Efficient Synthesis of Macrocyclic Paracyclophanes by Ring-Closing Metathesis Dimerization and Trimerization Reactions
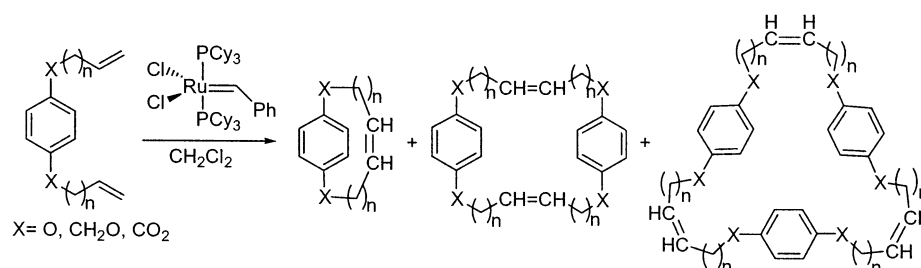
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ABSTRACT

Ring-closing metathesis reactions of para-disubstituted aromatic substrates produced macrocyclic [*n.n*]-, and [*n.n.n*]paracyclophanes efficiently through dimerization and trimerization reactions. Sufficiently long alkyl chains allowed direct monocyclizations to yield [*n*]paracyclophanes. A small library of paracyclophanes were generated by the combinatorial cross-metathesis approach.

Cyclophanes are unique in their structures and have interesting electronic properties. Recently, the functional properties of cyclophanes have drawn great attention.[1] Large cyclophanes can form inclusion complexes with metal ions, and small cyclophanes can make charge-transfer complexes. The [2.2]paracyclophanes have served as building blocks for many functional devices.[1b] Although much synthetic effort has been given toward the synthesis of paracyclophanes, the efficient synthesis of various sizes of macrocyclic paracyclophanes is still challenging. Typically, [2.2]paracyclophanes have been studied most extensively.

Ring-closing metathesis (RCM) reaction[2] is an attractive method for the synthesis of macrocyclic [*n*]paracyclophane (**1**), [*n.n*]paracyclophane (**2**), and [*n.n.n*]paracyclophane (**3**) (Figure 1). One of the special attractive features of ring-
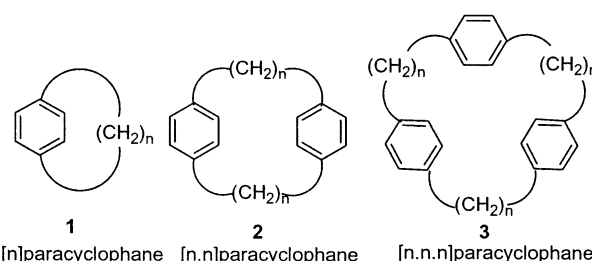

**Figure 1.** [*n*], [*n.n*], and [*n.n.n*]paracyclophanes.

closing olefin metathesis is macrocyclic dimerization (or trimerization) reaction, which operates when two reacting alkene termini are conformationally inaccessible for simple

(1) For reviews on paracyclophanes, see: (a) Vögtle, F.; Seel, C.; Windscheif, P.-M. *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Pergamon: Oxford, 1996; Vol. 2, Chapters 1 and 6. (b) Tsuji, T.; Ohkita, M.; Kawai, H. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 415–433. (c) De Meijere, A.; Koenig, B. *Synlett* **1997**, 1221–1232. (d) Tochtermann, W.; Kraft, P. *Synlett* **1996**, 1029–1035. (e) Kane, V. V.; De Wolf, W. H.; Bickelhaupt, F. *Tetrahedron* **1994**, *50*, 4575–4622.

cyclization to monomers. However, this type of macro-cyclization reaction is not well studied in the literature.[3-6] Up to now, only a few olefin metathesis macrocyclizations have been applied for the synthesis of natural paracyclophane compounds.[3,7] Herein we report an efficient synthesis of ether-linked [*n*]-, [*n.n*]-, and [*n.n.n*]paracyclophanes by ring-closing metathesis reactions.

The para-disubstituted substrates **5a–d** and **7a–b** were prepared by alkylation reactions of the corresponding diols **4** and **6** with suitable ω-alkenyl bromides (Scheme 1).

