

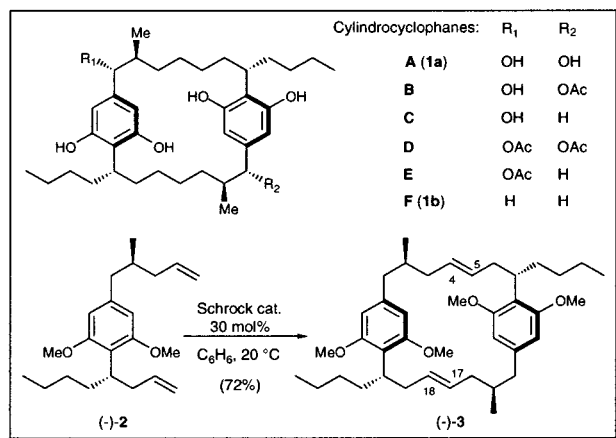
On the Reversible Nature of the Olefin Cross Metathesis Reaction

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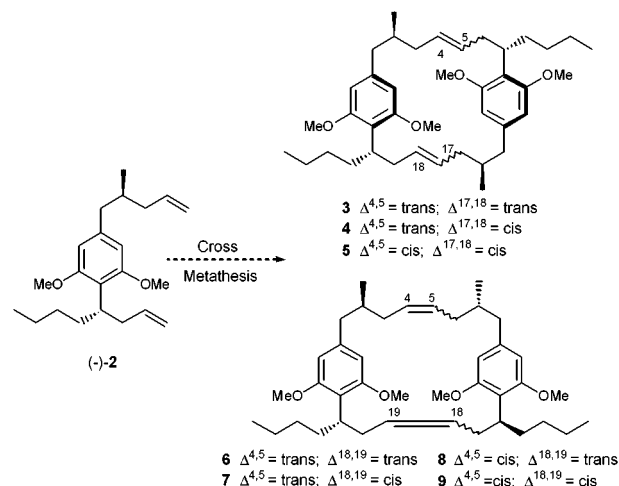
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The olefin ring-closing metathesis (RCM) reaction has emerged as one of the most powerful transforms in organic synthesis.¹ Indeed, the broad scope and reliability of this reaction has greatly simplified the total synthesis of a wide variety of architecturally complex natural and unnatural products.² We first became interested in the metathesis process during the synthesis of a family of novel naturally occurring paracyclophanes known as the cylindrocyclophanes (A–F).^{3,4}



During the course of this venture we demonstrated that cross metathesis dimerization (Scheme 1) provides an efficient tactic for the construction of the C₂-symmetric skeleton of the cylindrocyclophanes.^{4c} Of the seven possible cyclic dimers of (-)-2, including those having either seven carbons between the aromatic rings (3–5) or eight and six carbons (6–9), only (-)-3 was observed when subjected to either the Grubbs or Schrock

Scheme 1



catlysts,⁵ with the Schrock catalyst furnishing the best yield (72%).^{4c} The observation of only one of the seven possible dimers [(-)-3] suggested a cascade of reversible olefin metatheses,⁶ a result supported by recent work from the Grubbs and Hoveyda laboratories demonstrating the reversible nature of the olefin metathesis reaction.⁷

To explore the observed selectivity of this olefin dimerization, we carried out a series of Monte Carlo conformational searches⁸ using the MM2 force field⁹ (Macromodel 6.0). The calculations indicated that the [7,7]-*E,E*-macrocycle (3) indeed possesses the lowest-energy structure by ~2.6–4.7 kcal/mol relative to the other possible dimers (Figure 1),¹⁰ indicating that the naturally occurring [7,7]-paracyclophane skeleton is the thermodynamically most stable.

