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Ring-Closing Metathesis of $Co_2(CO)_6$–Alkyne Complexes for the Synthesis of 11-Membered Dienediynes: Overcoming Thermodynamic Barriers

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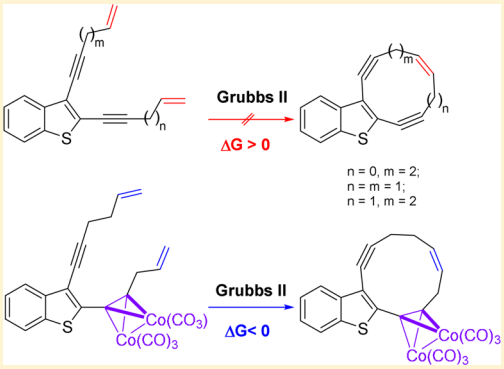
Supporting Information

ABSTRACT: The feasibility of ring-closing metathesis (RCM) as a synthetic entry to 10- and 11-membered dienediynes fused to a benzothiophene core was explored by experimental and theoretical investigations. An established sequence of iodocyclization of *o*-(buta-1,3-diynyl)thioanisoles followed by Sonogashira coupling to form diethynylbenzothiophenes was used to synthesize terminal benzothiophene-fused enediyne diolefins as substrates for RCM. Encountering an unexpected lack of reactivity of these substrates under standard RCM conditions, we applied DFT calculations to reveal that the underlying cause was a positive change in Gibbs free energy. The change in Gibbs free energy was also found to be positive for RCM of indole- and benzannulated terminal diolefins when affording smaller than 12-membered rings. We found that modification of the enediyne–diolefin substrate as the $Co_2(CO)_6$–alkyne complex allowed the target benzothiophene-fused 11-membered dienediyne to be obtained via RCM; the alkyne complexation strategy therefore provides one valid technique for overcoming challenges to macrocyclization of this kind.



INTRODUCTION

Naturally occurring macrocyclic enediyne antibiotics are well-known as potent anticancer agents,[1] and a broad range of synthetic analogues of these compounds have been synthesized and investigated by our colleagues in the synthetic community.[2−7] Recently, enediyne systems have widely been utilized as sequence intermediates in organic synthesis for construction of polycyclic molecules,[8−11] natural products,[12] and polymer materials[13] and have also been used themselves in the role of catalysts.[14] In the search among synthetic analogues of naturally occurring enediynes for new molecules possessing antineoplastic activity, only cyclic enediynes incorporated into 9- or 10-membered cycles are considered valid targets. This is because these small macrocyclic systems are able to undergo thermally induced cycloaromatization under mild conditions with the formation of highly reactive biradicals, which abstract hydrogen atoms from DNA molecules; this damage to the genetic information is often followed by cell death.[1] Despite the knowledge that macrocyclic enediynes fused to a heterocyclic core are therefore promising leads for new anticancer drugs, molecules fitting this classification are almost unknown. The synthesis and properties of only a small handful of such systems have been published so far; these feature cinnoline,[15] imidazole,[16] pyrimidine,[17] and benzofuran components.[18]

We recently reported an efficient strategy toward acyclic enediynes fused to heteroindenes based on electrophilic cyclization of *o*-functionalized (buta-1,3-diynyl)arenes and subsequent Sonogashira coupling.[19,20] Combination of this approach with ring-closing metathesis as a macrocyclization technique was efficient for construction of 12-membered dienediynes fused to benzothiophene and indole rings.[19,21] However, the macrocycles thus obtained possessed low reactivity toward thermally induced cycloaromatization. Consequently, we were motivated to synthesize smaller heteroindene-fused cyclic dienediynes by adapting this synthetic strategy. Taking into account that dibenzannulated 10-membered dienediyne **1** is known to undergo spontaneous cyclization during preparation,[22] both 10-membered (**2**, **3**) and 11-membered (**4**) dienediynes fused to a benzothiophene core were chosen as targets (Figure 1).

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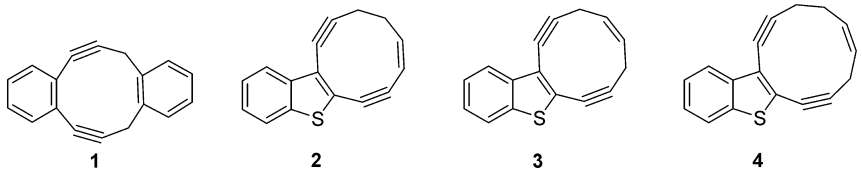
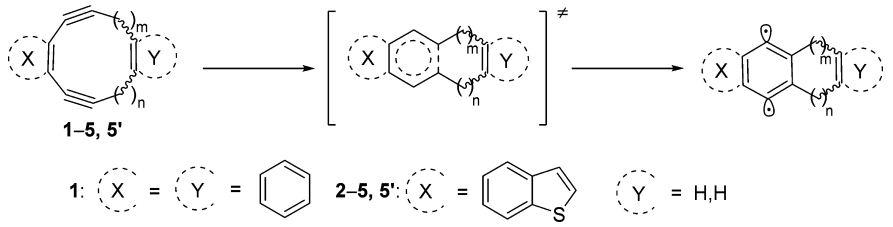


Figure 1. Dibenzannulated **10**-membered dienediyne **1** and related benzothiophene-fused dienediynes **2**–**4**.

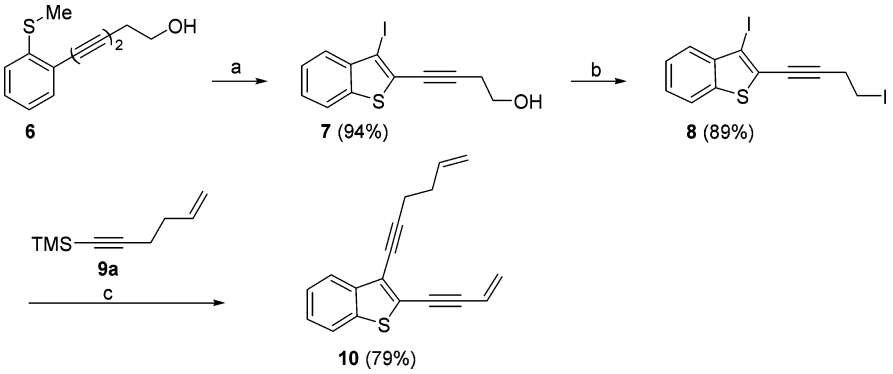
Table 1. Bergman Cyclization Activation Energies of Macrocyclic Dinediynes 1–5,5′ (DFT Calculations)[a]



entry	enediyne macrocycle	*m*	*n*	olefin config	ring size	$\Delta E^{\ddagger b}$
1	**1**	1	1	*Z*	10	26.2
2	**2**	2	0	*Z*	10	26.3
3	**3**	1	1	*Z*	10	25.5
4	**4**	2	1	*Z*	11	41.2
5	**5**	2	2	*Z*	12	48.1
6	**5′**	2	2	*E*	12	58.9

