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Ring Closing Metathesis Using Chiral Template Consisting of Hard and Soft Parts

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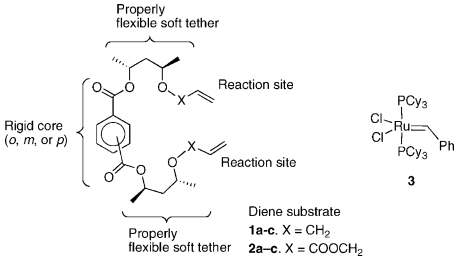
Summary: Macrocyclic compounds having 18-, 19-, 22-, and 23-membered rings were prepared quantitatively by ring closing metathesis of diene substrates consisting of a rigid *o*- or *m*-phthalate group and flexible but geometrically regulated 2,4-pentanediol tethers. From the *p*-phthalate analogues, the ring closing metathesis and the cyclic dimmer formation were observed to give 24-membered ring (70% yield) and 40-membered ring (65% yield) respectively.

Keywords: cyclization; dimer; metathesis; macrocycle; template

Introduction

Formation of macrocycles from a liner compound is still challenging issue. Ring closing metathesis is a newer class of the cyclization method, but many examples have already been reported by tuning the catalyst structure as well as the reaction conditions.[1] However, due to the equilibrium nature of the metathesis, kinetic control to perform the desired cyclization is often difficult.[2–4] In this report, we would like to present ring closing metathesis to give macrocycles starting from substrates that have a rigid core at the center of the molecule and flexible but properly regulated tether parts connecting olefins to the core. Three isomers of phthalate were employed as the rigid cores, and (2*R*,2*R*)-2,4-pentanediol was used as the properly flexible soft tether.



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The 2,4-pentanediol tether has been used to control the stereoselectivity of the intramolecular reaction. The tether is sufficiently flexible to allow the intramolecular reaction, but the flexibility is limited within a certain field to achieve strict regio- and stereoselectivities.[5] In addition to the cyclization efficiencies, the present study is concerned with the *E*/*Z*-stereoselectivity caused by the template structure.