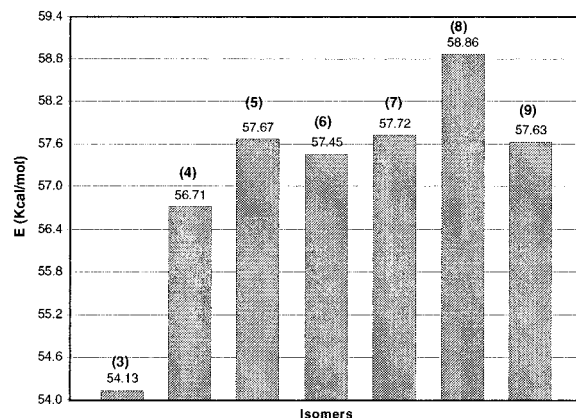


Figure 1. Energy values for the lowest-energy conformation of the seven possible geometrical/constitutional isomers (see Scheme 2).

To provide experimental evidence for the reversible cascade of the olefin metatheses in the dimerization of (-)-2, we selected trienes **14** and **15**, both predisposed to form the [8,6]-macrocycle

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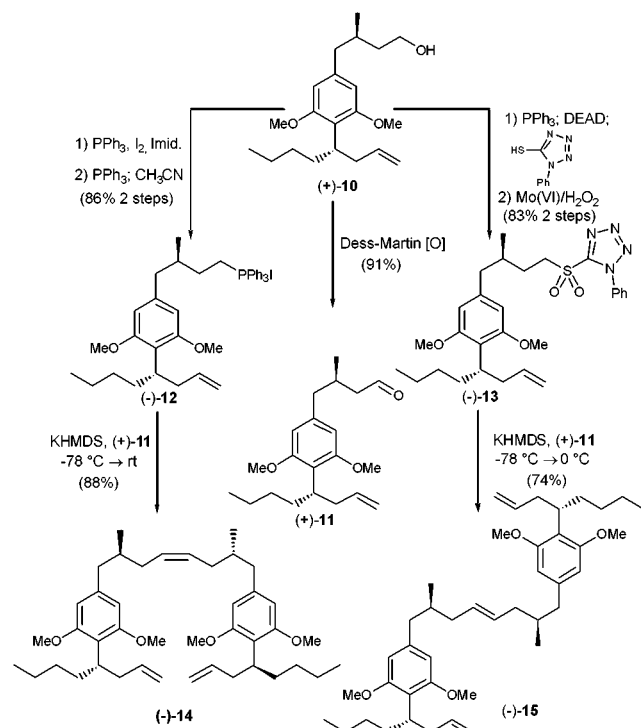
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Scheme 2



via RCM (Scheme 2). The conversion of **14** and **15** to the [7,7]-macrocyclic (**-**)-**3** instead of the analogous RCM products would provide clear evidence for the proposed reversible cascade.

We envisioned that Kocienski-modified Julia¹¹ and Wittig¹² olefinations with (+)-**11** would provide ready access to the requisite *Z* and *E* trienes, **14** and **15**, respectively. The required common aldehyde (+)-**11** was prepared in high yield via Dess–Martin oxidation¹³ of known alcohol (+)-**10**.^{4a} For the Wittig salt (**-**)-**12**, iodination of (+)-**10** (I₂, PPh₃, imidazole), followed by treatment with PPh₃ in acetonitrile at reflux furnished (**-**)-**12** in 86% (two steps). For sulfone (**-**)-**13**, Mitsunobu reaction¹⁴ of (+)-**10** with 1-phenyl-1*H*-tetrazole-*S*-thiol followed by hydrogen peroxide oxidation promoted by ammonium heptamolybdate tetrahydrate¹⁵ led to (**-**)-**13** in 83% (two steps). With the coupling partners in hand, treatment of Wittig salt (**-**)-**12** with KHMDS at $-78\text{ }^{\circ}\text{C}$ followed by addition of aldehyde (+)-**11** furnished the *Z*-triene (**-**)-**14** (88% yield, dr > 15:1). In a similar fashion, deprotonation of sulfone (**-**)-**13** with KHMDS followed by addition of aldehyde (+)-**11** furnished (**-**)-**15** in 74% yield (dr > 15:1).