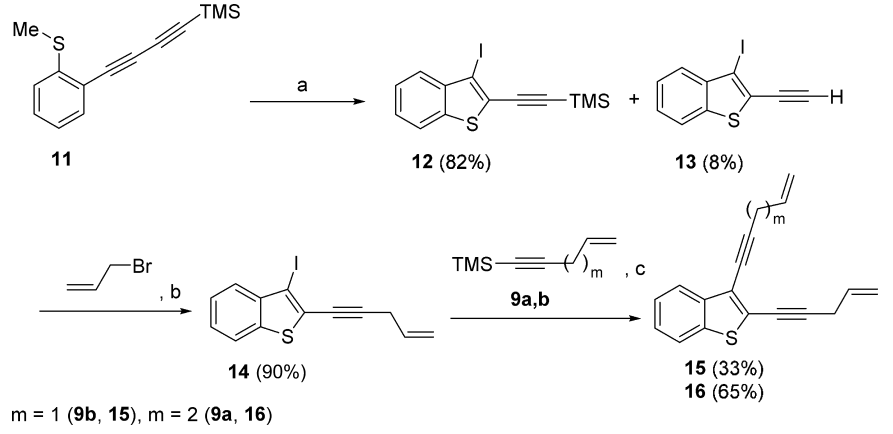
[a]For the details of DFT calculations, see the Supporting Information. [b]$\Delta E^{\ddagger}$ = E + ZPE, kcal/mol.

Scheme 1. Synthesis of Terminal Diolefin 10[a]



[a]Reagents and conditions: (a) I_2, rt, DCM; (b) I_2, imidazole, PPh_3, 0 °C to rt, THF; (c) $Pd(PPh_3)_4$, CuI, K_2CO_3, MeOH, 50 °C, DMF.

Scheme 2. Synthesis of Terminal Diolefins 15 and 16[a]



[a]Reagents and conditions: (a) I_2, DCM, rt; (b) CuI, K_2CO_3, MeOH, DMF, rt; (c) $Pd(PPh_3)_4$, CuI, KF, MeOH, DMF, 40 °C.

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RESULTS AND DISCUSSION

DFT calculations were carried out to evaluate the reactivity of molecules **1**−**4** to Bergman cyclization and compare with enediynes **5** and **5′** synthesized previously[21] (Table 1). The data obtained revealed that known dibenzannulated 10-membered dienediyne **1** and both 10-membered dienediynes **2** and **3** with activation energies to cycloaromatization of ∼26 kcal/mol are expected to be highly reactive in this process, even at ambient temperature.

The 11-membered dienediyne macrocycle **4** is believed to be less reactive ($\Delta E^{\ddagger}$ = 41.2 kcal/mol) than the 10-membered dienediynes **2** and **3** but considerably more reactive than both isomeric 12-membered dienediynes **5** and **5′** synthesized in our previous work.[21] Thus, the (*E*) isomer **5′** underwent cycloaromatization only upon heating to extreme temperature (230 °C) and through an alternative path to that of the classic Bergman cyclization.[21]

The syntheses of RCM substrates **10**, **15**, and **16** commenced with *o*-(buta-1,3-diynyl)thioanisole derivatives **6** and **11** (Scheme 1). Iodocyclization of diacetylenic alcohol **6** proceeded with the formation of 3-iodobenzothiophene **7**. Appel reaction of this compound with iodine afforded diiodobenzothiophene **8** in high yield (89%). Under our recently developed one-pot conditions for TMS group removal and Sonogashira coupling,[19] reaction of diiodide **8** with TMS-protected enyne **9a** proceeded smoothly and also led to the elimination of HI that gave the desired terminal diolefin **10** in high yield (79%, Scheme 1).

TMS-substituted diacetylene **11** (Scheme 2) was used for the synthesis of two other RCM substrates, **15** and **16**. The electrophilic cyclization of diacetylene **11** gave the mixture of TMS-substituted ethynyl benzothiophene **12** and the desilylated derivative **13** in high combined yield (90%).

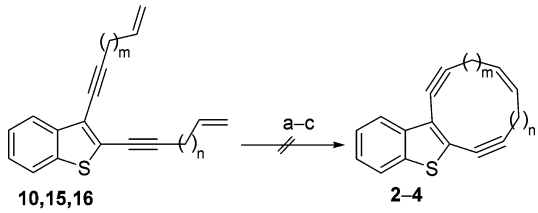
It was possible to use this mixture (**12**/**13**) without separation in the alkylation with allyl bromide under TMS-removal conditions in one pot. In this case, the Cu-catalyzed allylation of the terminal acetylene was a suitable alternative to organometallic reagents.[23] Although this reaction is known as a general method for the introduction of allyl moiety and has been extensively applied in the synthesis of natural products,[24,25] and even in the synthesis of enediyne systems,[26] a one-pot technique for the TMS-group removal/allylation has been reported only once for the KF/CuI-mediated allylation of TMS phenylacetylene in DMF at 80 °C.[27] In our case, much milder conditions were employed: addition of CuI and then allyl bromide to a prestirred mixture of acetylenes **12** and **13** with K_2CO_3/MeOH in DMF at room temperature gave the desired enyne **14** in high yield (90%). Importantly, changing the order of addition of CuI and allyl bromide affected the reaction adversely, and only traces of the compound **14** were detected in the reaction mixture along with a mixture of unidentified products.

In light of our recent results,[19] one-pot desilylation/Sonogashira coupling of iodobenzothiophene **14** with TMS-protected enynes **9a** and **9b** using a KF/MeOH/diisopropanolamine system was expected to give the desired diolefins **15** and **16** without any difficulties. However, the yields in both cases were quite low (14% and 22%, respectively). This could be explained in terms of a possible acetylene−allene rearrangement within the allylethynyl moiety, followed by enyne−allene cycloaromatization (Myers−Saito cyclization),[28−31] which is known to proceed at significantly lower temperatures than Bergman cyclization.[32] This process under the conditions of the Sonogashira coupling may result in formation of polymeric material and a significant decrease in reaction yields. The unexpected results obtained encouraged us to optimized the reaction conditions.[33] It was found that yields of the desired products were strongly dependent on the identity of the base and fluoride ion source. For example, substituting diisopropanolamine with diisopropylamine increased the yield of diolefin **15** to 27%, while substituting with triethylamine led to a complex mixture from either enyne **9a** or **9b**. Complex mixtures were also obtained when AgF or TBAF was used as a source of fluoride ion. Optimal yields of compounds **15** (33%) and **16** (65%) can be reached by carrying out the reaction using only the KF/MeOH system without additional base (Scheme 2). Mechanistic explanations include the involvement of pentacoordinated Si, which is known to be an attribute of the sila-Sonogashira coupling,[34] or if the mild basicity of fluoride ion in DMF was appropriate for Sonogashira coupling by the classic mechanism.[35]

With the substrates **10**, **15**, and **16** in hand for the synthesis of 10- and 11-membered dienediynes **2**−**4**, we were ready to close the target macrocycles by the RCM technique.