**Scheme 1.** Synthesis of Substrate Dienes[a]
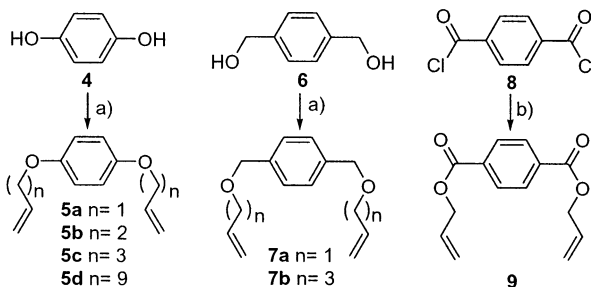
[a] Conditions: (a) NaH (2.4 equiv), *n*-Bu$_4$NI (cat.), DMF, Br-(CH$_2$)$_n$CH=CH$_2$ (3 equiv), 25 °C; (b) Et$_3$N, CH$_2$Cl$_2$, HOCH$_2$-CH=CH$_2$, from 0 to 25 °C.

Compound **9** was prepared from the terephthaloyl chloride (**8**) and allyl alcohol in the presence of triethylamine.

All substrates were reacted under the identical reaction conditions to compare product distributions for each substrate (Scheme 2). The results of the metathesis reactions were summarized in Table 1.[8] Reaction of **5a** (the substrate with the smallest alkyl chain) with 10 mol % Grubbs' catalyst (**10**) under refluxing dichloromethane solution (0.005 M concentration) furnished a single dimeric product **13a** in 74% isolated yield (Table 1, entry 1).[9] The next homologue **5b** (X = O, *n* = 2) cyclized into the dimer **13b** and trimer **14b** in 42 and 35% yields, respectively (Table 1, entry 2). Compound **5c** (X = O, *n* = 3) provided dimer **13c** in 81% yield (Table 1, entry 3). When benzyl ether was employed

Scheme 2. Ring-Closing Metathesis Macrocyclizations[a]

X= O, CH$_2$O, CO$_2$ Mes= C$_6$H$_2$-2,4,6-(CH$_3$)$_3$
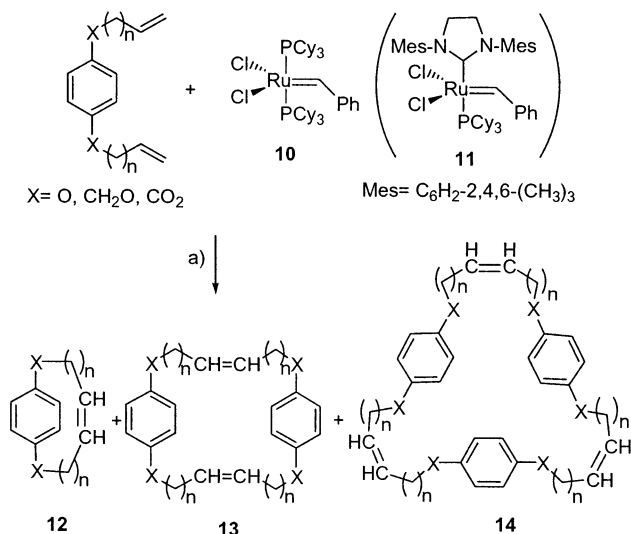
[a] Conditions: (a) 10 mol % **10** (or **11**), CH$_2$Cl$_2$, 45 °C, 0.005 M.

as in **7a** (X = CH$_2$O, *n* = 1), dimer **13e** (72%) and trimer **14e** (23%) were obtained (Table 1, entry 5). Substrate **9**, which is less reactive due to ester linkage, required more reactive catalyst **11**[10] to produce trimer **14g** (60%) (Table 1, entry 7). Use of catalyst **10** with (or without) Ti(O*i*Pr)$_4$ failed to give any desired products.[11]

Substrates with longer chains provided monomers in the metathesis macrocyclizations. Metathesis of **5d** (X = O, *n* = 9) furnished monomer **12d** (33%) along with dimer **13d** (47%) (Table 1, entry 4). Interestingly, **7b** (X = CH$_2$O, *n* = 3) transformed exclusively into the monomer **12f** (70%) with no dimer or trimer formation observed (Table 1, entry 6). The monomer **12f** was clearly distinguishable from the dimer by NMR data. The vinyl protons (δ 4.41) of **12f** shifted upfield due to aromatic ring current effects. However, those of larger ring monomer **13d** (δ 5.34) and dimer **13a** (δ 5.81) experience little or no such effects (Figure 2).
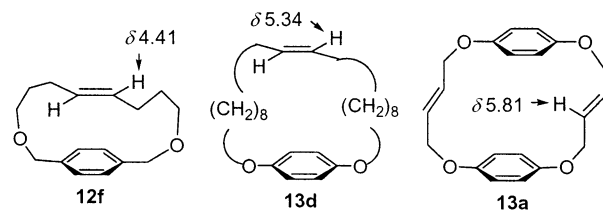

Figure 2. Selected ^{1}H NMR chemical shift of vinyl protons.

