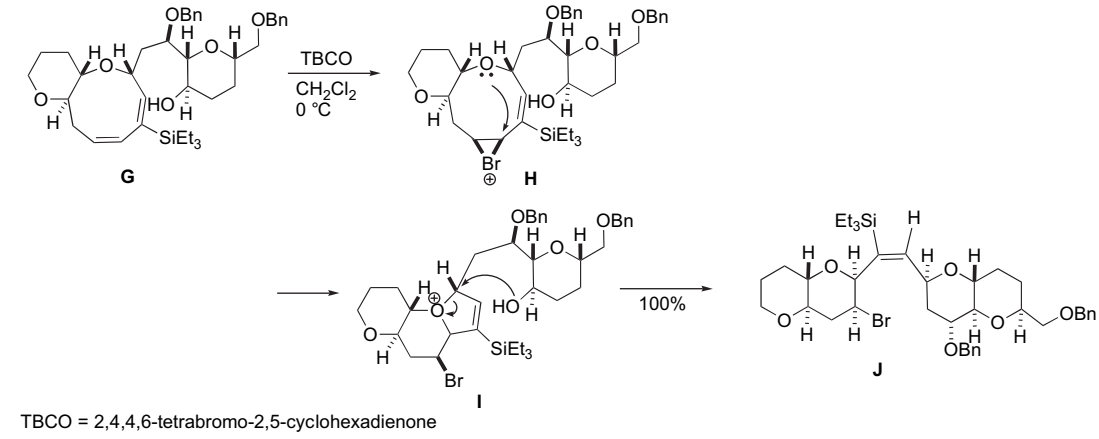
When we compared the possible reaction mechanism leading to compound **20** (Scheme 5), we have later observed a transannular mechanism with a nine-membered ring compound, which will be discussed later (Scheme 6).[14]

The iodoetherification in the tetrahydrooxocin **19** might not allow to include a strained 6/4-bicyclic intermediate (**A′**), but might allow to undergo transetherification from opening the eight-membered allylic ether (**A**) into closing the five-membered intermediate **B**. Iodoetherification between the secondary alcohol and olefin **C** would provide the 6/6-bicyclic iodide **20**. On the other hand, acidic ether transformation would occur through **D** to **E**. Iodoetherification might occur with interaction of the five-membered ring formation as **F** to form **20**.

Scheme 6 illustrates a mechanism of a similar case in a tetrahydrooxonin **G**. In this case, bromonium ion coordinates with one of the two olefins as in **H**, which allow a transannular interaction with an allylic carbon to form 6/6/5-tricyclic intermediate **I**. A transetherification to the new tetrahydropyran ring, in fact, afforded the tetracyclic vinyl silane **J**. An alternative mechanism may be possible through an opening of the nine-membered ring with assistance of the free




**Scheme 5**. Proposed rearrangement mechanism of the iodoetherification.




**Scheme 6**. Proposed transannular mechanism of the bromoetherification.

hydroxyl group, which could follow the bromoetherification. These acidic transformation is potentially the problem of medium size unsaturated ring system.

## 3. Conclusion

We have synthesized HIJ-ring model **2** via a new route. Its NMR spectra showed symmetric nature, which disagreed with our previous report. Thus, we confirmed the previous route again and concluded that the structure of final product in previous paper had to be revised as rearranged **21**.

## 4. Experimental

### 4.1. General

Infrared spectra (IR) were recorded on a JASCO FTIR-7000S spectrophotometer and are reported in wave number ($cm^{-1}$). Proton nuclear magnetic resonance ($^1H$ NMR) spectra were recorded on a BRUKER ARX-400 (400 MHz) or a BRUKER AVANCE-400 (400 MHz). Chemical shifts are reported in parts per million from tetramethylsilane and are assigned using tetramethylsilane ($\delta$ 0.00 ppm) as an internal standard. Data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broadened, m=multiplet), coupling constant(s), and assignment. Carbon nuclear magnetic resonance ($^{13}C$ NMR) spectra were recorded on a BRUKER ARX-400 (100 MHz) or a BRUKER AVANCE-400 (100 MHz). Chemical shifts are reported in parts per million from tetramethylsilane using the solvent resonance as an internal standard ($CDCl_3$: $\delta$ 77.00 ppm). Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Elemental analyses were performed by Analytical Laboratory at School of Bioagricultural Sciences, Nagoya University. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel $60F_{254}$ coated glass plates (Merck, Art 1.05715) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution and heated as developing agents.