First, experiments were carried out with compound **10** using different solvents (DCM and toluene), catalysts (Grubbs II and Hoveyda−Grubbs II), catalyst loading (from 7 to 30 mol %), and temperature ranges (room temperature or reflux in DCM or toluene) in sealed vials. Moreover when DCM was used as a solvent, heating of a degassed reaction mixture in a sealed vial and in a stream of Ar was examined. Unfortunately, all attempts to carry out the ring closure failed: only unconverted starting compound **10** was detected in the reaction mixture after 14 h irrespective of conditions used. The same results were obtained with two other terminal diolefins **15** and **16** irrespective of the type of catalyst loading (Grubbs II) used (Scheme 3).

Scheme 3. Attempts for the Synthesis of 10- and 11-Membered Dienediynes by RCM[a]



10,15,16 **2–4**

n = 0, m = 2 (**2,10**), n=m=1 (**3,15**), n = 1, m = 2 (**4,16**)

[a]Tested reagents and conditions: (a) for **10**, sealed vial, Grubbs II catalyst or Hoveyda−Grubbs II catalyst (10−30 mol %), DCM or toluene, *C* = 0.002 M, 45 °C (for DCM) or 115 °C (for toluene) (bath temperature), 14 h; (b) for **10**, Grubbs II (7 mol %), DCM, *C* = 0.002 M, reflux 14 h; (c) for **15** and **16**, sealed vial, Grubbs II catalyst (7−21 mol %), DCM, *C* = 0.002 M, 45 °C (bath temperature), 14 h.

Since most of the experimental results were obtained under equilibrium conditions preventing the release of ethene, we sought an explanation for the lack of the reactivity by evaluation of the feasibility of these reactions using change in Gibbs free energy obtained by DFT calculations. Thus, the calculated changes of Gibbs free energy values for the RCM of diolefins **10**, **15**, and **16** and the diolefin **17** previously used to synthesize a 12-membered structure[21] are in a good accordance with all experimental results (Table 2).

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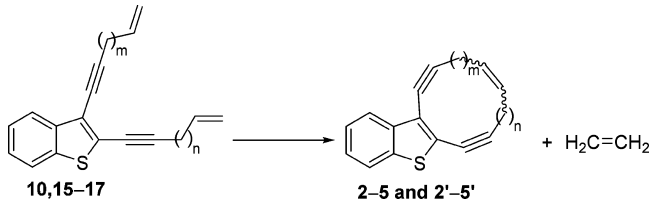
Table 2. Study of Reactivity of Benzothiophene-Fused Diolefins 10 and 15−17 in RCM by DFT Calculations[a]

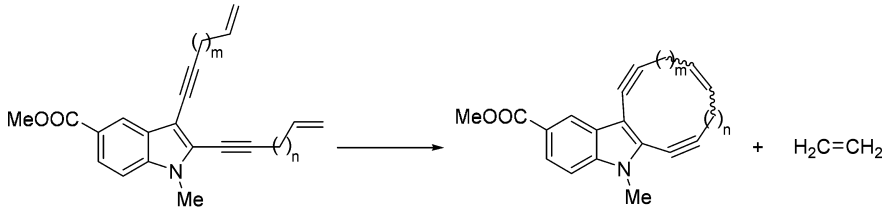


10,15–17 2–5 and 2′–5′

entry	diolefin	enediyne	*m*	*n*	double bond config	ring size	Δ*G* (kcal/mol)	exptl results
1	**10**	**2**	2	0	*Z*	10	5.8	NC[b]
		2′			*E*		22.7	
2	**15**	**3**	1	1	*Z*	10	9.0	NC
		3′			*E*		13.0	
3	**16**	**4**	2	1	*Z*	11	2.6	NC
		4′			*E*		2.7	
4	**17**	**5**	2	2	*Z*	12	−1.9	72% of *E*/*Z* (8.2:1)[c]
		5′			*E*		−3.2	

[a]For details of DFT calculations, see the Supporting Information. [b]NC = no conversion. [c]The experimental results for diolefin **17** were reported previously.[21]

Table 3. Study of the Reactivity of Indole-Fused Diolefins 18−21 in RCM by DFT Calculations[a]



18–21 22–25 and 22′–25′

entry	diolefin	enediyne	*m*	*n*	olefin config	ring size	Δ*G* (kcal/mol)	exptl results[b]
1	**18**	**22**	2	0	*Z*	10	6.3	
		22′			*E*		21.9	
2	**19**	**23**	1	1	*Z*	10	9.0	
		23′			*E*		12.5	
3	**20**	**24**	2	1	*Z*	11	2.4	
		24′			*E*		2.1	
4	**21**	**25**	2	2	*Z*	12	−1.4	78% of *E*/*Z* (6:1)[c]
		25′			*E*		−3.2	

[a]For the details of DFT calculations, see the Supporting Information. [b]The reactivity of diolefins **18−20** was not investigated experimentally. [c]The experimental results for the diolefin **21** were reported previously.[19]

It was calculated for the reaction of terminal diolefin **17** that the largest negative change in Gibbs free energy is proposed for the formation of (*E*) 12-membered dienediyne **5′** while the formation of *Z* isomer **5** is less favorable. The experimental data obtained previously are in a good accordance with this calculation. Thus, the RCM of diolefin **17** afforded a mixture of *E* and *Z* isomers in ratio 8.2:1.[21] In contrast, in the case of *E* and *Z* isomers of 10- and 11-membered dienediynes **2−4** and **2′−4′** the calculated Gibbs free energy change was positive, explaining the failure of compounds **10**, **15**, and **16** to cyclize under the RCM conditions explored.

