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(Citation)
Bulletin of the Chemical Society of Japan,88(9):1331-1337

(Issue Date)
2015-09-15

(Resource Type)
journal article

(Version)
Version of Record

(URL)
https://hdl.handle.net/20.500.14094/90003961

BCSJ

Studies on Diastereoselective Functionalization, Optical Resolution, and Racemization Behaviors of Macrocyclic Bisimidazole of Winding-Vine-Shaped Molecular Asymmetry

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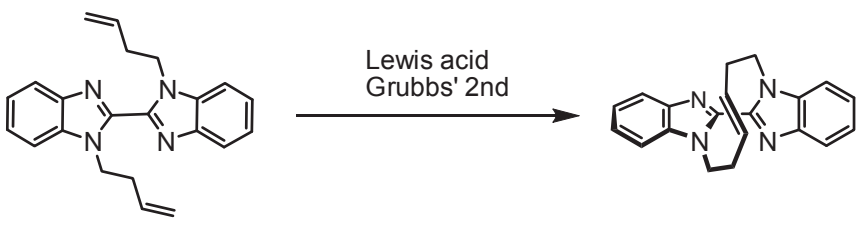
Received: May 9, 2015; Accepted: June 10, 2015; Web Released: June 18, 2015

Macrocyclic alkene containing bisimidazole showing molecular asymmetry, which is synthesized by ring-closing metathesis, is subjected to several functional group transformation reactions of the olefin moiety. Syn-addition reactions such as epoxidation, dihydroxylation, and hydrogenation are found to proceed whereas anti-addition does not proceed. Optical resolution of racemic bisimidazole is successfully achieved with a preparative chiral column. Racemization behaviors of bisimidazole derivatives are also studied under several conditions.

Molecular asymmetry, which does not involve stereogenic carbon but exhibits chirality, attracts considerable attention in a wide range of organic chemistry.[1] In particular, axially-chiral biaryl derivatives are known as a valuable catalyst in organocatalysis as well as ligands for a wide variety of metal-catalyzed asymmetric synthesis to induce chirality onto organic molecules by *si*/*re* face selection to sp^2 carbon,[2] desymmetrization of prochiral bifunctional compounds, kinetic resolution based on a chiral carbogenic center, etc.[3] We have recently reported that ring-closing metathesis (RCM)[4] of a bisbenzimidazole derivative bearing an ω-olefinic substituent at the nitrogen atom **1** leads to the formation of macrocyclic alkene **2**, which shows novel molecular asymmetry, as shown in Scheme 1.[5] The chirality is axially chiral caused by the restriction of free rotation of the carbon–carbon bond between imidazole rings by ring closure.[6] It is also recognized as helical chirality by the left or right-handed helicity of the alkylene chain between bisimidazole rings[7] as morning glory vine propagates along with a supporting bar composed of rigid (hetero)biaryl. In addition, the carbon–carbon double bond formed by RCM would also induce facial chirality,[8] one of whose face is covered with the bisimidazole structure. Thus, **2** showing chirality is categorized as a new class of molecular asymmetry, which has not been reported so far, named winding-vine-shaped molecular asymmetry.[9] The structure of the RCM product was clarified by X-ray crystal structure analysis, which showed formation of enantiopair in the single crystal, and that the molecule was shown to be separated analytically by HPLC with a chiral column. Accordingly, our concern is turned to further understanding of such novel molecular asymmetry.[5,9] We herein describe transformation of the olefinic moiety to introduce functional groups, optical resolution of the thus formed racemic **2** with a preparative chiral column, and racemization behaviors of **2** and the derivatives.