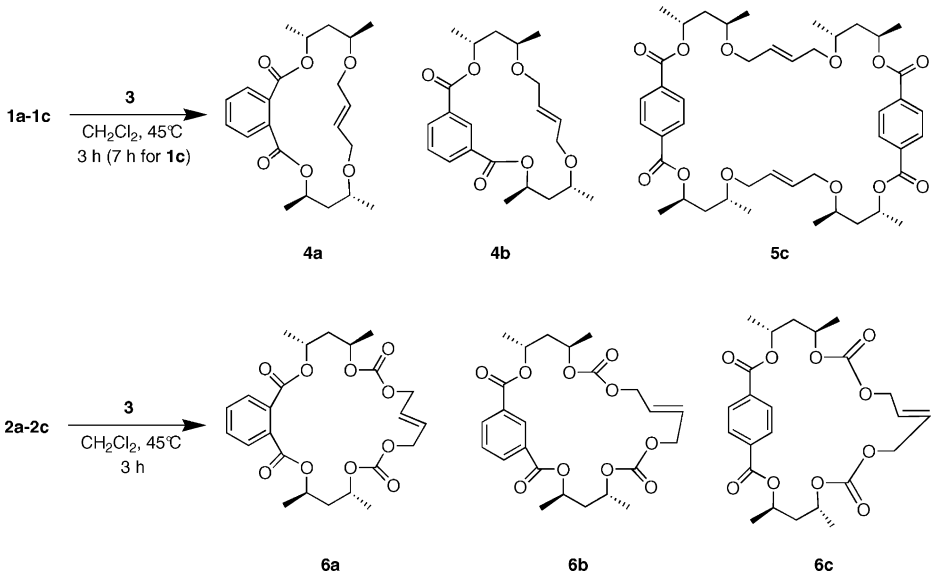
Results and Discussion

Two sets of the regioisomeric substrates, **1a-c** and **2a-c**, were prepared for the present study. Mono-allyl ether and mono-allylcarbonate of optically active (2*R*,4*R*)-2,4-pentanediol were prepared, and then introduced to *o*-, *m*-, or *p*-phthalic acid by the dehydration using 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (3.0 equiv.) in the presence of 4-dimethylaminopyridine (0.2 equiv.) in dichloromethane (85–90% yield). The substrate added to a solution of precatalyst **3** (5 mol%) in CH_2Cl_2 at 45 °C (substrate concentration: 10–15 mmol dm^{-3}). Except for **1c**, the metathesis occurred smoothly and completed within 3 h. The reaction of **1c** was a little sluggish, and took 7 h to complete the reaction. Stereoselectivity of *E*/*Z* at the generated olefin was determined by the ^1H NMR, and was assigned by removal of the phthalate part by the

$LiAlH_4$ reduction and comparing with the known isomers. The molecular weight of the product was determined on the basis of ESI-MS analyses. The product structures are shown in Scheme 1. The isolated yields and *E*/*Z*-ratios are summarized in Table 1.

The reaction of the *o*-phthalates **1a**, **2a** and *m*-phthalates **1b**, **2b** gave single products **4a–b** and **6a–b**, respectively and no other side products were detected (<1%). The ring size of the products, **4a**, **4b**, **6a** and **6b** are 18, 19, 22 and 23 respectively. The obtained products were assigned to be cyclic monomers by the careful MS analyses. The produced ring size was 18-membered ring for **4a**, 19-membered ring for **4b**, 22-membered ring for **6a**, and 23-membered ring for **6b**. Quantitative formation of such macrocyclic compounds in different ring sizes are outstanding, and must be due to the proper rigidity and flexibility of the template.

In the case of *p*-phthalate **1c** the efficiency for the ring closing metathesis was lower. When **1c** was treated with **3** under the same conditions as above, cyclic monomer **4c** was not produced at all, but cyclic dimer **5c** was obtained in 65% yield and was almost in the *E*-form. Since the metathesis could give paracyclophanes smaller than 20-membered ring,[6] the unsuccessful ring closure of **1c** did not



Scheme 1.
Templated metathesis reactions of **1a-c** and **2a–c** with precatalyst **3**.

Table 1.
Product yield and stereoselectivity for the metathesis of **1** and **2**.

No.	Substrate		Product yield and *E*/*Z* ratio[a]	
	Phthalate	$-X-CH=CH_2$	Cyclic monomer	Other product
1a	*ortho*-	allyl	**4a**. 98% (74: 26)	< 1%
1b	*meta*-	allyl	**4b**. 98% (>96: <4)	< 1%
1c	*para*-	allyl	**4c**. < 1%	Cyclic dimer (**5c**) 65% (>95: <5)[b]
2a	*ortho*-	allyloxycarbonyl	**6a**. 98% (82:18)	< 1%
2b	*meta*-	allyloxycarbonyl	**6b**. 98% (80: 20)	< 1%
2c	*para*-	allyloxycarbonyl	**6c**. 70% (90: 10)	< 5%[b]

[a]Shown in parentheses.[b]The major side product was a mixture of polymeric high molecular weight compounds.

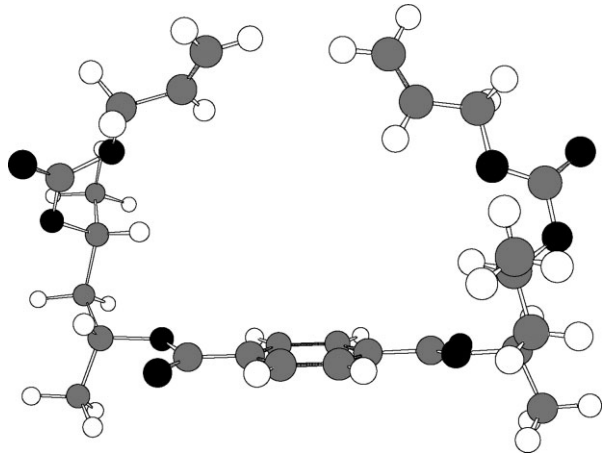
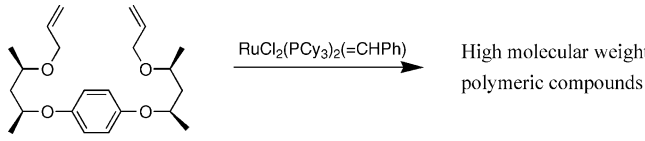


Figure 1.
One of the stable conformers of **2c** estimated by the MO calculation at the AM-1 level.