Silica gel 60 (particle size 63–200 μm, 70–230 mesh, ASTM, purchased from Kanto Chemical Co., Inc) was used for open-column chromatography. Silica gel 60 (spherical, particle size 40–50 μm, purchased from Kanto Chemical Co., Inc) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on 0.5 mm silica gel $60F_{254}$ coated glass plates (Merck, Art 1.05744). Unless otherwise noted, non-aqueous reactions were conducted in oven-dried (120 °C) or flame-dried glassware under inert atmosphere of dry nitrogen or argon. Dry THF was purchased from Kanto Chemical Co., Inc. in a bottle as tetrahydrofran, dehydrated. Anhydrous toluene was purchased from Kanto Chemical Co., Inc. in a bottle. Dry $CH_2Cl_2$ was purchased from Kanto Chemical Co., Inc. in a bottle as dichloromethane, dehydrated. $BF_3 \cdot OEt_2$ was distilled from $CaH_2$. All other commercially available reagents were used as received.

**4.1.1. Vinyl iodide 4.** To a solution of B-I-9-BBN (1.0 M hexane solution, 3.5 mL, 3.52 mmol) in dry $CH_2Cl_2$ (24 mL) was added dropwise acetylene **3** (610 mg, 3.35 mmol) dissolved in dry $CH_2Cl_2$ (10 mL) over 10 min at −20 °C under nitrogen atmosphere. After stirring for 2 h 30 min at the same temperature, AcOH (574 μL) was added dropwise to the reaction mixture over 5 min. The reaction mixture was stirred further for 30 min at 0 °C, then poured into $H_2O$. NaOH solution (3 M) was added to the mixture and the mixture was extracted with $CH_2Cl_2$ (×2). The combined organic extract was washed with saturated $NH_4Cl$ solution, $H_2O$, brine, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($SiO_2$: 30 g, hexane/AcOEt=4/1) to give vinyl iodide **4** (924 mg, 89%) as a yellow oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ 1.43–1.57 (1H, m, H-3a), 1.65–1.77 (2H, m, H-2 ×2), 2.04 (3H, s, –COC$H_3$), 2.13–2.21 (1H, m, H-3b), 2.42 (1H, ddd, *J*=15.0, 9.0, 1.0 Hz, H-6a), 2.64 (1H, ddt, *J*=15.0, 3.0, 1.5 Hz, H-6b), 3.37 (1H, td, *J*=11.0, 3.5 Hz, H-1a), 3.52 (1H, td, *J*=9.0, 3.0 Hz, H-5), 3.92 (1H, ddt, *J*=11.0, 4.0, 1.5 Hz, H-1b), 4.58 (1H, ddd, *J*=11.5, 9.0, 4.0 Hz, H-4), 5.78 (1H, t, *J*=1.5 Hz, –C=C$H_2$), 6.10 (1H, q, *J*=1.0 Hz, –C=C$H_2$). $^{13}$C NMR (100 MHz): δ 21.2, 25.1, 29.5, 47.7, 67.9, 71.3, 77.9, 106.8, 127.9, 170.2.

**4.1.2. Cyclic ketone cobalt complex 9.** A solution of cyclic *exo*-olefin cobalt complex **8** (1.62 g, 2.13 mmol) in dry THF (107 mL) and $H_2O$ (21 mL) was stirred with $OsO_4$ (4% $H_2O$ solution, 1.35 mL, 213 μmol), $NaIO_4$ (2.27 g, 10.6 mmol), and acetic acid (5.4 mL) at room temperature. Additional $NaIO_4$ (2.27 g, 10.6 mmol) was added to the reaction mixture in portion wise three times until the starting material was consumed completely for 12 h 20 min. The reaction mixture was poured into $H_2O$ and extracted with $Et_2O$ (×2). The combined organic extract was washed with $H_2O$, brine, dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography ($SiO_2$: 55 g, hexane/AcOEt=6/1) to give cyclic ketone cobalt complex **9** (1.21 g, 74%) as a dark brown oil and a mixture containing diol.