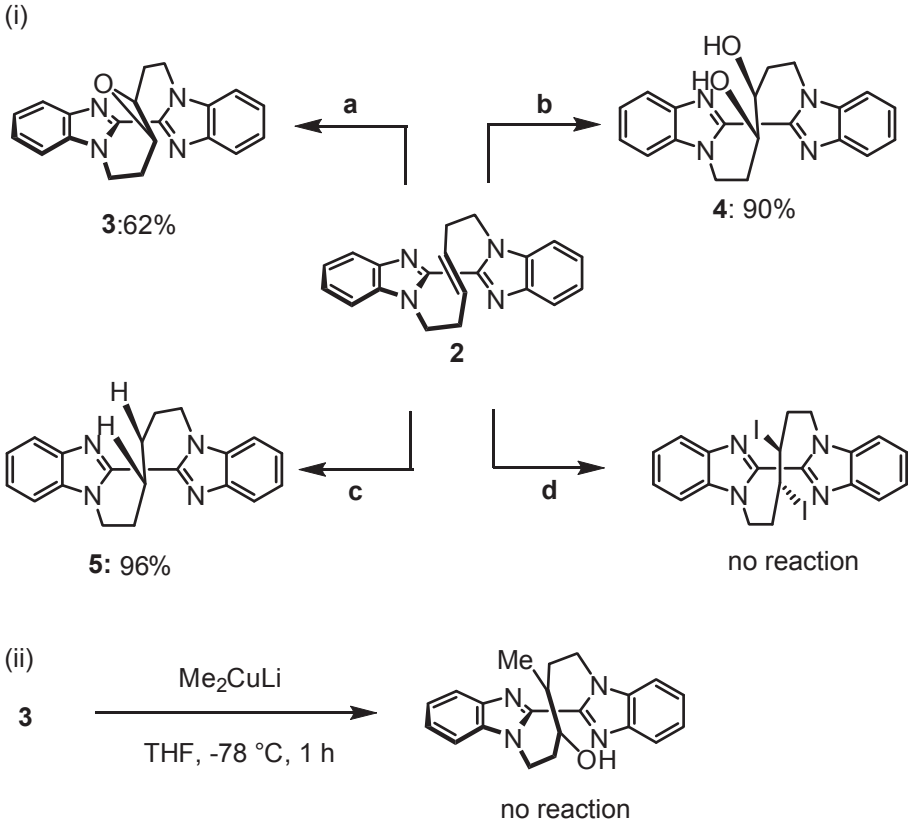
Results and Discussion

We first set out studies on the functionalization of the olefin moiety of **2** formed by ring-closing metathesis with a ruthenium catalyst. Several addition reactions at the carbon–carbon double bond can be designed as summarized in Scheme 2. When macrocyclic bisimidazole **2** was treated with oxone ($NaHSO_5$) in acetone/water (1:1), the corresponding epoxide **3** was obtained in 62% yield.[10] Since the reaction is well known to proceed in a syn-addition manner by the in situ formed dioxirane derived from acetone, the thus formed two stereogenic centers in **3** would possibly form diastereomeric isomers. However, HPLC analysis of **3** with a chiral column only displayed two detectable peaks based on the racemate and ^1H NMR analysis did not suggest the presence of diastereoisomers. Dihydroxylation proceeded catalyzed by potassium



1 **2**

Scheme 1. Formation of macrocyclic bisazole **2** by RCM.



Scheme 2. (i) Addition reaction to the alkene of **2** (a) oxone (2.0 equiv), acetone:H_2O = 1:1, 60 °C, 12 h. (b) $K_2OsO_4 \cdot 2H_2O$ (10 mol%), NMO (1.5 equiv), acetone:H_2O = 1:1, r.t., 15 h. (c) Pd/C (10 mol %), MeOH, H_2 (1 atm) r.t., 24 h. (d) I_2 (1.0 equiv), $CHCl_3$, r.t., 8 h. (ii) Attempted ring opening of epoxide **3** with Me_2CuLi.

osmate ($K_2OsO_4 \cdot H_2O$) (10 mol %) in the presence of *N*-methylmorpholine *N*-oxide (NMO) as an oxidant to give *cis*-diol **4** in 90% yield.[11] The diasteroisomer of **4** was not observed by ^{1}H NMR analyses similar to the case of **3**. Hydrogenation was also found to take place with Pd/C as a catalyst under hydrogen atmosphere (1 atm) to afford saturated product **5** in 96% yield,[12] whose facial chirality arising from the C–C double bond disappeared but may still involve potential helical and axial chiralities whereas separation of the racemate of **5** has not been achieved by HPLC with a chiral column. On the other hand, addition of iodine to the double bond of **2** did not occur at all to result in recovery of the starting material.

These reactions suggested that *syn*-addition to the carbon–carbon double bond occurred smoothly whereas the reaction known to proceed in an *anti*-addition manner did not take place. The results would be caused by the effective block of a face of the carbon–carbon double bond by bisimidazole rings albeit possible formation of iodonium salt on the unblocked face of olefin. The shielded bisbenzimidazole moiety would not allow the resulting attack of iodide ion, bringing about no reaction. Attempted ring opening of epoxide **3** with Me_2CuLi,[13] which would proceed by the attack of the methyl group in a S_N2 manner leading to the ring-opened product, was also examined to result in no reaction (recovery of 60% **3**) as shown in Scheme 2 (ii).