At this point, we were curious about the result of cross-metathesis ring closure of two different alkenes. This type

(2) For reviews on metathesis, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (b) Chang, S.; Grubbs, R. H. *Tetrahedron* **1998**, *54*, 4413−4450.

(3) (a) Smith, A. B., III; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925−5937. (b) Smith, A. B., III; Kozmin, S. A.; Adams, C. M.; Paone, D. V. *J. Am. Chem. Soc.* **2000**, *122*, 4984−4985. (c) Smith, A. B., III; Adams, C. M.; Kozmin, S. A. *J. Am. Chem. Soc.* **2001**, *123*, 990−991.

(4) (a) Paquette, L. A.; José, M.-A. *Tetrahedron Lett.* **2001**, *42*, 967−970. (b) Paquette, L. A.; Fabris, F.; Tae, J.; Gallucci, J. C.; Hofferberth, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 3391−3398.

(5) Chen, G.-W.; Kirschning, A. *Chem. Eur. J.* **2002**, *8*, 2717−2729.

(6) Lee, C. W.; Grubbs, R. H. *J. Org. Chem.* **2001**, *66*, 7155−7158.

(7) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773−775.

(8) All new compounds were characterized by FAB-MS and other spectroscopic data.

(9) (*E,E*)-Stereochemistry of **13a** was confirmed by an alternative synthesis from hydroquinone, *trans*-1,4-dichloro-2-butene, and K$_2$CO$_3$ under refluxing acetonitrile according to the modified literature procedure (Vartanyan, S. A.; Akopyan, T. R.; Paronikyan, E. G.; Darbinyan, G. A. *Arm. Khim. Zh.* **1980**, *33*, 308−310).

(10) Scholl, M.; Ding, S.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(11) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130−9136.

Table 1. Metathesis of Alkene Substrates[a]

entry	starting diene	reaction time (h)	monomer	dimer	trimer	total yield (%)
1	**5a** X = O, n = 1	14		**13a** (74)		74
2	**5b** X = O, n = 2	32		**13b** (42)[c]	**14b** (35)	77
3	**5c** X = O, n = 3	20		**13c** (81)[c]		81
4	**5d** X = O, n = 9	21	**12d** (33)	**13d** (47)		80
5	**7a** X = CH₂O, n = 1	21		**13e** (72)	**14e** (23)	95
6	**7b** X = CH₂O, n = 3	21	**12f** (70)			70
7	**9** X = CO₂, n = 1	22			**14g** (60)	60[d]

^{a} Conditions: 10 mol % **10**, CH₂Cl₂, 45 °C, 0.005 M. ^{b} Isolated yields. Single isomers, (E,E) or (Z,Z), were obtained for most cases except **13b** and **13c**. ^{c} (E,Z)-Isomers were obtained. The (E,Z) double bonds in **13b** and **13c** were reduced to the corresponding alkanes (Scheme 3). Full characterizations of (E,Z)-products were performed at this stage. ^{d} Catalyst **11** (7 mol %) was used.

of mixed ring closure could create compound libraries of macrocyclic paracyclophanes (Table 2). To minimize problems anticipated from the heterocoupling reactions, we first carefully selected substrates that cyclized into dimers only from Table 1. Substrates **5a** and **5c** were clearly the best combination. When substrates **5a** and **5c** were mixed together and treated with Grubbs' catalyst **10** under standard cyclization conditions, heterodimer **17** (25%) was formed in addition to homodimers **13a** (30%) and **13c** (34%) (Table 2, entry 2). Double bonds of compound **17** were reduced to give the known compound **15**, which was synthesized previously from dimerization of **5b** (Scheme 3).