The mixture was dissolved in dry THF (10.7 mL), $H_2O$ (2.1 mL), to which $NaIO_4$ (450 mg) was added. After stirring for 17 h 40 min, the reaction mixture was poured into $H_2O$ and extracted with $Et_2O$ (×2). The combined organic extract was washed with $H_2O$, brine, dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($SiO_2$: 1 g, hexane/AcOEt=8/1) to give cyclic ketone cobalt complex **9** (22.7 mg, 2%) as a dark brown oil. Total yield was 76%.

$[\alpha]_D^{24}$ +130.0 (*c* 0.07, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ 1.07 (9H, s, –Si$^t$Bu), 1.41–1.52 (1H, m, H-3a), 1.55–1.85 (4H, m, H-2 ×2, H-11a, H-12a), 1.87–1.97 (1H, m, H-12b), 2.00–2.07 (1H, m, H-3b), 2.09–2.17 (1H, m, H-11b), 2.75 (1H, dd, *J*=12.0, 3.5 Hz, H-6a), 3.19 (1H, td, *J*=10.0, 4.5 Hz, H-4), 3.27–3.35 (1H, m, H-1a), 3.32 (1H, dd, *J*=12.0, 5.0 Hz, H-6b), 3.50 (1H, ddd, *J*=10.0, 5.0, 3.5 Hz, H-5), 3.70–3.82 (2H, m, H-13 ×2), 3.95 (1H, ddt, *J*=11.5, 4.5, 2.0 Hz, H-1b), 4.62 (1H, dd, *J*=9.5, 3.5 Hz, H-10), 7.35–7.46 (6H, m, aromatic), 7.65–7.70 (4H, m, aromatic). $^{13}$C NMR (100 MHz): δ 19.2, 25.8, 26.7, 29.5, 30.8, 34.8, 47.3, 63.3, 68.2, 79.4, 80.3, 82.9, 87.9, 100.9, 127.6, 129.6, 133.7, 133.8, $135.5_1$, $135.5_4$, 198.1, 200.3. IR (KBr): $\nu_{max}$ 2937, 2859, 2101, 2062, 2031, 1672, 1553, 1428, 1306, 1214, 1138, 1088, 1037, 1006, 824 cm$^{-1}$. Anal. Calcd for $C_{37}H_{42}Co_2O_{10}Si$: C, 56.06; H, 5.34. Found: C, 56.07; H, 5.11.

**4.1.3. Enone 10.** A solution of cyclic ketone cobalt complex **9** (530 mg, 729 μmol) in dichloroethane (24 mL) was heated with bis(trimethylsilyl)acetylene (330 μL, 1.46 mmol) and $Et_3SiH$ (1.2 mL, 7.29 mmol) at 60 °C for 5 h. The mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography ($SiO_2$: 30 g, hexane/AcOEt=4/1) to give the vinyl silane (structure not shown 377 mg, 87%) as a dark brown oil.