Both trienes were subjected to the Schrock catalyst (Scheme 3), employing conditions identical to the dimerization of (**-**)-**2** (32–35 mol %, 20 °C, C₆H₆). Although the substrates were predisposed to form the [8,6]-cyclophane, only the [7,7]-*E,E*-paracyclophane (**-**)-**3** was observed in yields ranging from 75 to 81%. Presumably both substrates undergo a cascade of reversible olefin metathesis reactions which eventually led to the [7,7]-*E,E*-paracyclophane.

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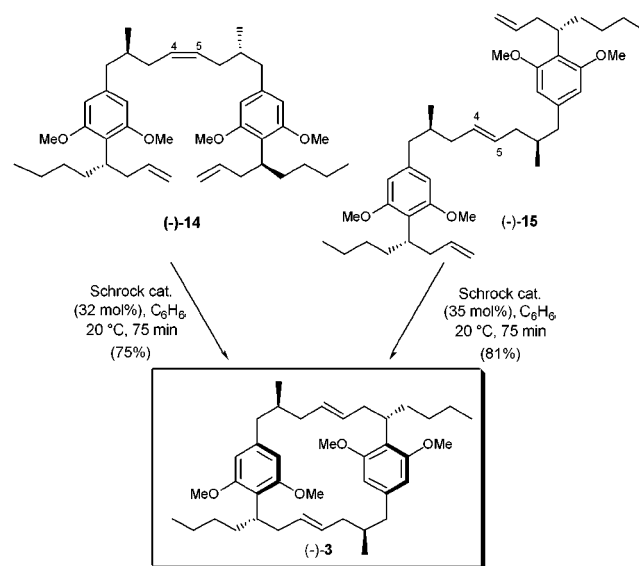
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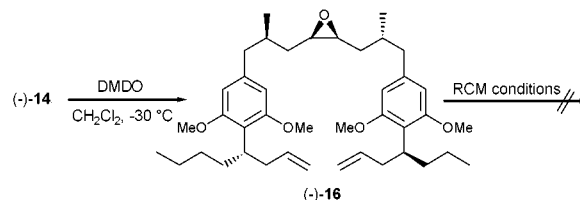
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Scheme 3



With experimental support for the reversibility of the cross olefin metathesis in the dimerization of (**-**)-**2**, we sought to explore the feasibility of preparing the high-energy [8,6]-cyclophane congeners via olefin metathesis. Our intent was to mask the C(4,5) olefin of (**-**)-**14** as an epoxide, assemble the [8,6]-paracyclophane via RCM, and then reinstall the C(4,5) olefin. Toward this end, chemoselective epoxidation of the C(4,5) disubstituted olefin in (**-**)-**14** was envisioned (Scheme 4); epoxidation from either face would give the same product, due to the inherent C₂-symmetry of (**-**)-**14**. Use of *m*CPBA in a variety of solvents however led to (**-**)-**16** in low yield (<25%) due to competing oxidation of the electron-rich aromatic systems. After significant experimentation we discovered that dimethyldioxirane (DMDO) provided useful amounts of epoxide (**-**)-**16**, albeit again in modest yield (43%, 66% based on recovered starting material). Unfortunately, all attempts at RCM with either the Schrock^{5a} or the Grubbs catalysts^{5b,c} led either to no reaction or polymerization. This observation supports the Monte Carlo calculations, indicating the relative high energy of the [8,6]-paracyclophane skeleton.

Scheme 4



In summary, the conversion of (**-**)-**14** and (**-**)-**15** to (**-**)-**3** establishes unambiguously that the ring-closing metathesis protocol can lead to the thermodynamically most stable member of a set of structurally related isomers. This self-editing process has important strategic implications for the design and implementation of future synthetic strategies.

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Supporting Information Available: Spectroscopic and analytical data for compounds **3**, **10–16** and selected experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.