In addition to analytical HPLC of **2** with a chiral column to separate two peaks of the racemic mixture, separation of the enantiomer with a preparative chiral column has also been successful to result in clear base-line separation to isolate isomers of faster elute (+)-**2** ($[\alpha]_D = +136°$) and the second (−)-**2** ($[\alpha]_D = -145°$).[9] Although X-ray analysis to clarify crystal structure of each enantiomer had been attempted, it was found that the separated enantiomer showed amorphous characteristics and thus caused difficulties in obtaining a single crystal of (+)- or (−)-**2**.[14] Indeed, XRD analysis of the enantiopure **2** only showed broad signals, while that of the racemate (±)-**2** indicated sharp peaks suggesting the good crystallinity as shown in Figure 1a and Figure 1b. Measurement of circular dichroism (CD) spectra was also performed as shown in Figure 2. Both peaks of each enantiomer showed symmetric signals to suggest that the two separated products are actually both enantiomers of **2**. The CD spectra indicated positive Cotton effect in (+)-**2** and the negative one in (−)-**2** at ca. 290 nm, respectively, and the peaks are close to the λ_{max} of the UV–vis spectrum of **2** (Figure 2).

We also studied racemization behaviors of bisimidazole derivatives of molecular asymmetry. Accompanied by bisbenzimidazole **2** several other bisimidazole derivatives were also prepared and subjected to resolution with a chiral column. Macrocyclic alkene **6** composed of 4,5-dibromoimidazole rings was prepared from 2,4,5-tribromoimidazole through *N*-alkylation with 4-bromo-1-butene followed by debrominative homocoupling leading to the metathesis precursor. The RCM reaction of the thus obtained product afforded the correspond-

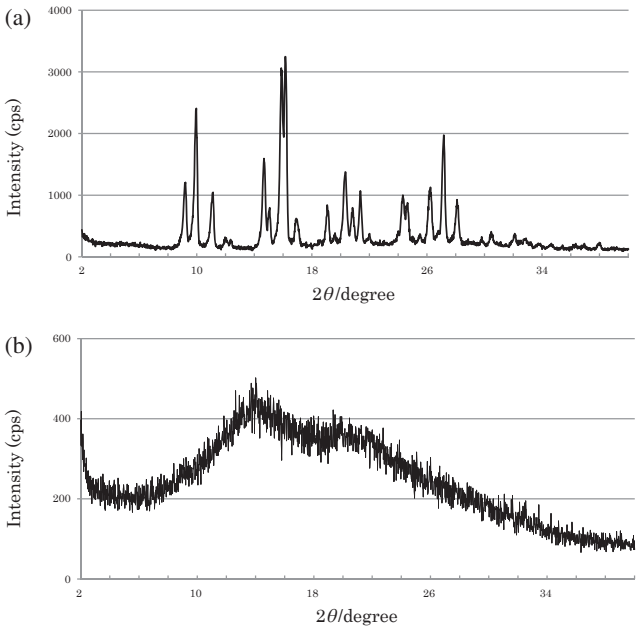


Figure 1. XRD analysis of (a) racemic benzimidazole derivative **2** and (b) enantiopure benzimidazole derivative **2**.

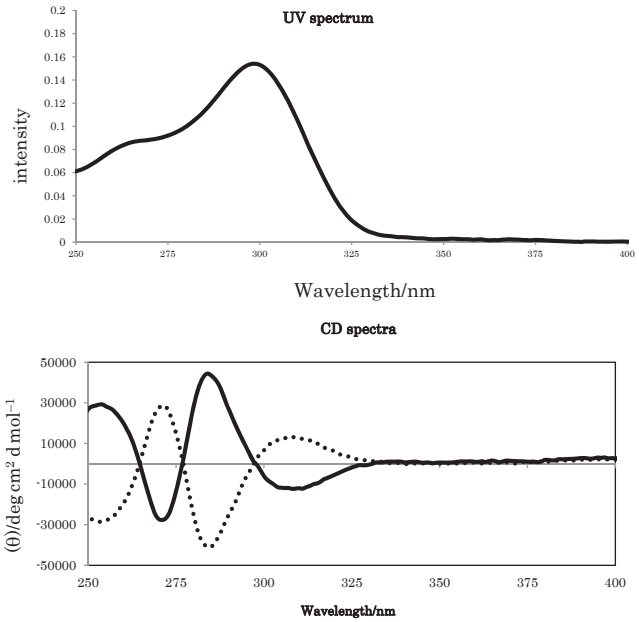
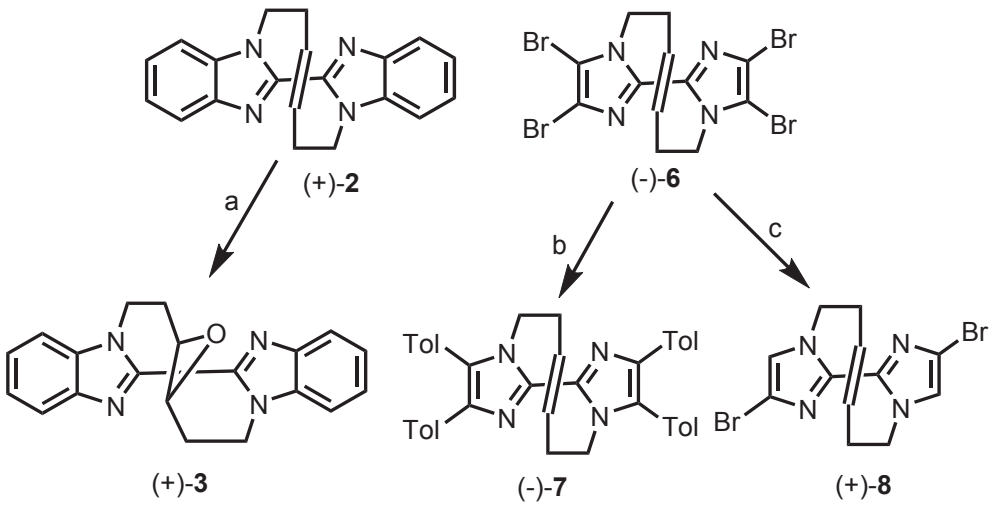