$[\alpha]_D^{22}$ −74.3 (*c* 0.48, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ 0.59–0.67 (6H, m, –Si(C$H_2$CH$_3$)$_3$), 0.95 (9H, t, *J*=7.5, –Si(CH$_2$C$H_3$)$_3$), 1.04 (9H, s, –Si$^t$Bu), 1.35–1.48 (2H, m, H-3a, H-11a), 1.52–1.74 (5H, m, H-2 ×2, H-11b, H-12 ×2), 1.94–2.04 (1H, m, H-3b), 2.62–2.67 (2H, m, H-6 ×2), 3.01 (1H, ddd, *J*=10.0, 9.5, 4.5 Hz, H-4), 3.34 (1H, td, *J*=11.5, 2.5 Hz, H-1a), 3.49 (1H, ddd, *J*=9.5, 9.0, 7.0 Hz, H-5), 3.60–3.69 (2H, m, H-13 ×2), 3.85 (1H, ddt, *J*=11.5, 4.5, 2.0 Hz, H-1b), 3.92 (1H, dt, *J*=8.5, 2.5 Hz, H-10), 5.56 (1H, d, *J*=2.5 Hz, C-9), 7.34–7.45 (6H, m, aromatic), 7.62–7.67 (4H, m, aromatic). $^{13}$C NMR (100 MHz): δ 2.9, 7.1, 19.2, 25.3, 26.9, 28.8, 30.2, 32.2, 49.0, 63.5, 67.6, 79.5, 80.4, 81.6, 127.6, 127.6, 129.7, 129.6, $133.9_7$, $134.0_3$, 134.8, 135.6, 140.0, 144.5, 208.3. IR (KBr): $\nu_{max}$ 3072, 2955, 2857, 2100, 2062, 2032, 1677, 1590, 1463, 1428, 1390, 1336, 1284, 1237, 1209, 1196, 1181, 1006, 966, 824 cm$^{-1}$. Anal. Calcd for $C_{35}H_{52}O_4Si_2$: C, 70.89; H, 8.84. Found: C, 70.91; H, 8.92.

This vinyl silane (780 mg, 1.32 mmol) was dissolved in dry THF (132 mL), and mixed with TBAF (1.0 M THF solution, 1.45 mL, 1.45 mmol) at 0 °C. After stirring for 5 min at the same temperature, the reaction mixture was poured into $NH_4Cl$ solution and extracted with AcOEt (×3). The combined organic extract was washed with $H_2O$, brine, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica

gel column chromatography ($SiO_2$: 20 g, hexane/AcOEt=20/1–1/1) to give enone **10** (540 mg, 85%) as a brown oil.

$[\alpha]_D^{25}$ −41.0 (*c* 0.42, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.06 (9H, s, –Si$^t$Bu), 1.40–1.54 (2H, m, H-3a, H-11a), 1.60–1.74 (5H, m, H-2 ×2, H-11b, H-12 ×2), 2.03–2.09 (1H, m, H-3b), 2.76 (1H, dd, *J*=10.0, 5.5 Hz, H-6a), 2.82 (1H, t, *J*=10.0 Hz, H-6b), 3.12 (1H, ddd, *J*=10.0, 9.5, 4.5 Hz, H-4), 3.37 (1H, ddd, *J*=12.0, 11.5, 3.0 Hz, H-1a), 3.47 (1H, ddd, *J*=10.0, 9.5, 5.5 Hz, H-5), 3.66–3.71 (2H, m, H-13 ×2), 3.86–3.92 (1H, m, H-1b), 3.98 (1H, dq, *J*=8.5, 2.5 Hz, H-10), 5.66 (1H, dd, *J*=12.0, 2.5 Hz, H-9), 5.92 (1H, dd, *J*=12.0, 2.5 Hz, H-8), 7.37–7.47 (6H, m, aromatic), 7.65–7.70 (4H, m, aromatic). $^{13}C$ NMR (100 MHz): $\delta$ 19.2, 25.3, 26.9, 28.7, 30.3, 32.3, 49.1, 63.4, 67.7, 79.4, 80.3, 80.8, 127.6, 127.7, 129.6, 130.1, 133.9, $134.7_7$, $134.7_9$, 135.6, 204.7. IR (KBr): $\nu_{max}$ 2931, 2858, 2092, 2052, 2029, 1694, 1428, 1390, 1334, 1289, 1183, 1096, 824 $cm^{-1}$. Anal. Calcd for $C_{29}H_{38}O_4Si$: C, 72.76; H, 8.00. Found: C, 72.74; H, 8.00.