In order to determine whether the change in Gibbs free energy is positive for the RCM of terminal diolefins affording smaller than 12-membered cycles, irrespective of a scaffold fused to enediyne system, the corresponding reactions for four indole- and four benzannulated terminal diolefins were also investigated by the DFT method. It was found that the replacement of a sulfur atom with nitrogen did not influence the reactivity of diolefins in the RCM process (Table 3). This reaction could be practically useful only for the synthesis of 12-membered cycles **25** and **25′** because of the negative change in Gibbs free energy for the formation of both (*E*)- and (*Z*)-macrocycles, which was experimentally shown previously.[19] RCM macrocyclizations for the preparation of smaller indole-fused cyclic systems of **22−24** and **22′−24′** are thermodynamically forbidden (Table 3).

Regarding using the RCM in the synthesis of benzene-fused dienediynes, it was calculated that for the construction of 10- and 11-membered cycles this reaction is also unfavorable. The calculations also revealed that even 12-membered dienediyne with the *Z* configuration of a double bond formed cannot be synthesized using the RCM because of the positive change in Gibbs free energy for this process (Table 4).

Taken together, the revelations provided by the DFT calculations pose a significant problem to our goal of synthesizing targets of the type **2−4** (Figure 1). To overcome this broad challenge, we turned to the idea of protection of a triple bond in order to reduce (R)C−C_{sp}−C_{sp}−C(R) bond angles from the value of 180° affording the decrease in strain energy of RCM products. Commonly used reagents for triple-

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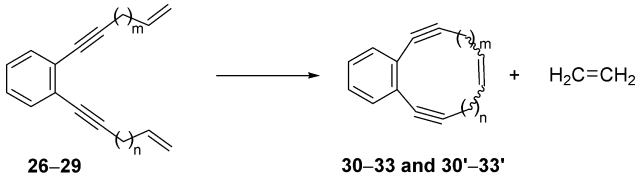
Table 4. Study of the Reactivity of Benzene-Fused Diolefins 26–29 in RCM by DFT Calculations[a,b]

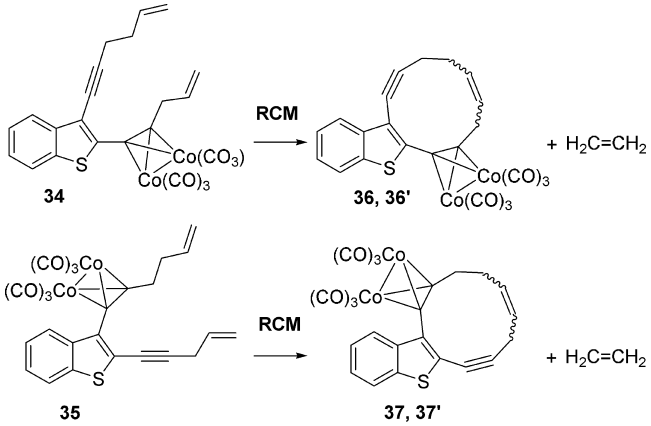


26–29 30–33 and 30′–33′

entry	diolefin	enediyne	*m*	*n*	olefin config	ring size	Δ*G* (kcal/mol)
1	**26**	**30**	2	0	*Z*	10	3.6
		30′			*E*		21.2
2	**27**	**31**	1	1	*Z*	10	5.9
		31′			*E*		10.8
3	**28**	**32**	2	1	*Z*	11	8.5
		32′			*E*		4.8
4	**29**	**33**	2	2	*Z*	12	3.4
		33′			*E*		−3.2

[a]The reactivity of diolefins **26–29** was not investigated experimentally. [b]For the details of DFT calculations, see the Supporting Information.

Table 5. Study of the Reactivity of $Co_2(CO)_6$-Protected Diolefins 34 and 35 in RCM by DFT Calculations[a]



diolefin	RCM product	olefin config	ring size	Δ*G* (kcal/mol)	exptl results
34	**36**	*Z*	11	−4.2	16% of *Z*-isomer
	36′	*E*		−1.8	
35	**37**	*Z*	11	−3.2	
	37′	*E*		9.1	

[a]For details of the DFT calculations, see the Supporting Information.

bond protection of enediyne derivatives are difluorocarbene, which allows the formation of a cyclopropenone ring as a protective group,[36] and dicobalt octacarbonyl, $Co_2(CO)_8$, for the conversion of triple bonds to the corresponding alkyne–$Co_2(CO)_6$ complexes.[37−39] This complex affords stable compounds with significantly bent C_{sp}–C_{sp}–C(R) angles (up to 140°) in contrast to free (linear, 180°) alkynes.[40] In the case of enynes, the use of difluorocarbenes can be associated with some difficulties in the form of competitive [2 + 1] cycloaddition of difluorocarbene to a triple or a double bond. Therefore, taking into account that alkyne–$Co_2(CO)_6$ complexes were used in order to impart the reactivity to some enynes toward the RCM conditions allowing the formation of medium[41,42] and macrocyclic[43] ring systems possessing a triple bond, the synthesis of alkyne–$Co_2(CO)_6$ complexes was chosen as a synthetic strategy.

Terminal diolefin **16** was chosen for these experiments because it was calculated to require the lowest Gibbs free energy change from among the diolefins synthesized (Table 2). Moreover, it was calculated that the change in Gibbs free energy for the RCM of both possible regioisomeric Co complexes **34** and **35** derived from the terminal diolefin **16** is negative (−4.2 and −3.2 kcal/mol, respectively) in the case of the formation of macrocycles **36**, **37** with a *Z* double-bond configuration (Table 5). On the other hand, formation of Co-protected macrocycle **36′** with an *E* configuration of the double bond is less favorable (Δ*G* = −1.8 kcal/mol), whereas the formation of (*E*)-macrocycle **37′** is infeasible because of the positive change in the Gibbs free energy (Δ*G* = 9.1 kcal/mol).

Encouraged by this preliminary prediction, we started the proposed synthetic path. The formation of $Co_2(CO)_6$ complexes of diolefin **16** was found to proceed with the preferred complexation by the triple bond at the C-2 position of a benzothiophene ring (Scheme 4). This finding was in agreement with the data reported by Arnanz and co-workers: the reaction of 2,3-bis(trimethylsilylethynyl)thiophene with $Co_2(CO)_8$ also afforded C-2 Co complex as a major product.[44] This preferred complexation with the less electron rich triple bond at C-2 of a thiophene ring was postulated as being favorable due to stabilization by enhanced back-donation from the Co *d*-orbitals to the π^*-MO of a triple bond ligand.[44,45] All attempts to synthesize dicobalt complex of diolefin **16** involving both triple bonds failed even when 4-fold excess of $Co_2(CO)_8$ per one alkyne bond was used.