Figure 2. UV spectrum of benzimidazole derivative **2** and CD spectra of (+)-**2** (solid) and (−)-**2** (dotted).



Scheme 3. Preparetion of enantioenriched bisazole derivatives for racemization studies. a) *m*CPBA;[18] b) 4-Me(C_6H_4)B(pin) (pin: MeC_2O_2, 6 equiv), [$Pd_2(dba)_3$]/4PPh_3 (14 mol %)/K_2CO_3, 80 °C, 90 h; c) EtMgCl (2.5 equiv), 0 °C then H_2O.

ing 4,4′,5,5′-tetrabromobisimidazole **6**.[9] Resolution was then carried out in a similar manner with preparative chiral column (DAICEL CHIRALPAK-IF) to afford (+)- and (−)-**6**. The separated enantiomers exhibited $[\alpha]_D$ values of +54° ((+)-**6**) and $[\alpha]_D = -51°$ ((−)-**6**), respectively. Furthermore, several functional group transformations were also conducted with the optically active **6**. Cross coupling with arylboronic acid was carried out as reported previously with slight racemization to afford **7** in 91% ee.[9,15,16] Treatment of **6** with two equivalents of Grignard reagent EtMgCl underwent the 4,4′-selective debrominative protonation via halogen–metal exchange leading to **8**,[17] in which decrease of the optical purity was hardly observed under the reaction conditions. The enantioenriched epoxide **3** was obtained by oxidation of the resolved **2** (Scheme 3).

The obtained bisimidazole derivatives were thereby subjected to study racemization behaviors. Macrocyclic compounds **2**, **3**, **6**, **7**, and **8** were heated at 80, 100, and 140 °C, respectively, in 1,2-dichloroethane or chlorobenzene. Figures 3a–3c shows the relationship of the enantiomeric excess of the bisimidazole derivatives with the time conversion, which were analyzed by HPLC (DAICEL CHIRALPAK IF), at each temperature. Enantiomeric excess of bisbenzimidazole **2**, tetrakis(tolylated)-bisimidazole **7**, and 4,4′-dibromobisimidazole **8** were found to decrease slowly at 80 °C. In contrast, little racemization of epoxide **3** and tetrabromobisimidazole **6** was observed. When the temperature was raised to 100 °C, **2**, **7**, and **8** racemized faster than those at 80 °C. By contrast, the enantiopurities of **3** and **6** were kept higher even after 24 h. Racemization of **2**, **7**, and **8** occurred immediately at 140 °C while that of **6** was