**4.1.4. *trans*/*syn*/*trans*-Fused tricyclic ketone 11.** To a solution of enone **10** (17.8 mg, 37.2 μmol) in dry THF (1.9 mL) was added TBAF (1.0 M THF solution, 37.2 μL, 37.2 μmol) at room temperature. After stirring for 2 h, additional TBAF (1.0 M THF solution, 37.2 μL, 37.2 μmol) was added to the reaction mixture. The reaction mixture was stirred further for 13 h 15 min at the same temperature, then poured into $NH_4Cl$ solution and extracted with AcOEt (×2). The combined organic extract was washed with $H_2O$, brine, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($SiO_2$: 1 g, hexane/AcOEt=10/1–1/1) to give *trans*/*syn*/*trans*-fused tricyclic ketone **11** (7.6 mg, 85%) as a white solid.

$[\alpha]_D^{24}$ +1.6 (*c* 1.18, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.46–1.60 (2H, m, H-3a, H-11a), 1.64–1.72 (4H, m, H-2 ×2, H-12 ×2), 2.06–2.13 (2H, m, H-3b, H-11b), 2.72 (2H, ddd, *J*=11.0, 4.5, 2.0 Hz, H-6a, H-8a), 2.81 (2H, t, *J*=11.0 Hz, H-6b, H-8b), 3.24 (2H, ddd, *J*=11.0, 9.0, 5.0 Hz, H-4, H-10), 3.29–3.37 (2H, m, H-1a, 13a), 3.44 (2H, ddd, *J*=11.0, 9.0, 4.5 Hz, H-5, H-9), 3.87 (2H, ddt, *J*=11.0, 4.0, 2.0 Hz, H-1b, H-13b). $^{13}C$ NMR (100 MHz): $\delta$ 25.5, 32.3, 50.1, 67.6, 82.0, 85.0, 205.1. IR (KBr): $\nu_{max}$ 3005, 2938, 2851, 2724, 1701, 1450, 1376, 1340, 1289, 1179, 1092, 1048, 1016, 991, 966, 896, 874, 848 $cm^{-1}$. Anal. Calcd for $C_{13}H_{20}O_3$: C, 64.98; H, 8.39. Found: C, 64.97; H, 8.22.

**4.1.5. *trans*/*syn*/*trans*-Fused tricyclic ketone 11 and *trans*/*syn*/*cis*-fused tricyclic ketone 12.** A solution of enone **10** (190 mg, 397 μmol) in $CH_3NO_2$ (40 mL) containing $TsOH\cdot H_2O$ (411 mg, 2.3 mmol) was stirred at room temperature for 12 h 30 min. The reaction mixture was poured into $NaHCO_3$ solution and extracted with $CH_2Cl_2$ (×3). The combined organic extract was washed with $H_2O$, brine, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography ($SiO_2$: 20 g, hexane/AcOEt=1/1) to give *trans*/*syn*/*trans*-fused tricyclic ketone **11** (38.6 mg, 40%) as a white solid and *trans*/*syn*/*cis*-fused tricyclic ketone **12** (43.8 mg, 46%) as a yellow oil.

*trans*/*syn*/*cis*-Fused tricyclic ketone **12**. $[\alpha]_D^{25}$ +91.7 (*c* 0.53, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.42–1.81 (7H, m, H-2 ×2, H-3a, H-11 ×2, H-12 ×2), 2.03–2.11 (1H, m, H-3b), 2.53 (1H, dd, *J*=14.0, 4.5 Hz, H-8a), 2.63 (1H, dd, *J*=11.0, 4.0 Hz, H-6a), 2.72 (1H, t, *J*=11.0 Hz, H-6b), 3.01 (1H, dd, *J*=14.0, 11.0 Hz, H-8b), 3.13 (1H, ddd, *J*=11.0, 9.0, 5.0 Hz, H-4), 3.33 (1H, td, *J*=11.0, 4.0 Hz, H-1a), 3.40 (1H, ddd, *J*=11.0, 9.0, 4.0 Hz, H-5), 3.52–3.59 (1H, m, H-13a), 3.63 (1H, dt, *J*=12.0, 2.0 Hz, H-13b), 3.67 (1H, dt, *J*=9.0, 4.5 Hz, H-10), 3.86 (1H, ddt, *J*=11.0, 4.0, 2.0 Hz, H-1b), 4.48 (1H, dt, *J*=10.0, 4.5 Hz, H-9). $^{13}C$ NMR (100 MHz): $\delta$ 23.7, 25.5, 26.3, 31.1, 43.9, 46.8, 62.6, 67.7, 73.6, 76.4, 80.3, 81.0, 203.9. IR (KBr): $\nu_{max}$ 2939, 2864, 2731, 1701, 1445, 1374, 1290, 1187, 1078, 961, 922, 844 $cm^{-1}$. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.98; H, 8.52.