The mixture of both regioisomers **34** and **35** obtained was used in the next RCM step without separation. The macrocyclization step in refluxing DCM under Grubbs II catalysis proceeded with the preferred formation of a single reaction product **36** derived from the main isomer **34**. We believe that minor isomer **35** was converted to oligomeric derivatives, as neither substrate **35** nor any RCM monomer products were isolated from the reaction mixture. Despite low yield and the required high catalyst loading, the strategy based on bending of C_{sp}–C_{sp}–C(R) angles via the formation of alkyne–$Co_2(CO)_6$ complex worked successfully. Thus, the experimental results obtained confirmed the theoretical predictions of the DFT analysis described above (Table 5). The structure of the macrocycle **36** was confirmed by NMR and X-ray analyses (Figure 2). The X-ray studies revealed the *Z* configuration of the double bond formed.

Macrocycle **36** exists in the solid state as a mixture of two enantiomers with planar chirality due to the possible different orientation of the double bond: over or above the plane of the molecule. The X-ray data also indicated the significant bending of both C_{sp}–C_{sp}–C(R) angles: C(Co)–C(Co)–C of 145.0° and C–C(Co)–C(Co) of 147.2°. These data are in good agreement with calculated values of the same bond angles.[46]

The structural investigation of the compound **36** by NMR corroborated the restricted interconversion between both enantiomers at room temperature (Scheme 5). Thus, H^A atoms were found to be diastereotopic with a significant difference in chemical shift values (∼1 ppm). Variable-temperature ^{1}H NMR experiments were helpful to estimate that the coalescence temperature of this process is 42 °C, while the activation energy for the interconversion is 14.2 kcal/mol.[47]

Taking into account the significant bending of both C_{sp}–C_{sp}–C(R) angles in the synthesized macrocycle **36**, we decided to evaluate the influence of the geometry change to the ring-

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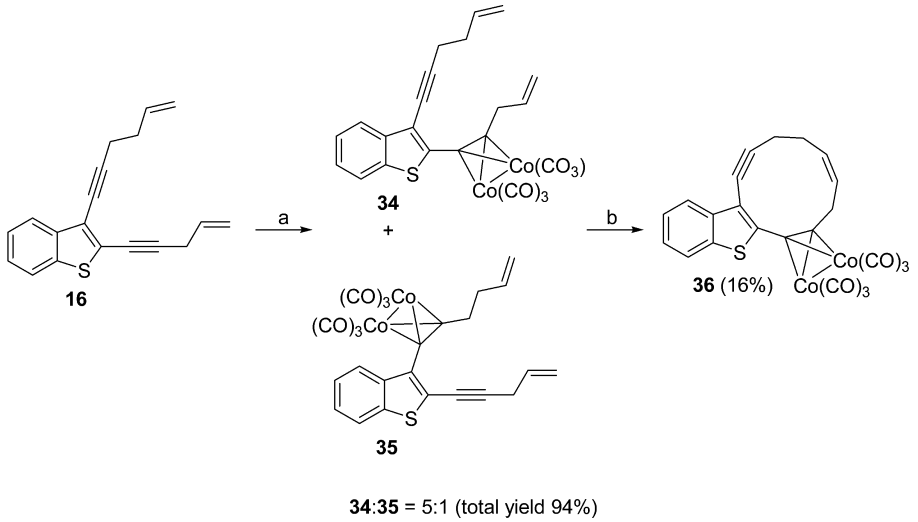
Scheme 4. RCM of $Co_2(CO)_6$ Complex of Dienediyne 16[a]



[a]Reagents and conditions: (a) $Co_2(CO)_8$ (2.6 equiv), THF, rt, 1.5 h; (b) Grubbs II catalyst (40 mol %), DCM, *C* = 0.001 M, reflux, 5 h.

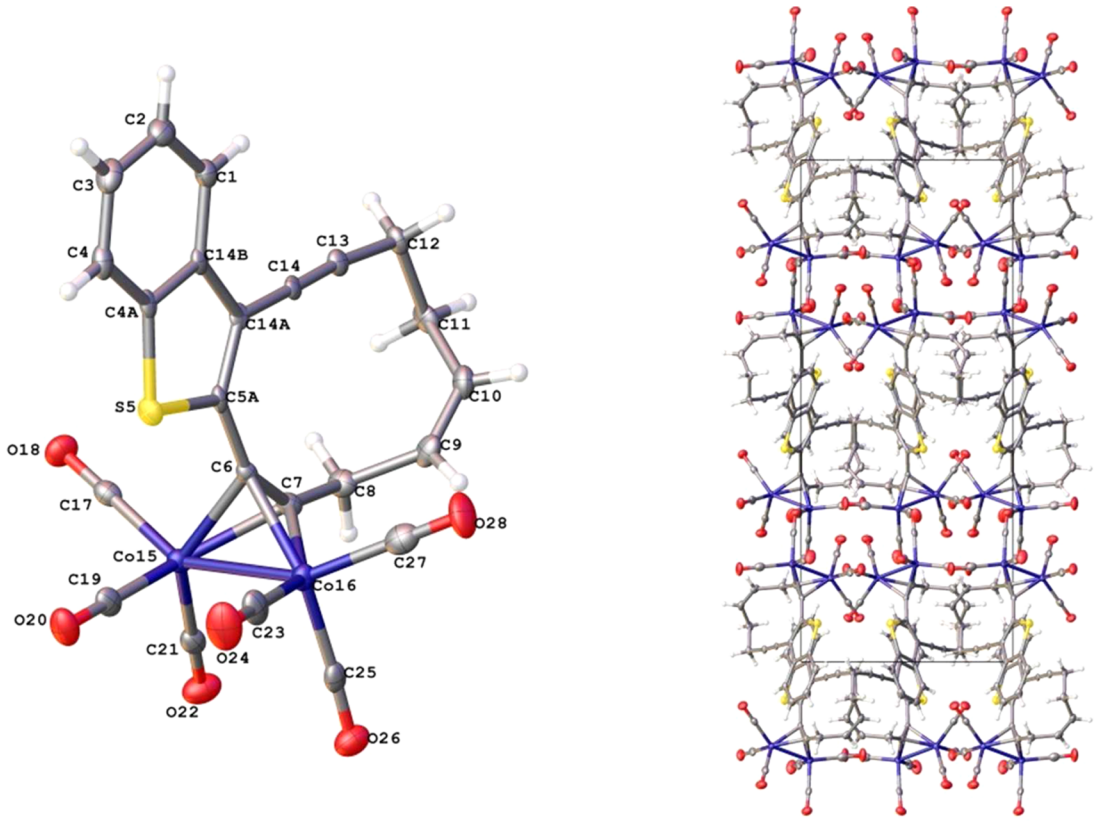
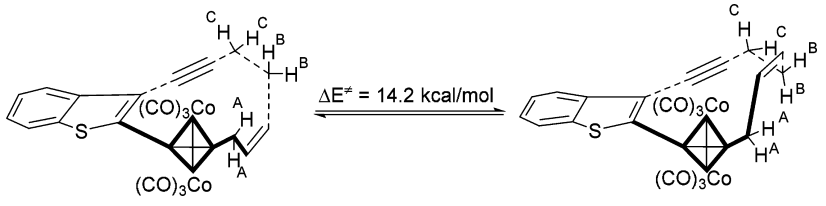


Figure 2. Molecular structure of $Co_2(CO)_6$-protected macrocycle **36**.

