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Ring-Closing Metathesis with Vicinal Dibromoalkenes as Protected Alkynes: A Synthetic Approach to Macrocyclic Enynes

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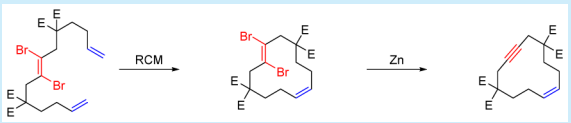
Supporting Information

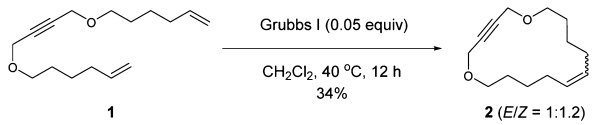
ABSTRACT: A new strategy to access macrocyclic enynes was developed. To block undesired ene−yne cyclization pathways, alkynes were protected via bromination and the resultant acyclic *vic*-(*E*)-dibromotrienes participated in selective ene−ene ring closing metathesis reactions. Zinc-promoted deprotection of (*E*)-dibromodienes provided macrocyclic enynes in high yields.



Cyclic enynes gained importance with interest in annulene chemistry in the 1960s,[1] and their significance increased as novel biologically active natural products were discovered.[2] Enyne rings constitute the core of potent antitumor antibiotics[3−8] and cytotoxic alkaloids.[9] Cyclic enynes were also used in natural product syntheses[10] and transannular rearrangements.[11] These discoveries stimulated studies on the construction of enyne rings. Traditional syntheses encompass functionalized acyclic enynes participating in intramolecular transformations.[10a,12−15] Other methods involved introduction of alkyne or alkene units via cycloelimination reactions[16,17] and intermolecular processes involving double coupling[18,19] or substitution.[20] However, these methods suffer from tedious substrate preparations, low yields, and limited product scope.

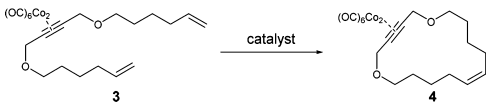
Ring-closing metathesis (RCM) is one of the most powerful tools in organic synthesis,[21] so ene−ene RCM of dienynes could be an efficient alternative for the preparation of macrocyclic enynes. However, a thermodynamically favored ene−yne RCM pathway is preferred in transformations with an ene−ene vs ene−yne reactivity competition.[22,23] Few exceptions are observed for this chemoselectivity.[10d,24−26] Indeed, our attempts at RCM of dienyne **1** led to low yields of enyne **2** (Scheme 1).

Scheme 1. Synthesis of Cyclic Enyne 2



Attempting to circumvent this reactivity $\{Co_2(CO)_6\}$−alkyne complexes were employed as protected alkynes in RCM.[10c,22a−c,25b,27] However, this often led to side reactions, high catalyst loadings, and poor yields. Most metathesis reactions require heat,[21a] and $\{Co_2(CO)_6\}$−dienynes complexes readily undergo thermal Pauson−Khand reactions.[22c,27e,28] More importantly, these complexes can release π-acidic CO which reacts with the catalyst leading to metathesis-inactive complexes.[29] In fact, we tested the synthesis of dicobalt complex **4** without success (Table 1). Cyclic enyne **4** was formed in yields

Table 1. Synthesis of Cyclic Enyne Complex 4



entry	solvent	°C	h	catalyst[a] (equiv)	yield (%)[b]
1	CH_2Cl_2	25	12	Grubbs I (0.02)	12
2	toluene	25	12	Grubbs I (0.05)	0
3	CH_2Cl_2	25	12	Grubbs II (0.05)	0
4	CH_2Cl_2	40	24	Grubbs I (0.05)	0
5	CH_2Cl_2	25	24	Grubbs I (0.15)	14
6	CH_2Cl_2	0	72	Grubbs I (0.10)	13

[a]Grubbs I = $(PCy_3)_2Cl_2Ru$ = CHPh (Grubbs' 1st generation), Grubbs II = $(PCy_3)(C_{20}H_{26}N_2)Cl_2Ru$ = CHPh (Grubbs' second generation). [b]Yields were determined by ^{1}H NMR and only the *Z* isomer was observed.[30]

even lower than the yield of metal-free enyne **2** from an RCM reaction of "unprotected" dienyne **1** (Scheme 1). The destructive effects of CO on catalysis were clear, and development of an alternative protection method was essential.