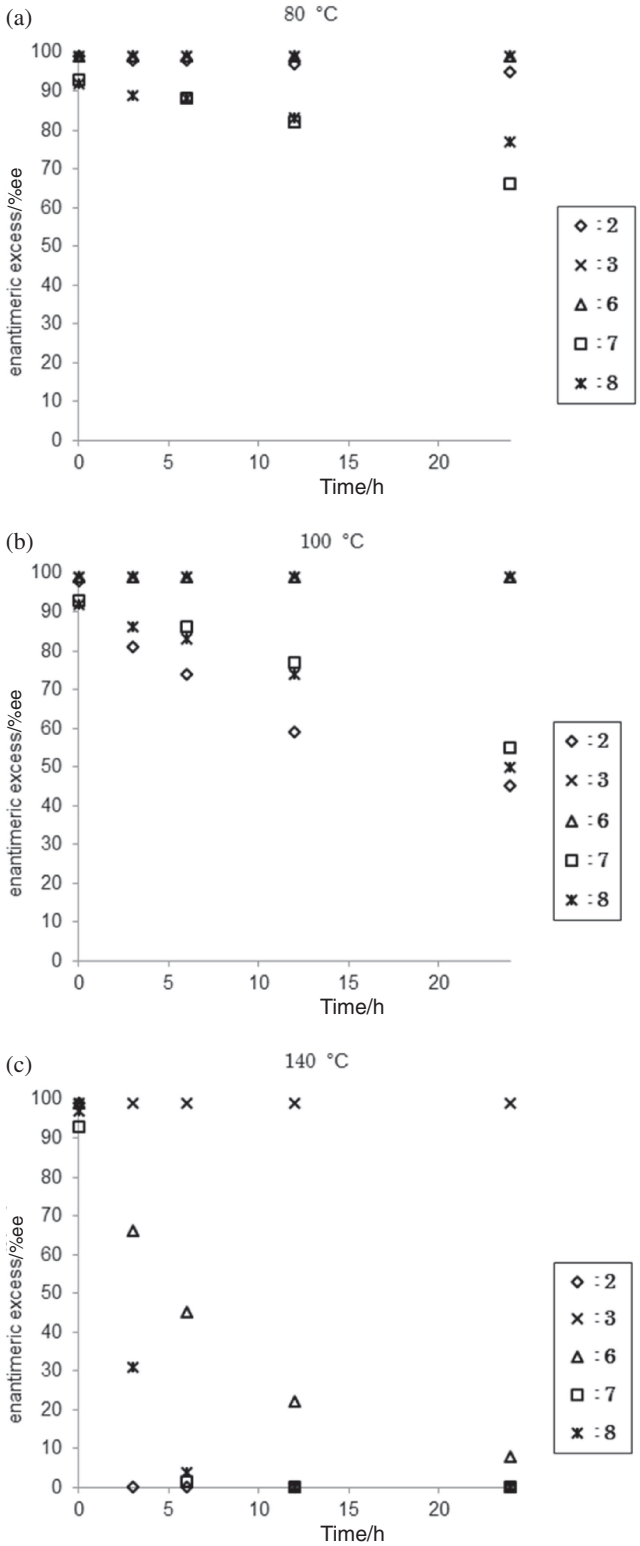


Figure 3. Racemization behavior of macrocyclic compounds **2**, **3**, **6**, **7**, and **8** (a) at 80 °C in 1,2-dichloroethane (b) at 100 °C in chlorobenzene, and (c) at 140 °C in chlorobenzene. Enantiomeric excess was measured by HPLC analysis with a chiral column.

relatively slower. It should be pointed out that enantiomeric excess of **3** bearing epoxide did not decrease at all even at such a high temperature with a marked contrast to other bisimidazole derivatives. Considering the racemization of bisimidazole derivatives, inversion of facial chirality is induced along with rotation of azole–azole bond as well as helicity of the alkylene chain.[19] Introduction of the epoxy ring to the olefin moiety would inhibit rotation of the epoxy ring into the proximal side to the imidazole rings because of steric repulsion compared with the corresponding C–C double bond and thus rotation of the imidazole–imidazole bond was not induced, accordingly. Although attempted racemization studies of **5** has not yet been achieved due to analytical difficulties by HPLC with a chiral column, racemization of **5** would be easier than that of **2** bearing olefin probably because of more flexible rotation of sp^3 methylene groups.

Conclusion

In summary, we have shown that functional group transformations of olefin moiety of novel bisimidazole derivatives of molecular asymmetry are achieved with several addition reactions that proceed in a *syn* manner. These addition reactions were suggested to proceed diastereoselectively because of the steric barrier caused by aromatic rings of bisimidazole. Successful resolution of the enantiomer of macrocyclic bisimidazole derivatives with a chiral column was shown in a preparative manner to isolate enantiopure bisbenzoimidazole and tetrabrominated bisimidazole. Studies on racemization behaviors revealed that several imidazole derivatives do not racemize up to 80 °C and slow racemization started to occur whereas the rate of racemization depended on the structure. Introducing epoxide to this macrocyclic alkene remarkably inhibited the racemization due to increasing of the activation energy for the rotation of the azole–azole bond. These results provide deeper understanding of the nature of a series of winding-vine-shaped molecular asymmetric compounds and further molecular design of such derivatives.

Experimental

General. NMR spectra were measured on a BRUKER Avance-500 (500 MHz for ^{1}H; 125 MHz for ^{13}C) at the Center for Support of Research and Education Activities of Kobe University. The chemical shifts are expressed in ppm with $CDCl_3$ (7.26 ppm for ^{1}H; 77.0 ppm for ^{13}C), DMSO-d_6 (2.54 ppm for ^{1}H; 39.5 ppm for ^{13}C) as internal standards. IR spectra were recorded on a Bruker Alpha with an ATR attachment (Ge). UV spectrum was measured by an ALS SEC-2000 UV/vis spectrometer. High resolution mass spectra (HRMS) were measured on a JEOL JMS-T100LP AccuTOF LC-Plus (ESI) with a JEOL MS-5414DART attachment. HPLC analysis was carried out with a JASCO LC-2000 Plus with chiral column Daicel Chiralpak IF (0.46 cm I.D. × 25 cm, flow rate: 1.0 mL min^{-1}) using hexane/ethanol (1:1) as an eluent and UV (254 nm) detector. Optical rotation was measured on a Horiba SEPA-300 polarimeter or JASCO P-2100 as a solution in a 1 dm^3 cell. CD spectrum was measured on a JASCO J-820 spectrometer. XRD analysis was carried out with a RINT-Ultima+2200. For thin layer chromatography (TLC) analyses throughout this work, Merck precoated TLC plates (silica gel