**4.1.6. Vinyl triflate 13.** The *trans*/*syn*/*trans*-fused tricyclic ketone **11** (39.6 mg, 165 μmol) in dry THF (4.2 mL) was cooled to −78 °C and treated dropwise with KHMDS (0.5 M toluene solution, 494 μL, 247 μmol) under argon atmosphere. After stirring for 30 min at the same temperature, $PhNTf_2$ dissolved in dry THF (4 mL) was added dropwise to the reaction mixture for over 5 min. The reaction mixture was stirred further for 30 min, then poured into $NH_4Cl$ solution, and extracted with $Et_2O$ (×2). The combined organic extract was washed with $H_2O$, brine, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography ($SiO_2$: 4 g, hexane/AcOEt=6/1) to give vinyl triflate **13** (54.8 mg, 86%) as a yellow oil.

$[\alpha]_D^{23}$ +1.6 (*c* 0.64, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.40–1.54 (2H, m, H-3a, H-11a), 1.62–1.71 (4H, m, H-2 ×2, H-12 ×2), 1.99–2.07 (1H, m, H-11b), 2.08–2.15 (1H, m, H-13b), 2.51 (1H, dt, *J*=15.0, 2.0 Hz, H-8a), 3.04 (1H, dd, *J*=15.0, 4.5 Hz, H-8b), 3.24–3.31 (2H, m, H-1a, H-13a), 3.28 (1H, ddd, *J*=11.0, 9.0, 5.0 Hz, H-4), 3.32 (1H, ddd, *J*=9.5, 4.5, 2.0 Hz, H-9), 3.43 (1H, ddd, *J*=11.0, 9.0, 4.5 Hz, H-10), 3.72 (1H, dd, *J*=9.0, 5.5 Hz, H-5), 3.89 (2H, ddt, *J*=11.5, 4.5, 2.0 Hz, H-1b, H-13b), 5.75 (1H, dd, *J*=5.5, 2.0 Hz, H-6). $^{13}C$ NMR (100 MHz): $\delta$ 25.2, 25.9, 31.1, 31.4, 34.6, 67.3, 68.4, 77.3, 78.4, 79.5, 81.2, 118.4 (q, *J*=320 Hz), 124.8, 147.1. IR (KBr): $\nu_{max}$ 2948, 2857, 1684, 1417, 1209, 1148, 1090, 1014, 956, 903, 866 $cm^{-1}$. Anal. Calcd for $C_{14}H_{19}F_3O_6S$: C, 45.16; H, 5.14. Found: C, 45.16; H, 5.34.

**4.1.7. *endo*-Olefin 14.** Vinyl triflate **13** (49.6 mg, 128 μmol) in dry THF (6.4 mL) was cooled to −40 °C and $Fe(acac)_3$ (4.5 mg, 12.8 μmol) and NMP (25 μL) were added to the solution under argon atmosphere. MeMgBr (0.82 M THF solution, 313 μL, 257 μmol) was added dropwise to the mixture at the same temperature. After stirring for 1 h 50 min at the same temperature, additional $Fe(acac)_3$ (4.5 mg, 12.8 μmol) and MeMgBr (0.82 M THF solution, 160 μL, 131 μmol) were added to the reaction mixture. The reaction mixture was stirred further for 1 h, then poured into $NH_4Cl$ solution, and extracted with $Et_2O$ (×2). The combined organic extract was washed with $H_2O$, brine, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography ($SiO_2$: 4 g, hexane/AcOEt=8/1) to give *endo*-olefin **14** (27.4 mg, 90%) as a yellow oil.