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Scheme 2.
Approach of metathesis reaction using substrate **7**.

simply originate from insufficient length of the tether but the olefins could not reach the reaction position due to the tether regulation. It should be noted that the high efficiency and high *E*-selectivity from **1c** to **5c** should be due to the effects of the template including the initially produced olefin. In contrast, the reaction of **2c** proceeded smoothly, and gave the cyclic monomer **6c** in 70% yield ($E/Z = 90/10$), which is a paracyclophane having 24-membered ring.

Figure 1 indicates one of the stable conformers of **2c** estimated by the MO calculation at the AM-1 level. The 2,4-pentanediol tether regulates the geometry of the olefins to make them close, but does not fix the positions tightly. The template geometrically shut the two olefins in a certain common space to promote their intermolecular metathesis reaction.

Use of the template having a rigid core and soft tethers was found to be effective to perform the ring closing metathesis, unless the two olefins could reach to the each reaction site. Substrate **1c** showed such kind of exception. Substrate **7** displays another limitation of the present template design. The substrate, a precursor for the 18-membered ring, was prepared from mono-allyl (2*R*,4*R*)-2,4-pentanediol and hydroquinone by the Mitsunobu reaction. By the treatment of **7** with **3**, neither cyclic monomer nor cyclic dimer was detected (<1%), but high molecular weight polymeric compound was obtained. The two terminal olefins in **7** are overreached to perform intramolecular metathesis reaction both in the liner monomer **7** and the liner dimer of **7**.

Conclusion

Seven diene substrates were tested for the metathesis with the $RuCl_2(PCy_3)_2(=CHPh)$

(**3**). The five substrates gave the ring closing metathesis, while the one resulted in the cyclic dimer. The very high yields were obtained for a certain range of the products, and that must indicates properness of the template structure having the rigid core and soft tether. The obtained cyclic products containing different oxy-functional groups may work as host molecules for cationic species.

Experimental Part

General

The catalyst **3** was obtained from Aldrich. All solvents and chemicals were used after proper purifications. The NMR spectra were recorded on a JEOL ECA-600 (600.17 MHz for ^{1}H; 150.92 MHz for ^{13}C) spectrometer in $CDCl_3$. ESI-MS was obtained on a JEOL JMS-T100LC. All the reactions were carried out under nitrogen atmosphere.

Metathesis Conditions

To a solution of catalyst **3** (5 mg, 6 μmol) in dry methylene chloride (10 mL) was added substrate (0.12 mmol). After stirring the mixture at 45 °C for 3 hours (7 h for **1c**), the reaction mixture was concentrated and purified on silica gel (3–6% AcOEt in hexane).