RCM reactivity is principally determined by olefin substitution patterns. Trisubstituted alkenes have low reactivity and tetrasubstituted alkenes have almost no metathesis reactivity, especially for initiation.[21a,31] We utilized this low reactivity as the basis for an alkyne protection strategy. We proposed that tetrasubstituted *vic*-dibromoalkenes with general structure **8** would serve as protected alkynes and be inert in metathesis reactions[32] while being deprotected via zinc-promoted elimination (Scheme 2).[30] Since its discovery in the late 1800s, alkyne bromination has had limited use as a protection method.[33] In this regard, our strategy provides an interesting example of this tactic.

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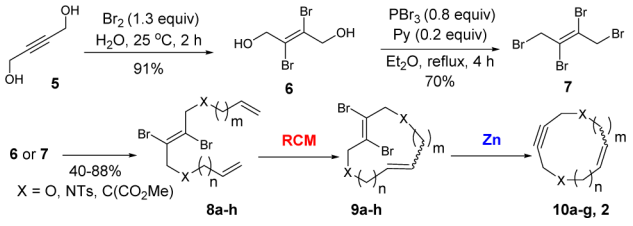
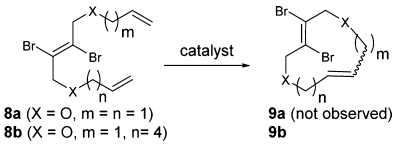
Scheme 2. Substrate Preparation and Enyne Synthesis



RCM of **8a** was tested to synthesize the 10-membered-ring product **9a** (Table 2). However, mixtures of polar polyether oligomers were formed instead of the target molecule possibly due to its high ring strain.

Table 2. Optimization of the RCM Reaction



entry	solvent	°C	h	catalyst (equiv)	**9b**, yield, %[a] (*E*/*Z*)
1[b]	CH_2Cl_2	25	12	Grubbs I (0.20)	30 (8:1)
2[b]	CH_2Cl_2	25	12	Grubbs II (0.05)	0
3[c]	CH_2Cl_2	40	12	Grubbs I (0.05)	69 (2.5:1)
4[c,d]	CH_2Cl_2	40	12	Grubbs III (0.05)	10 (100:0)
5[c]	CH_2Cl_2	40	12	Grubbs II (0.05)	0

[a]Yields are of isolated products.[30] *E*/*Z* ratios were determined by NMR spectroscopy. [b][**8b**] = 0.005 M. [c][**8b**] = 0.002 M. [d]Grubbs III = $C_{31}H_{38}Cl_2N_2ORu$ (Hoveyda−Grubbs second generation).[34b]

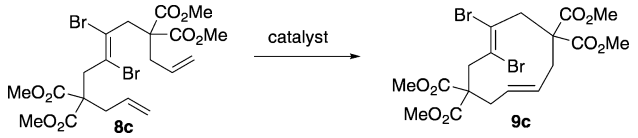
To avoid oligomerization, we considered larger rings, so triene **8b** was tested in RCM reactions (Table 2). At rt with the Grubbs I catalyst, the target ring was formed in a 30% yield (Table 2, entry 1), but with a high catalyst loading of 20%. A trial with the more reactive[34a] Grubbs II catalyst at rt failed to form **9b** and instead gave a mixture of decomposition products (entry 2). Since the alkyne protecting group is heat-tolerant, we tested the RCM of **8b** in refluxing CH_2Cl_2 with the Grubbs I catalyst and the reaction gave **9b** in a 69% yield (entry 3). In refluxing DCM, Grubbs III[34b] was less effective (entry 4) while Grubbs II gave a complex mixture of metathesis products (entry 5).

All-carbon rings have less ring strain compared to ether analogs, as C−C σ-bonds are longer than C−O σ-bonds.[20b] Thus, although 10-membered-ring **9a** failed to form, we tested the synthesis of 10-membered-ring **9c** (Table 3). In contrast to **8a**, **8c** was resistant to oligomerization, but it exhibited low RCM reactivity. Optimal conditions for formation of macrocycle **9b** only afforded trace amounts of **9c** (Table 3, entry 1). Higher temperatures and longer reaction times did not improve the yield (entry 2). To increase the metathesis reaction rate, both the substrate concentration and catalyst loading were increased (entries 4−6). Under these conditions with the more active Grubbs II catalyst, ring **9c** was obtained in a 90% yield (entry 6). The stereoselectivity of the catalysts were opposite which might reflect kinetic versus theromdanamic control and has precedent in the formation of a 10-membered lactone.[35]

Using the optimized RCM conditions for **9b** and **9c**, a variety of dibromotrienes were prepared and reacted to obtain protected macrocycles in good to high yields (Figure 1).[30]

The structural scope of these RCM processes includes all carbon diene rings (**9c**, **9d**), cyclic ethers (**9b**, **9f**, **9g**, **9h**), and a