60 F_{254}) were used. Purification by HPLC with preparative SEC column (JAI-GEL-2H) was performed by JAI LC-9201.

Epoxidation of Macrocyclic Alkene 2. To a 25 mL Schlenk tube equipped with a magnetic stirring bar were added macrocyclic alkene **2** (31.4 mg, 0.1 mmol), anhydrous acetone (0.5 mL), and water (0.5 mL) under air atmosphere at room temperature. Then oxone (123 mg, 0.2 mmol) was added and stirring was continued for 12 h at 60 °C to confirm completion of the reaction by TLC analysis. Water was added to quench the reaction and the organic layer was separated. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried over anhydrous magnesium sulfate. The solution was concentrated under reduced pressure to leave a crude solid, which was purified by flash column chromatography on silica gel using hexane/isopropyl acetate (1:1) as an eluent to afford the corresponding epoxide **3** (20.6 mg, 62%). IR (ATR): 3053, 2963, 2925, 1484, 1460, 1421, 1382, 1357, 1333, 1283, 1246, 1185, 1157, 1134, 1007, 962, 922, 878, 798, 748 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.14–2.24 (m, 2H), 1.58 (d, $J = 9.69$ Hz, 2H), 2.32 (d, $J = 14.0$ Hz, 2H), 4.50 (d, $J = 14.6$ Hz, 2H), 5.10 (t, $J = 14.6$ Hz, 2H), 7.36–7.47 (m, 6H), 7.88–7.94 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 32.4, 40.5, 54.8, 110.1, 120.8, 123.4, 124.4, 134.0, 142.6, 143.5. HRMS (DART+) calcd. for $C_{20}H_{19}N_4O^+$ ($[M + H]^+$) 331.1559, found 331.1551.

Dihydroxylation of Macrocyclic Alkene 2. To a 25 mL Schlenk tube equipped with a magnetic stirring bar were added $K_2OsO_4 \cdot H_2O$ (4 mg, 0.01 mmol), NMO (62.5 µL, 0.3 mmol) anhydrous acetone (0.5 mL), and water (0.5 mL) under air atmosphere at room temperature. Then macrocyclic alkene **2** (62.8 mg, 0.2 mmol) was added and stirring was continued for 12 h at room temperature to confirm completion of the reaction by TLC analysis. Water was added to quench the reaction and the organic layer was separated. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried over anhydrous magnesium sulfate. The solution was concentrated under reduced pressure to leave a crude solid, which was purified by flash column chromatography on silica gel using dichloromethane/MeOH (10:1) as an eluent to afford the corresponding **4** (62.7 mg, 90%). Attempted HPLC analysis with a chiral column has not been successful so far. IR (ATR): 3330, 2929, 1464, 1417, 1369, 1281, 1240, 1202, 1167, 1158, 1124, 1098, 1064, 1019, 933, 902, 844, 811, 799 cm^{-1}. ^1H NMR (300 MHz): δ 1.63–1.73 (m, 2H), 1.98–2.08 (m, 2H), 2.24–2.32 (m, 2H), 4.03 (dt, $J = 4.0$, 14.5 Hz, 2H), 4.23 (d, $J = 7.7$ Hz, 2H), 4.66 (dd, $J = 5.2$, 15.1 Hz, 2H), 7.43 (dt, $J = 1.1$, 7.6 Hz, 2H), 7.50 (dt, $J = 1.1$, 7.7 Hz, 2H), 7.87 (d, $J = 8.0$ Hz, 2H), 7.90 (d, $J = 8.0$ Hz, 2H). ^{13}C NMR (125 MHz): δ 31.0, 40.9, 62.9, 112.1, 120.2, 123.1, 124.0, 133.8, 142.7, 144.1. HRMS (DART+) calcd for $C_{20}H_{21}N_4O_2^+$ ($[M + H]^+$) 349.1665, found 349.1659.