Spectral Data

4a: IR (neat) 2968, 2924, 2868, 2361, 2338, 1722, 1445, 1350, 1315, 1289, 1151, 1107, 1068, 750 cm^{-1}; ^{1}H NMR δ 7.58-7.46 (AA′ BB′, 4H), 5.92 (t-like, $J = 3.4$ Hz, 2H), 5.64 (m, 2H), 4.38 (m, 0.7H, minor component), 4.17 (m, 1.3H, major), 3.95 (dd, $J = 9.8$, 4.8 Hz, 0.7H, minor), 3.85 (m, 1.3H, major), 3.74 (m, 1.3H, major), 3.65 (m, 0.7H, minor), 1.69 (m, 4H), 1.33 (d, $J = 6.5$ Hz, 2H, minor), 1.32 (d, $J = 6.4$ Hz, 4H, major), 1.14 (d, $J = 6.1$ Hz, 2H, minor) 1.10 (d, $J = 6.2$ Hz, 4H); ^{13}C NMR δ 167.60 (minor), 166.96 (major), 133.73 (minor), 133.19 (major), 131.38 (minor), 130.40 (major), 130.36 (C × 2), 128.07 (major), 127.68 (minor), 70.85 (minor), 70.06 (major), 68.74 (major), 68.69 (minor), 68.16 (major), 63.75 (minor), 44.65 (major), 44.47 (minor), 21.09 (major), 20.95 (minor), 19.91 (minor), 19.42 (Major); HRMS (ESI) m/z ($M + Na^+$) calcd for $C_{22}H_{30}NaO_6$ 413.1941, found 413.1940. **4b**: IR (neat) 2976, 2933, 2360, 2337, 1718, 1455, 1438, 1377, 1355, 1304, 1246, 1142, 1095, 732 cm^{-1}; ^{1}H NMR δ 8.59 (s, 1H), 8.11 (d, $J = 7.6$ Hz, 2H), 7.47 (t, $J = 7.6$ Hz, 1H), 5.44–5.38 (m, 4H), 3.89 (d like, $J = 12.4$ Hz, 2H), 3.69 (d like, $J = 9.6$ Hz, 2H), 3.59 (m, 2H), 1.92 (ddd, $J = 15.2$, 9.4, 2.0 Hz, 2H), 1.72 (ddd, $J = 14.8$, 8.3, 2.7 Hz, 2H), 1.37 (d, $J = 6.50$ Hz, 6H), 1.10 (d, $J = 18$ Hz, 6H); ^{13}C NMR δ 165.63, 132.85, 131.50, 131.16, 129.47, 128.29, 70.85, 68.78, 68.46, 41.99, 20.53, 19.48; HRMS (ESI) m/z ($M + Na^+$) calcd for $C_{22}H_{30}NaO_6$ 413.1941, found 413.1942. **5c**: IR (neat) 2970, 2929, 2855, 2360, 2337, 1716, 1455, 1407, 1376, 1268, 1150, 1018, 732 cm^{-1}; ^{1}H NMR 8.03 (m, 8H), 5.52 (t, $J = 6.9$ Hz, 4H), 5.43 (m, 2H), 5.32 (m, 2H), 3.92 (ddd, $J = 22.3$, 11.5, 3.7 Hz, 4H), 3.82 (m, 4H), 3.48 (m, 2H), 3.37 (m, 2H), 1.80 (m, 4H), 1.70 (m, 2H), 1.60 (m, 2H), 1.40 (d, $J = 6.5$ Hz, 6H), 1.35 (d, $J = 6.2$ Hz, 6H), 1.19 (d, $J = 6.18$ Hz, 6H), 1.16 (d, $J = 6.2$ Hz, 6H); ^{13}C NMR δ 166.39, 135.20, 129.66, 129.49, 129.46, 71.53, 71.46, 69.86, 69.66, 46.31, 20.90, 20.76; HRMS (ESI) m/z ($M + Na^+$) calcd for $C_{44}H_{60}NaO_{12}$ 803.3982, found 803.3992. **6a**: IR (neat) 2982, 2937, 2360, 2341, 1743, 1729, 1449, 1380, 1263, 1142, 1069, 787 cm^{-1}; ^{1}H NMR δ 7.71-7.67 (m, 2H), 7.51-7.47 (m, 2H), 5.72 (t, $J = 3.5$ Hz, 0.20H, *cis*), 5.68 (t, $J = 2.76$ Hz, 1.80H, *trans*), 5.34 (m, 2H), 5.02 (m, 2H), 4.75 (dd, $J = 12.4$, 1.4 Hz, 2H), 4.28 (dd, $J = 12.4$, 1.4 Hz, 2H), 1.92 (m, 4H), 1.34 (d, $J = 6.5$ Hz, 6H), 1.32 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR δ 166.46, 154.04, 132.39, 130.68, 128.78, 127.19, 71.59, 68.16, 66.24, 41.98, 20.39; HRMS (ESI) m/z ($M + Na^+$) calcd for $C_{24}H_{30}NaO_{10}$ 501.1737, found 501.1734. **6b**: IR (neat) 2988, 2923, 2858, 2364, 2337, 1743, 1716, 1455, 1390, 1259, 1145, 1114, 1076, 733 cm^{-1}; ^{1}H NMR δ 8.16 (s, 1H), 8.21 (d, $J = 2.0$ Hz, 1H), 8.20 (d, $J = 2.0$ Hz, 1H), 7.50 (t, $J = 7.6$ Hz, 1H), 5.54 (t, $J = 4.1$ Hz,