Table 3. Synthesis of Protected Cyclic Diene 9c



entry	solvent[b]	°C	h	catalyst (equiv)	yield, %[a] (*E*/*Z*)
1[c,d]	CH_2Cl_2	40	12	Grubbs I (0.05)	2 (100:0)
2[c,d]	DCE	85	36	Grubbs I (0.05)	9 (1.7:1)
3[d]	CH_2Cl_2	40	12	Grubbs II (0.05)	50 (1:5.3)
4[e]	CH_2Cl_2	40	12	Grubbs I (0.10)	54 (1.7:1)
5[c,d,e]	DCE	85	36	Grubbs I (0.10)	2 (100:0)
6[e]	CH_2Cl_2	40	12	Grubbs II (0.10)	90 (1:5)

[a]Yields are of isolated products.[30] *E*/*Z* ratios were determined by NMR spectroscopy. [b]DCE = 1,2-dichloroethane. [c]For entries 1, 2, and 5, 90%, 78%, and 68% of **8c** were recovered, respectively. [d][**8c**] = 0.002 M. [e][**8c**] = 0.004 M.

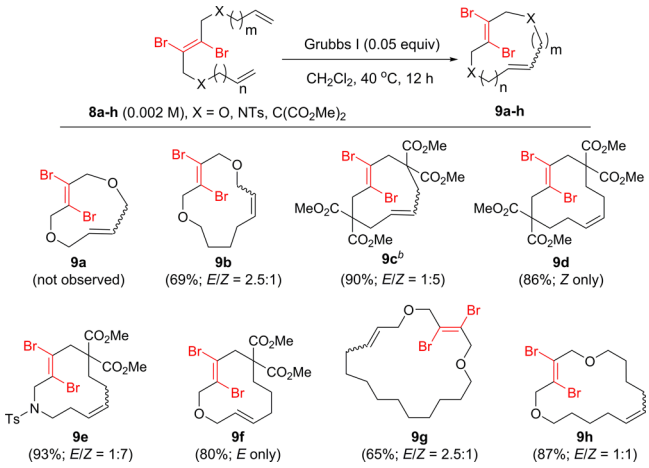


Figure 1. Synthesis of protected macrocycles via RCM. Yields are of isolated products.[30] *E*/*Z* ratios were determined by ^{1}H and ^{13}C NMR spectroscopy. For **9c**, conditions in Table 3, entry 6 were used.

cyclic sulfonamide (**9e**). Tetrasubstituted *vic*-dibromoalkenes were excellent protecting groups, as each reaction proceeded smoothly providing only the terminal ene−ene RCM product. The RCM was not limited to formation of medium rings, as 19-membered **9g** and 16-membered **9h** were synthesized successfully in 65% and 87% yields, respectively (Figure 1).

The ^{1}H NMR spectra of **9b**−**f** and **h** exhibited unexpected diastereotopicity for protons α and β to the dibromoalkene units.[30] This was attributed to rigidity imposed by the bromine atoms restricting rotations leading to favored conformations with the geminal protons and esters located in different environments. Larger and less strained **9g** did not exhibit such behavior. The *Z*-isomer of **9c** was interesting, as the ^{1}H NMR displayed two sets of multiplets for the vinyl protons, suggesting it exists as a mixture of two planar chiral conformers and interconversion between the enantiomeric conformers is slow on the NMR time scale.[25] To support these proposals, quantum-chemical simulations were performed.[30] Calculated chemical shifts and coupling constants based on populations of conformers were in good agreement with the experimental spectra.

Stereoselective synthesis of large rings via metathesis is challenging, although stereoselective RCM catalysts for macrocyclization were recently reported.[36,37] Traditional metathesis catalysts lack kinetic selectivity, as *E*/*Z* ratios are determined by

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the stabilities of the macrocycles based on ring size and/or substitution patterns.[36,37] RCM of dibromotrienes **8** exhibited similar behavior. While formation of symmetric 16-membered **9h** showed no stereoselectivity, 13-membered **9b** and 19-membered **9g** formed with a modest 2.5:1 *E*/*Z* ratio. There is a pronounced allylic chalcogen effect[38] in macrocyclization RCM. Under identical conditions, 12-membered rings **9d** and **9f** formed as single isomers, but with opposite selectivity. Substrates with allyl ether linkages (**8b**, **8f**, **8g**) gave *E* macrocyclic isomers as the sole or major isomer (Figure 1).

Macrocyclic dienes **9b**−**h** were then subjected to deprotection. Zn metal effectively promoted elimination reactions and cyclic enynes were formed in high yields (Figure 2).