$[\alpha]_D^{26}$ +10.7 (*c* 0.22, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.36–1.50 (4H, m, H-2a, H-3a, H-11a, H-12a), 1.51–1.70 (2H, m, H-2b, H-12b), 1.82 (3H, s, –Me), 1.95–2.02 (1H, m, H-11b), 2.03–2.11 (1H, m, H-3b), 2.08 (1H, dd, *J*=13.5, 2.0 Hz, H-8a), 2.83 (1H, dd, *J*=13.5, 4.5 Hz, H-8b), 3.13 (1H, ddd, *J*=11.0, 9.0, 4.5 Hz, H-4), 3.22–3.36 (4H, m, H-1a, H-9, H-10, H-13a), 3.71 (1H, dd, *J*=9.0, 5.0 Hz, H-5), 3.82–3.91 (2H, m, H-1b, H-13b), 5.36 (1H, d, *J*=5.0 Hz, H-6). $^{13}C$ NMR (100 MHz): $\delta$ 25.6, 26.0, 26.3, 31.4, 31.6, 35.6, 67.2, 68.3, 76.4, 78.4, 80.9, 82.7, 127.8, 135.2. IR (KBr): $\nu_{max}$ 2937, 2855, 1439, 1272, 1214, 1148, 1090, 1027, 966, 855 $cm^{-1}$. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.65; H, 9.29.

**4.1.8. HIJ-ring model 2.** To a solution of *endo*-olefin **14** (27.4 mg, 115 μmol) in dry $CH_2Cl_2$ (5.6 mL) was added [(cod)py($Cy_3$P)Ir]$PF_6$ (9.3 mg, 11.5 μmol) at 0 °C under hydrogen atmosphere. After stirring for 1 h 10 min, the reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography ($SiO_2$: 0.8 g, hexane/AcOEt=4/1) to give HIJ-ring model **2** (27.6 mg, 99%) as a white solid.

$[\alpha]_D^{29}$ 0.29 (*c* 1.07, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.02 (3H, d, *J*=7.5 Hz, –Me), 1.41 (2H, m, H-3a, H-11a), 1.56 (2H, ddd, *J*=13.5, 10.5, 9.0 Hz, H-6a, H-8a), 1.61 (4H, m, H-2 ×2, H-12 ×2), 1.79 (2H, ddd, *J*=13.5, 3.5, 1.5 Hz, H-6b, H-8b), 1.88 (1H, m, H-7), 2.02 (2H, m, H-3b, H-11b), 3.05 (2H, ddd, *J*=10.0, 9.0, 3.5 Hz, H-5, H-9), 3.13 (2H, ddd, *J*=10.5, 9.0, 4.5 Hz, H-4, H-10), 3.25 (2H, m, H-1a, H-13a), 3.80 (2H, ddt, *J*=11.5, 4.0, 2.0 Hz, H-1b, H-13b). $^{13}C$ NMR (100 MHz): $\delta$ 25.9 (C2, C12), 28.0 (C7), 28.1 (Me), 33.0 (C3, C11), 46.4 (C6, C8), 67.4 (C1, C13), 81.7 (C5, C9), 84.4 (C4, C10). IR (KBr): $\nu_{max}$ 2936, 2846, 2713, 1450, 1376, 1345, 1326, 1294, 1265, 1224, 1180, 1147, 1098, 1026, 969, 947, 895 $cm^{-1}$. Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.97; H, 10.01.

**4.1.9. Reduction product 2 and 16.** *exo*-Olefin **15** (3.3 mg, 13.8 μmol) was dissolved in EtOH (1.4 mL) and $PtO_2$ was added (0.3 mg, 1.3 μmol) at room temperature under hydrogen atmosphere. After stirring for 1 h, the reaction mixture was filtered through a Celite column by washing with MeOH. The filtrate was concentrated under reduced pressure, then the residue was purified by silica gel column chromatography (hexane/AcOEt=5/1) to give reduction product **2** and **16** (2.8 mg, 86%) as a pale yellow oil.