Scheme 5. Interconversion Process for Enantiomers of Dienediyne $Co_2(CO)_6$ Complex 36 in $CDCl_3$



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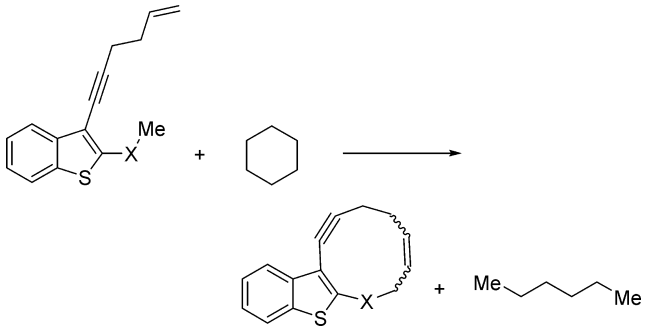
strain energy (SE) of target macrocycles. The values of SE of macrocycles **4**, **4′**, **5**, **5′**, and **36** were calculated by the method described previously for the evaluation of SE of cyclooctynes and enediynes (Table 6).[48−50] The data obtained revealed that

Table 6. Strain Energies (SE) of Enediynes 4, 4′, 5, and 5′ and Co Complex 36[a]



4, 4', 5, 5', 36

entry	macrocycle	X	olefin configuration	SE, kcal/mol
1	**4**	C≡C	*Z*	10.2
2	**4'**	C≡C	*E*	10.2
3	**5**	C≡C−CH_2	*Z*	3.6
4	**5'**	C≡C−CH_2	*E*	2.1
5	**36**	$(CO)_3Co$−$Co(CO)_3$	*Z*	1.7

[a]For details of the DFT calculations, see the Supporting Information.

Co complexion reduces the SE from the value of 10.2 kcal/mol (for dienenediyne **4**) to 1.7 kcal/mol (for Co complex **36**). Moreover, the value of SE of $Co_2(CO)_6$ complex **36** was found to be similar to the SE of both 12-membered macrocycles **5** and **5′**, which were easily obtained using RCM technique with the preferred formation of less strained product **5′**.[21] To conclude, the surplus SE of RCM products may be assumed as an explanation for the thermodynamic infeasibility of RCM for the synthesis of smaller than 12-membered dienediyne rings.

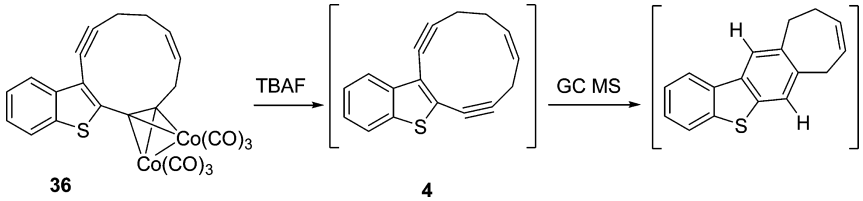
Attempted Co-decomplexation from macrocycle **36** was carried out using mild conditions: TBAF in THF, previously employed for the decomposition of $Co_2(CO)_6$−alkyne complexes of some enediynes.[51] HRMS data and ^{1}H NMR analysis of the reaction mixture revealed that the triple-bond deprotection gave the desired dienediyne **4**. This compound did not undergo Bergman cycloaromatization at room temperature. In contrast, GC/MS analysis of this mixture proved the spontaneous Bergman cyclization of the dienediyne **4** under the GC/MS conditions with the formation of compound with molecular mass [M + 2] as the main reaction product (Scheme 6).[52]

In summary, on the basis of experimental and DFT calculation data, the ring-closing metathesis was found to be a restricted technique for the synthesis of 10- and 11-membered dienediynes fused to *S,N*-heteroindenes and the benzene ring. Good agreement of experimental and calculated data indicates that the values of Gibbs free energy change of the RCM reactions can be useful for simple estimation of the probability of similar reactions to proceed. To overcome thermodynamic barriers, a $Co_2(CO)_6$−alkyne complex was successfully employed as the substrate to afford the first example of the ring-closing metathesis in the synthesis of 11-membered dienediyne macrocycle. However, a low yield on a final step makes the approach based on the RCM less attractive for the synthesis of dienediynes fused to heterocycles with a ring size smaller than 12. The search for more efficient macrocyclization techniques is underway.

EXPERIMENTAL SECTION

General Information and Methods. Solvents, reagents, and chemicals used for reactions were purchased from commercial suppliers. Catalysts $Pd(PPh_3)_4$, Grubbs II and Hoveyda−Grubbs II catalyst were purchased from Sigma-Aldrich. Solvents were dried under standard conditions; chemicals were used without further purification. Compounds **6**, **9a**, **11**,[19] and **9b**[53] were synthesized by known procedures without any modification. All reactions were carried out under Ar in flame-dried glassware. Evaporation of solvents and concentration of reaction mixtures were performed in vacuo at 30−40 °C on a rotary evaporator. Thin-layer chromatography (TLC) was carried out on silica gel plates (silica gel 60, F^{254}) with detection by UV or staining with a basic aqueous solution of $KMnO_4$. Normal-phase silica gel (silica gel 60, 230−400 mesh) was used for preparative chromatography. Melting points (mp) determined are uncorrected. IR spectra were recorded for thin films on KBr or using the ATR technique. Absorption values are reported in reciprocal centimeters (cm^{-1}). ^{1}H NMR spectra were recorded at 300 MHz (for the mixtures of **12**/**13**, and **34**/**35**) and at 400 MHz for all other compounds in $CDCl_3$. ^{13}C NMR spectra were measured at 100 MHz in $CDCl_3$. COSY experiments for compounds **10**, **15**, and **16** and variable-temperature NMR experiments for $Co_2(CO)_6$ complex **36** were measured at 500 MHz in $CDCl_3$. The ^{1}H NMR data are reported as the chemical shift (δ), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constants (*J*, Hz), number of protons, and assignment.[54] The ^{13}C NMR data are reported as the chemical shift (δ) and type of carbon (p, primary; s, secondary; t, tertiary; q, quaternary), determined from DEPT 135 experiments (for Co complexes DEPT 135 experiments were not performed). Chemical shifts are reported as δ values (ppm) and referenced to residual solvent (δ = 7.26 ppm for ^{1}H; δ = 77.00 ppm for ^{13}C). Low-resolution mass spectra (MS) were obtained using electron-impact ionization (EI), 70 eV, or fast atom bombardment (FAB) ionization with 3-nitrobenzyl alcohol (3-NBA) matrix. High-resolution mass spectra (HRMS) were measured using EI or FAB. All mass spectra were measured using a double-focusing sector field instrument with reversed Nier−Johnson geometry. GC−MS experiments were carried out at a heating rate of 15 °C min^{-1} from a temperature of 60 up to 150 °C. The single-crystal X-ray diffraction studies for the compound **36** were carried out on a diffractometer at 100(2) K using Mo Kα radiation (λ = 0.71073 Å). For further information, see the Supporting Information.