0.4H, *cis*), 5.50 (t, $J = 2.8$ Hz, 1.6H, *trans*), 5.37 (m, 2H), 5.09 (m, 2H), 4.60 (dd, $J = 12.5$, 1.4 Hz, 2H), 4.30 (dd, $J = 12.5$, 1.4 Hz, 2H), 2.06 (ddd, $J = 15.6$, 9.7, 2.8 Hz, 2H), 1.94 (ddd, $J = 15.2$, 8.7, 2.8 Hz, 2H), 1.36 (d, $J = 6.5$ Hz, 6H), 1.32 (d, $J = 6.5$ Hz, 6H). ^{13}C NMR δ 165.15, 154.12, 133.76, 130.96, 130.60, 128.29, 127.23, 71.31, 67.66, 66.54, 40.80, 20.39, 20.25; HRMS (ESI) *m*/*z* ($M + Na^+$) calcd for $C_{24}H_{30}NaO_{10}$ 501.1737, found 501.1595. **6c**: IR (neat) 2981, 2928, 2360, 2332, 1742, 1715, 1505, 1455, 1381, 1273, 1103, 1080, 1018, 731 cm^{-1}; ^{1}H NMR δ 8.05 (s, 4H), 5.47 (t, $J = 2.8$ Hz, 2H), 5.46–5.43 (m, 2H), 5.08 (m, 2H), 4.43 (dd, $J = 12.4$, 1.4 Hz, 2H), 4.33 (dd, $J = 12.4$, 1.4 Hz, 2H), 2.06 (ddd, $J = 15.5$, 8.1, 2.8 Hz, 2H), 2.0 (ddd, $J = 15.5$, 7.7, 2.8 Hz, 2H), 1.39 (d, $J = 6.2$ Hz, Hz, 6H), 1.33 (d, $J = 6.2$ Hz, 6H); ^{13}C NMR δ 165.17, 154.12, 134.26, 129.37, 127.11, 71.39, 67.86, 66.67, 39.96, 20.07, 19.98; HRMS (ESI) *m*/*z* ($M + Na^+$) calcd for $C_{24}H_{30}NaO_{10}$ 501.1737, found 501.1665.

[1] (a) M. Schuster, S. Blechert, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036. (b) A. Deiters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199. (c) R. R. Schrock, C. Czekelius, *Adv. Synth. Catal.* **2007**, *349*, 55. (d) C. Samojlowicz, M. Bieniek, K. Grela, *Chem. Rev.* **2009**, *109*, 3708.

[2] S. J. Miller, S. –H. Kim, Z. –R. Chen, R. H. Grubbs, *J. Am. Chem. Soc.* **1985**, *117*, 2108.

[3] A. Fürstner, in: *Templated Organic Synthesis*, Ed. by F., Diedrich, P. J. Stang, Wiley-VCH, Weinheim, **2000**, pp. 249–273.

[4] S. Monfette, D. E. Fogg, *Chem. Rev.* **2009**, *109*, 3783.

[5] T. Sugimura, in: *Recent Research Developments in Organic Chemistry*, Vol. 2 (Ed., G. Pandalai), Transworld Research Network, Trivandrum **1998**, pp. 47–53. T. Sugimura, *Euro. J. Org. Chem.* **2004**, 1185.

[6] For the metathesis of *p*-phenyl substituted dienes, see: J. Tae, Y. K. Yang, *Org. Lett.* **2003**, *5*, 741.