It is noteworthy that the reaction rates were significantly slowed for the cyclization of heteromixtures (required 30 h for the mixture of **5a** and **5c**) compared to those of the homocoupling reactions (required 14 h for **5a** and 20 h for **5c**). The pairs of **5a**/**5d** and **5c**/**7a** produced heterodimers **18** (40%) and **19** (25%), respectively, along with homodimers (Table 2, entries 3 and 5). On the other hand, the pairs of **5a**/**5b**, **5a**/**7a**, and **5c**/**7b** yielded no heterodimers (Table 2, entries 1, 4, and 6). The product distributions observed in

the homocoupling reactions (see Table 1) were reserved in the heterocoupling reactions with only minor deviations.

Scheme 3. Reduction of Double Bonds[a]
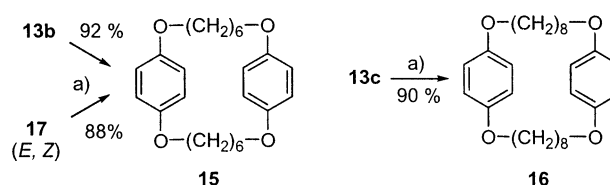
^{a} Conditions: (a) 10% Pd–C, H₂ (1 atm), CH₂Cl₂, 25 °C.

Controlled experiments revealed the order of reactivity of substrates with different chain lengths in the metathesis macrocyclizations. The relative rates of substrate consumptions and product appearances monitored by TLC analysis can be summarized as follows: **5c** > **5a**, **5a** > **5d**, **5c** > **5d**, **5a** > **5b**, **5a** > **7a**, **5c** > **7b**, and **5c** > **7a**. Therefore, the

Table 2. Cross-Metathesis of Alkene Mixtures[a]

homodimers   heterodimer

entry	starting dienes	reaction time (h)	monomer	homodimers	homotrimer	heterodimer	total yield (%)
1	**5a** + **5b**	33		**13a** (41) + **13b** (17)	**14b** (6)		64
2	**5a** + **5c**	30		**13a** (30) + **13c** (34)		**17** (25)[c]	89
3	**5a** + **5d**	36	**12d** (11)	**13a** (24) + **13d** (9)		**18** (40)[c]	84
4	**5a** + **7a**	35		**13a** (38) + **13e** (25)	**14e** (11)		74
5	**5c** + **7a**	37		**13c** (30) + **13e** (21)	**14e** (9)	**19** (25)	85
6	**5c** + **7b**	36	**12f** (22)	**13c** (31)			53
7	**5c** + **5d**	35	**12d** (20)	**13c** (19) + **13d** (25)		**20** (21)[c]	85
8	**5a** + **5c** + **7a**	44		**13a** (13) + **13c** (16) + **13e** (14)		**17** (20) + **19** (18)	81

^{a} Conditions: 10 mol % **10**, CH₂Cl₂, 45 °C, 0.005 M. ^{b} Isolated yields. ^{c} (E,Z)-Heterodimers were obtained.

relative rate order is **5c** (X = O, n = 3) > **5a** (X = O, n = 1) > **5b** (X = O, n = 2), **7a** (X = CH_2O, n = 1), **5d** (X = O, n = 9). The substrate **5c** with the medium chain length (X = O, n = 3) cyclized faster than the shorter or the longer ones in the macrocyclization reactions.

Finally, we tried cross-metathesis with three different alkene substrates to generate higher diversity. The combination of **5a**, **5c**, and **7a** produced five different dimers in 81% combined total yield (Table 2, entry 8). Products include two heterodimers [**17** (20%), **19** (18%)] and three homodimers [**13a** (13%), **13c** (16%), **13e** (14%)].

The observed efficient metathesis macrodimerization and -trimerization are noteworthy because only a few productive metathesis dimerizations are known in the literature[3−6] and efficient metathesis trimerizations are unknown to the best of our knowledge except for minor side product formations in the course of macrocyclizations.[5]

In conclusion, we have demonstrated efficient synthesis of macrocyclic [n]-, [$n.n$]-, and [$n.n.n$]paracyclophanes by ring-closing metathesis reactions. The cyclization modes depend on the chain lengths of alkenyl ethers. Short chains produced mainly [$n.n$]- and [$n.n.n$]paracyclophanes through dimerization and trimerization reactions. Sufficiently long alkyl chains allowed direct monocyclization to yield [n]-paracyclophanes. In addition, we were able to generate a small library of paracyclophanes in a highly efficient way by the cross-metathesis of different alkene substrates.

Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^{1}H NMR and ^{13}C NMR for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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