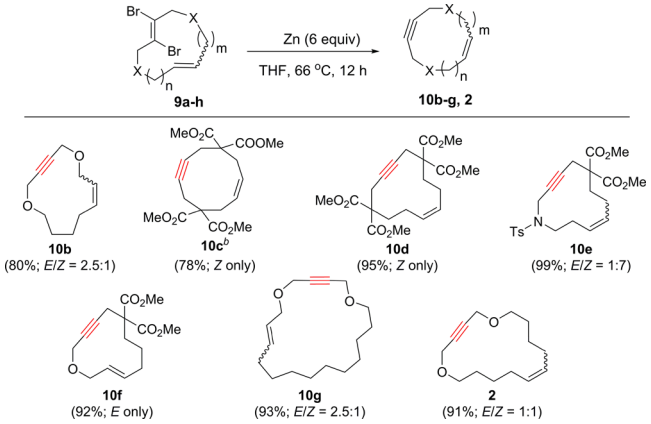


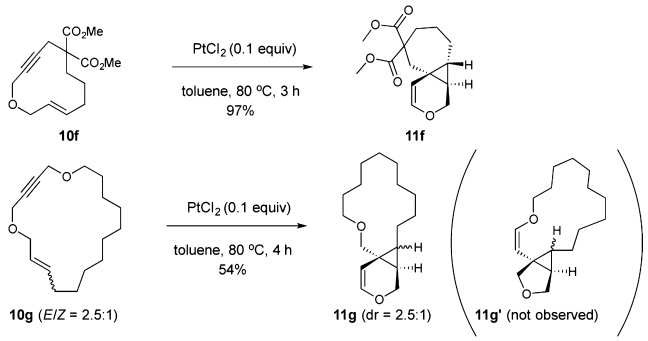
Figure 2. Synthesis of enyne macrocycles. Yields are of isolated products.[30] *E*/*Z* ratios were determined by NMR spectroscopy. For **10c**, heating in a sealed tube at 60 °C for 4 d achieved complete consumption of **9c** where only the *Z* isomer was isolated in a 78% yield.[30]

Isomeric distributions were not affected by deprotection, as the *E*/*Z* ratios were maintained. Rings with allyl and homoallyl moieties (**10b**−**g**) are typically inaccessible by RCM of unprotected acyclic dienynes since ene−yne RCM is preferred.[22,23] This method is superior to the $Co_2(CO)_6$−alkyne protection method which suffered from low yields and catalyst deactivation. Macrocycles **2** and **4** were initially synthesized in very low yields while our approach provided **2** in a 79% overall yield (Figures 1, 2). Zn-promoted deprotection of strained ring **9c** afforded the pure *Z* isomer of **10c** in a 93% yield based upon initial *Z* isomer content (Figure 2). Deslongchamps reported the preparation of *E*- and *Z*-isomers of enyne **10c** via intramolecular S_N2 reactions.[12b] Our method was more efficient, by requiring fewer steps and giving a higher yield.

Pt-catalyzed intramolecular cyclopropanations of allyl propargyl ethers[39,40] and transannular cycloisomerizations of 1,5-enyne rings with propargylic alkoxy substituents[11a] were reported. Inspired by these studies, we subjected macrocycles **10f** and **10g** to Pt(II)-catalyzed rearrangements, and tricyclic enol ethers **11f** and **11g** were obtained in good yields (Scheme 3).[30]

Experimental[11a,39,40] and theoretical[41] studies revealed that Pt-catalyzed cyclopropanations are regio- and diastereoselective. Transannular cycloisomerizations involve a 1,2-hydride shift from an alkyne−Pt complex leading to a vinyl platinacarbene followed by stereospecific cyclopropanation.[11a] Vinyl carbene formation is facilitated by delocalization of β-heteroatom electrons.[11a,40f,41] Pt-catalyzed reaction of **10f** produced a single isomer, and the heteroatom effect dictated the regioselectivity.

Scheme 3. Pt(II)-Catalyzed Cycloisomerization Reactions



The isomeric ratio of **10g** was preserved in cycloisomerization to **11g**, and NMR spectra confirmed that the 3,4-dihydropyran ring **11g** was preferred over a tetrahydrofuran ring (**11g′**).

In conclusion, a new strategy to access macrocyclic enynes was developed. Vicinal-dibromo tetrasubstituted alkenes were excellent protected alkynes, and (*E*)-dibromotrienes participated in selective ene−ene RCM reactions. The RCM reactions were general, tolerated high temperatures, and used low catalyst loadings. Diverse macrocyclic enynes in various ring sizes were prepared in high yields by Zn-promoted deprotection reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02595.

Experimental details and spectral data for isolated products (PDF)
NMR spectra (PDF)
Calculations (PDF)

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Notes

The authors declare no competing financial interest.

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