**4.1.10. Rearrangement product 20.** Iodine (31.0 mg, 122 μmol) was placed in a small vessel and dissolved with $CH_3CN$ (2.5 mL), and cooled to 0 °C. To this mixture was added dropwise a solution of alcohol **19** (8.4 mg, 35 μmol) dissolved in $CH_3CN$ (1.0 mL). After stirring for 5 min at the same temperature, the reaction mixture was warmed to room temperature and stirred further for 1 h 40 min. The reaction mixture was quenched with saturated $Na_2SO_3$ solution and the mixture was stirred until the yellow color disappeared. The mixture was extracted with AcOEt (×2). The combined organic extract was washed with $H_2O$, brine, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($SiO_2$: 1.5 g, hexane/AcOEt=2/1) to give rearrange product **20** (9.6 mg, 75%) as a yellow oil.

$^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.85 (3H, d, *J*=6.5 Hz, –Me), 1.38 (1H, td, *J*=12.0, 11.0 Hz, H-6a), 1.45–1.57 (1H, m, H-3a), 1.68–1.74 (2H, m, H-2 ×2), 1.77–1.96 (4H, m, H-11a, H-7, H-12 ×2), 2.00 (1H, dt, *J*=12.0, 4.0 Hz, H-6b), 2.05 (1H, m, H-3b), 2.24–2.32 (1H, m, H-11b), 2.53 (1H, dd, *J*=9.0, 1.5 Hz, H-8), 3.05 (1H, ddd, *J*=11.0, 9.0, 4.0 Hz, H-5), 3.17 (1H, ddd, *J*=11.0, 9.0, 4.0 Hz, H-4), 3.38–3.46 (1H, m, H-1a), 3.87–3.94 (3H, m, H-1b, H-13 ×2), 4.06 (1H, dd, *J*=9.0, 1.5 Hz, H-9), 4.26 (1H, dt, *J*=9.0, 6.5 Hz, H-10). $^{13}C$ NMR (100 MHz): $\delta$ 16.6, 25.6, 25.9, 29.3, 33.9, 36.4, 37.8, 42.7, 67.9, 68.9, 77.9, 78.0, 79.6, 80.4.

**4.1.11. Reduction product 21.** To a solution of **20** (14.4 mg, 39.3 μmol) in toluene (780 μL) were added tri-*n*-butyltin hydride (53 μL, 197 μmol) and AIBN (1.4 mg, 8.5 μmol) at room temperature. The reaction mixture was warmed to 55 °C and stirred for 1 h 35 min. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography ($SiO_2$: 0.7 g, hexane/AcOEt=4/1) to give reduction product **21** (8.8 mg, 94%) as a yellow oil.

$^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.91 (3H, d, *J*=6.5 Hz, –Me), 1.23 (1H, td, *J*=12.5, 10.5 Hz, H-6a), 1.40–1.57 (4H, m, H-3a, H-7, H-9a, H-11a), 1.66–1.77 (2H, m, H-2 ×2), 1.82 (1H, ddd, *J*=14.0, 9.0, 2.0 Hz, H-9b), 1.83–1.93 (2H, m, H-12 ×2), 1.96 (1H, dt, *J*=12.0, 4.0 Hz, H-6b), 1.99–2.08 (2H, m, H-3b, H-11b), 3.40 (1H, td, *J*=11.5, 4.0 Hz, H-1a), 3.75 (1H, td, *J*=7.5, 6.5 Hz, H-13a), 3.87 (1H, dt, *J*=8.5, 6.5 Hz, H-13b), 3.90 (1H, ddt, *J*=11.5, 4.5, 2.0 Hz, H-1b), 4.11 (1H, dddd, *J*=9.0, 8.0, 6.0, 3.5 Hz, H-10). $^{13}C$ NMR (100 MHz): $\delta$ 17.7, 25.7, 25.8, 29.5, 32.0, 36.1, 38.7, 39.2, 67.8, 67.9, 75.8, 77.8, 78.4, 80.6.

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