Scheme 6. Alkyne Decomplexation and Cyclization of Macrocycle 36



36 **4**

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*4-(3-Iodobenzo[b]thiophene-2-yl)but-3-yn-1-ol (**7**).*[19] To an Ar-flushed solution of 6-[2-(methylsulfanyl)phenyl]hexa-3,5-diyn-1-ol (**6**) (7.34 mmol, 1.59 g) in DCM (50.0 mL) was added a solution of iodine (7.34 mmol, 1.86 g) in DCM (50.0 mL) dropwise. The reaction mixture was stirred at room temperature for 1.5 h. Then the reaction mixture was diluted with a 5% aqueous solution of $Na_2S_2O_3$, the organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layers were washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel using cyclohexane/ethyl acetate (3:1) as the eluent to give 2.26 g (94%) of **7** as a yellowish solid. Mp: 73−75 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.01 (t, J = 6.5, 1H), 2.83 (t, J = 6.1, 2H), 3.88−3.93 (m, 2H), 7.38−7.46 (m, 2H), 7.68−7.72 (m, 2H).

*3-Iodo-2-(4-iodobut-1-ynyl)benzo[b]thiophene (**8**).* A stirred solution of benzothiophene **7** (2.25 mmol, 739 mg), PPh_3 (4.32 mmol, 1.13 g), and imidazole (7.50 mmol, 510 mg) in anhydrous THF (15.0 mL) was cooled to −5 °C, and a well-ground powder of iodine (4.63 mmol, 1.17 g) was added to the reaction mixture in one portion in a stream of Ar. The reaction mixture was stirred under Ar at 0 °C over 2 h. To reach the full conversion of **7**, an additional amount of PPh_3 (0.864 mmol, 226 mg) and imidazole (1.87 mmol, 128.0 mg) was added to the reaction mixture at −5 °C under Ar, and the reaction mixture was stirred for additional 1 h at 0 °C. Then the reaction mixture was quenched with a 10% aqueous solution of $Na_2S_2O_3$ and extracted with diethyl ether, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography using pentane as the eluent to give 879 mg (89%) of **8** as a beige solid. Mp: 74−75 °C (lit.[19] mp 74−75 °C). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.14 (t, J = 7.3, 2H), 3.38 (t, J = 7.3, 2H), 7.38−7.46 (m, 2H), 7.68−7.72 (m, 2H).

*2-(But-3-en-1-ynyl)-3-(hex-5-en-1-ynyl)benzo[b]thiophene (**10**).* To a stirred solution of diiodobenzothiophene **8** (1.95 mmol, 854 mg) in DMF (10.0 mL) was added $Pd(PPh_3)_4$ (0.0975 mmol, 112 mg). The reaction vial was evacuated and flushed with Ar several times. Afterward, CuI (0.292 mmol, 55.0 mg) followed by K_2CO_3 (15.6 mmol, 2.11 g) were added, the reaction vial was sealed and degassed once again, and the reaction mixture was stirred for 5 min. Then, MeOH (15.6 mmol, 0.506 g, 0.640 mL) followed by (hex-5-en-1-yl)trimethylsilane (**9a**) (3.9 mmol, 593 mg) was added. The reaction mixture was allowed to stir at 50 °C for 4 h, cooled, poured into a saturated solution of NH_4Cl, and extracted with ethyl acetate. The combined organic layers were washed with a saturated solution of NH_4Cl and two times with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel using pentane as the eluent to give 406 mg (79%) of **10** as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.43−2.48 (m, 2 H, CH_2), 2.67 (t, ^3J = 7.1, 2H, CH_2), 5.09−5.12 (m, 1H, CH^B), 5.19 (dq, ^3J = 17.1, ^4J = ^2J = 1.6, 1H, CH^A), 5.64 (dd, ^3J = 11.2, ^2J = 2.0, 1H, $CH^{B\prime}$), 5.83 (dd, ^3J = 17.6, ^2J = 2.0, 1H, $CH^{A\prime}$), 5.96−6.07 (m, 2H, CH^X), 6.12 (dd, ^3J = 17.6, ^3J = 11.2, 1H, $CH^{X\prime}$), 7.36−7.43 (m, 2H, H^{Ar}), 7.69−7.73 (m, 1H, H^{Ar}), 7.83−7.87 (m, 1H, H^{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 19.8 (s), 33.0 (s), 74.3 (q), 83.1 (q), 97.0 (q), 97.3 (q), 116.0 (s), 116.9 (t), 122.0 (t), 123.4 (q), 123.5 (t), 125.0 (t), 126.1 (t), 128.0 (s), 136.8 (t), 138.6 (q), 139.0 (q) (one C_q signal overlaps with others). IR (KBr, thin film) ν_{max} (cm^{-1}): 3066, 3005, 2978, 2920, 2842, 2223, 2192, 1641, 1603, 1508, 1458, 1434, 1361, 1320, 1288, 1225, 1160, 1134, 1120, 1069, 1016, 992, 967, 917, 758, 730, 643. MS (EI, 70 eV), m/z: 262 (100, M^+), 221 (77), 184 (49), 176 (13), 139 (12). HRMS (m/z): calcd for $C_{18}H_{14}S$ $[M]^+$ 262.0816, found 262.0815.

*Mixture of [(3-Iodobenzo[b]thiophene-2-yl)ethynyl]-trimethylsilane (**12**) and 2-Ethynyl-3-iodobenzo[b]thiophene (**13**).*[19] To an Ar-flushed solution of trimethyl[[2-(methylsulfanyl)-phenyl]buta-1,3-diyn-1-yl]silane (**11**) (10.9 mmol, 2.67 g) in dry DCM (50.0 mL) was added a solution of iodine (10.9 mmol, 2.78 g) in dry DCM (150 mL) dropwise (~30 min) at room temperature. The reaction mixture was stirred at room temperature for 1.5 h, anhydrous powder of $Na_2S_2O_3$ was added to the reaction mixture, and the suspension obtained was stirred for 15 min and filtered. DCM was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel using pentane as the eluent to give 3.43 g of the mixture of **12** and **13** in molar ratio (9.8:1) according to ^{1}H NMR as a dark oil. Calculated overall yield of **12** was 3.17 g (82%), and that of **13** was 260 mg (8%). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.32 (s, 9H from **12**), 3.74 (s, 1H from **13**), 7.38−7.47 (m, 2H from **12** and 2H from **13**), 7.62−7.80 (m, 2H from **12** and 2H from **13**).