Hydrogenation of Macrocyclic Alkene 2. To a 25 mL Schlenk tube equipped with a magnetic stirring bar were added macrocyclic alkene **2** (31.4 mg, 0.1 mmol), Pd/C (10.6 mg 0.01 mmol), and anhydrous methanol (1.0 mL), under nitrogen atmosphere at room temperature. Then stirring was continued for 20 h at room temperature under H_2 atmosphere to confirm completion of the reaction by NMR analysis. The reaction solution was purified by flash column chromatography on silica gel using hexane/ethyl acetate (1:1) as an eluent to afford the corresponding macrocyclic alkane **5** (30.6 mg, 96%). IR (ATR): 2940, 1468, 1457, 1427, 1416, 1364, 1330, 1281, 1245, 1166, 746, 721, 664 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.22 (d, $J = 11.4$ Hz, 2H), 0.95–1.10 (br, 2H), 1.36 (t, $J = 13.5$ Hz, 2H), 2.00–2.12 (m, 2H), 4.35–4.44 (m, 4H), 7.34–7.42 (m, 4H), 7.46–7.51 (m, 2H), 7.86–7.91 (m, 2H) ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.6, 32.8, 41.4, 110.9, 120.8, 123.0, 123.8, 133.8, 143.2, 144.8. HRMS (DART+) calcd. for $C_{20}H_{21}N_4^+$ ($[M + H]^+$) 317.1766, found 317.1737.

Preparation of Di([*d*]-4,5-dibromoimidazo)[1,2-*a*:2,1-*c*]-1,8-diaza-7-(*E*)-cyclodecene 6. To a 25 mL Schlenk tube equipped with a magnetic stirring bar were added 4,4′,5,5′-tetrabromobisimidazole (0.83 g, 1.5 mmol) and 1,2-dichloroehtane (15 mL) under a nitrogen atmosphere at room temperature. Then, ZnI_2 (95 mg, 0.30 mmol) was added and stirring was continued for 0.5 h at room temperature. Grubbs 2nd generation catalyst (63 mg, 0.075 mmol) was added and the resulting mixture was stirred for 24 h at 80 °C. The reaction was confirmed to be complete by TLC analysis. Water was added to quench the reaction and the organic layer was separated. The aqueous layer was extracted with chloroform and the combined organic layers were dried over anhydrous magnesium sulfate. The solution was concentrated under reduced pressure to leave a crude solid, which was purified by flash column chromatography on silica gel using hexane/isopropyl alcohol (5:1) as an eluent to afford **6** (42 mg, 50%). IR (ATR): 2962, 2922, 1482, 1454, 1438, 1412, 1394, 1383, 1357, 1328, 1287, 1229, 1206, 1158, 1105, 1095, 1071, 1005, 973, 923, 908, 886, 802, 729, 680, 646, 628, 616 cm^{-1}. ^1H NMR (500 MHz): δ 1.90–2.02 (m, 2H), 2.26–2.34 (m, 2H), 4.13–4.31 (m, 4H), 4.40–4.52 (m, 2H). ^{13}C NMR (125 MHz): δ 33.1, 45.8, 105.4, 116.7, 129.0, 139.5. HRMS (DART+) calcd. for $C_{12}H_{11}Br_4N_4^+$ ($[M + H]^+$) 530.7677, found 530.7629.

Preparation of (−)-Di([*d*]-4,5-di(4-methyphenyl)imidazo)-[1,2-*a*:2,1-*c*]1,8-diaza-7(*E*)-cyclodecene 7. To a 25 mL Schlenk tube equipped with a magnetic stirring bar were added $[Pd_2(dba)_3] \cdot CHCl_3$ (14 mg, 0.014 mmol), PPh_3 (29 mg, 0.11 mmol), and anhydrous DMF (0.5 mL) under a nitrogen atmosphere at room temperature. After stirring for 0.5 h at room temperature, chiral (−)-**6** (49 mg, 0.092 mmol, 99% ee), which was separated with a preparative chiral column (Daicel Chiralpak IF) using hexane/ethanol = 1:1 as an eluent, dissolved in 1.0 mL of DMF was added to the mixture. Then, 4-methylphenylboronic acid pinacol ester (0.120 g, 0.55 mmol) and potassium carbonate (0.10 g, 0.73 mmol) were added. Further stirring was continued for 90 h at 80 °C and completion of the reaction was confirmed by TLC analysis. Water was added to quench the reaction and the organic layer was separated. The aqueous layer was extracted with chloroform and the combined organic layers were dried over anhydrous magnesium sulfate. The solution was concentrated under reduced pressure to leave a crude oil, which was purified by flash column chromatography on silica gel using hexane/isopropyl acetate (5:1) as an eluent to afford the corresponding coupling product (−)-**7** (30 mg, 52%). The enantioselectivity was estimated by HPLC analysis with a chiral column (Daicel IF) using hexane/ethanol = 1:1 as an eluent to exhibit 91% ee. $[\alpha]_D^{24} = -76.8$ (*c* 1.0, $CHCl_3$); IR (ATR): 3022, 2963, 2920,

1558, 1543, 1520, 1492, 1545, 1422, 1405, 1373, 1354, 1338, 1323, 1232, 1204, 1183, 1120, 974, 963, 823, 739 cm^{-1}. ^1H NMR (300 MHz): δ 1.75–1.93 (m, 2H), 1.99–2.11 (m, 2H), 2.28 (s, 6H), 2.46 (s, 6H), 3.93 (d, $J = 13.9$ Hz, 2H), 4.48 (t, $J = 12.9$ Hz, 2H), 4.57–4.69 (m, 2H), 7.02 (d, $J = 8.1$ Hz 4H), 7.32 (dd, $J = 8.4$, 10.3 Hz, 8H), 7.44 (d, $J = 8.03$ Hz, 4H). ^{13}C NMR (125 MHz): δ 21.1, 21.4, 34.0, 53.4, 126.4, 128.8, 129.4, 129.7, 130.0, 130.2, 130.9, 131.0. HRMS (DART+) calcd. for $C_{40}H_{39}N_4^+$ ($[M + H]^+$) 575.3175, found 575.3181.

Preparation of (+)-Di([*d*]-4-bromoimidazo)[1,2-*a*:2,1-*c*]-1,8-diaza-7(*E*)-cyclodecene 8. To a 25 mL Schlenk tube equipped with a magnetic stirring bar were added chiral macrocyclic alkene (−)-**6** (38.5 mg, 0.073 mmol, 99% ee) and anhydrous tetrahydrofuran (THF) under nitrogen atmosphere at room temperature. Then 0.93 M EtMgCl in THF was added slowly at 0 °C, and the resulting mixture was stirred for 5 h at room temperature. Water was added to the reaction mixture to stop the reaction and the organic layer was extracted with chloroform. After concentration under reduce pressure, the residue was purified by flash column chromatography on silica gel using hexane/*i*PrOAc (1:1) as an eluent to afford the corresponding (+)-**8** (15.7 mg, 58%). The enantioselectivity was estimated by HPLC analysis with a chiral column (Daicel Chiralpak IF) using hexane/ethanol = 1:1 as an eluent to exhibit 93% ee. IR (ATR): 3137, 2919, 2850, 1500, 1455, 1421, 1407, 1394, 1354, 1289, 1240, 1158, 1122, 1055, 1004, 980, 956, 926, 802, 755, 741 cm^{-1}. ^1H NMR (300 MHz): δ 2.21–2.30 (m, 2H), 2.62 (d, $J = 12.8$ Hz, 2H), 4.29 (dt, $J = 14.0$, 3.47, 2H), 4.54 (ddd, $J = 2.29$, 12.9, 14.0 Hz, 2H), 4.77–4.81 (m, 2H), 7.54 (s, 2H). ^{13}C NMR (125 MHz): δ 35.0, 46.2, 114.7, 120.0, 129.7, 139.0. HRMS (DART+) calcd. for $C_{12}H_{12}N_4Br_2^+$ ($[M + H]^+$) 372.9487, found 372.9489.

Preparation of Chiral Epoxide 3. To a 25 mL Schlenk tube equipped with a magnetic stirring bar were added chiral macrocyclic alkene **2** (31.4 mg, 0.1 mmol, 99% ee) and $CHCl_3$ (1.0 mL) under aerobic atmosphere at 60 °C. Then, *m*CPBA (54 mg, 0.5 mmol) was added and stirring was continued for 16 h at 60 °C to confirm completion of the reaction by TLC analysis. Water was added to quench the reaction and the organic layer was separated. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried over anhydrous magnesium sulfate. The solution was concentrated under reduced pressure to leave a crude solid, which was purified by flash column chromatography on silica gel using hexane/isopropyl acetate (1:1) as an eluent to afford the corresponding epoxide **3** (11.6 mg, 35%). The enantioselectivity was estimated by HPLC analysis with a chiral column (Daicel IF) using hexane/ethanol = 1:1 as an eluent to exhibit 99% ee. $[\alpha]_D^{24} = +41.4$ (*c* 0.39 $CHCl_3$).

This work was supported by Kakenhi, MEXT Japan (No. 24655083) and Special Coordination Funds for Promoting Science and Technology, Creation of Innovation Centers for Advanced Interdisciplinary Research Areas (Innovative Bioproduction Kobe). The authors thank Professor Takashi Nishino for fruitful discussion on XRD analysis and Professors Akihiko Kondo, Chiaki Ogino, and Satoru Wakai for measurement of CD spectra.

Supporting Information

Further experimental details, HPLC profiles on racemization behaviors, and spectroscopic data. This material is available free of charge on J-STAGE.

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18 Although the use of oxone as an oxidant resulted in a superior yield, slight racemization was observed. (>99% ee to 90% ee).
19 The Gibbs free energy for the racemization of **2** at 100 °C has been estimated as 130 kJ mol^{-1} in our previous report.[9]