*3-Iodo-2-(pent-4-en-1-ynyl)benzo[b]thiophene (**14**).* To an Ar-flushed solution of the mixture of **12** and **13** (1.52 g of the mixture, 3.94 mmol, 1.405 g of **12** and 0.401 mmol, 114 mg of **13**) in absolute DMF (35.0 mL) was added K_2CO_3 (34.7 mmol, 4.79 g), and the reaction mixture was evacuated and flushed with Ar several times. After that, MeOH (34.7 mmol, 1.11 g, 1.41 mL) was added, and the reaction mixture was stirred for 3 min. The CuI (0.434 mmol, 82.0 mg) was added in one portion in the stream of Ar, and the reaction mixture was stirred for an additional 1−2 min. Then allyl bromide (52.1 mmol, 6.31 g, 4.51 mL) was injected to the reaction mixture in one portion, and the mixture obtained was stirred at room temperature for 14 h. The mixture was poured into a saturated solution of NH_4Cl and extracted with ethyl acetate. The combined organic layers were washed with a saturated solution of NH_4Cl and twice with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel using pentane as the eluent to give 1.26 g (90%) of **14** as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.33 (dt, ^3J = 5.2, ^4J = 1.8, 2H, CH_2), 5.24 (dq, ^3J = 10.0, ^4J = ^2J = 1.8, 1H, CH^B), 5.55 (dq, ^3J = 17.0, ^4J = ^2J = 1.8, 1H, CH^A), 5.89−5.98 (m, 1H, CH^X), 7.37−7.46 (m, 2H, H^{Ar}), 7.68−7.71 (m, 2H, H^{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.2 (s), 77.4 (q), 86.8 (q), 96.9 (q), 117.0 (s), 122.0 (t), 125.4 (q), 125.6 (t), 126.0 (t), 126.3 (t), 131.3 (t), 138.60 (q), 140.4 (q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3060, 3014, 2882, 2226, 1640, 1452, 1430, 1413, 1318, 1297, 1281, 1248, 1161, 1068, 1019, 988, 915, 855, 766, 750, 723. MS (EI, 70 eV), m/z: 324 (100, M^+), 197 (33), 169 (10), 165 (18), 152 (18). HRMS (m/z): calcd for $C_{13}H_9IS$ $[M]^+$ 323.9470, found 323.9467.

General Procedure for the Synthesis of Terminal Diolefins 15 and 16. To a degassed stirred solution of 3-iodobenzothiophene **14** (1.00 equiv) in DMF were added $Pd(PPh_3)_4$ (5 mol %), CuI (10 mol %), and KF (5.00 equiv). The reaction vial was sealed, evacuated, and flushed with Ar several times. Then MeOH (10.0 equiv) followed by TMS-protected enyne **9a** or **9b** (2.00 equiv) were added. The reaction mixture was allowed to stir at 40 °C for 14 h. After cooling, the reaction mixture was poured into a saturated solution of NH_4Cl and extracted with ethyl acetate. The combined organic layers were washed with a saturated solution of NH_4Cl and twice with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel using pentane as the eluent.

*2,3-Di(pent-4-en-1-ynyl)benzo[b]thiophene (**15**).* Enediyne **15** was synthesized in accordance with the general procedure from 3-iodobenzothiophene **14** (0.200 mmol, 64.0 mg) and (pent-4-en-1-ynyl)trimethylsilane **9b**[53] (0.400 mmol, 55.0 mg) in DMF (2.00 mL). Purification of the crude product by column chromatography gave 17.0 mg (33%) of **15** as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.33−3.36 (m, 4H, $2CH_2$), 5.19−5.24 (m, 2H, CH^B, $CH^{B\prime}$), 5.47−5.58 (m, 2H, CH^A, $CH^{A\prime}$), 5.87−6.01 (m, 2H, CH^X, $CH^{X\prime}$), 7.36−7.43 (m, 2H, H^{Ar}), 7.70−7.72 (m, 1H, H^{Ar}), 7.84−7.87 (m, 1H, H^{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.1 (s), 24.3 (s), 76.1 (q), 76.3 (q), 93.1 (q), 96.9 (q), 116.4 (s), 116.8 (s), 122.0 (t), 122.5 (q), 123.3 (t), 124.9 (t), 125.9 (t), 126.1 (q), 131.5 (t), 132.1 (t), 138.1 (q), 138.9 (q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3083, 3062, 3014, 2981, 2922, 2222, 1641, 1459, 1433, 1415, 1363, 1320, 1284, 1217, 1160, 1131, 1067, 1016, 989, 917, 853, 803, 753, 730. MS (EI, 70 eV), m/z: 262 (26, M^+), 234 (5), 222 (11), 221 (12), 205 (19), 195 (10), 175 (8), 153 (9), 58 (37), 43 (100). HRMS (m/z): calcd for $C_{18}H_{14}S$ $[M]^+$ 262.0816, found 262.0813.

*3-(Hex-5-en-1-ynyl)-2-(pent-4-en-1-ynyl)benzo[b]thiophene (**16**).* Enediyne **16** was synthesized in accordance with the general procedure

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from 3-iodobenzothiophene **14** (1.00 mmol, 324 mg) and (hex-5-en-1-ynyl)trimethylsilane **9a**[19] (2.00 mmol, 304 mg) in DMF (5.00 mL). Purification of the crude product by column chromatography gave 181 mg (65%) of **16** as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.42−2.47 (m, 2H, CH_2^b), 2.65 (t, ^3J = 7.1, 2H, CH_2^a), 3.33 (dt, ^3J = 5.1, ^4J = 1.8, 2H, CH_2^c), 5.10 (dq, ^3J = 10.2, ^4J = ^2J = 1.1, 1H, CH^B), 5.15−5.24 (m, 2H, CH^A, $CH^{B\prime}$), 5.51 (dq, ^3J = 17.0, ^4J = ^2J = 1.8, 1H, $CH^{A\prime}$), 5.88−6.05 (m, 2H, CH^X, $CH^{X\prime}$), 7.35−7.42 (m, 2H, H^{Ar}), 7.69−7.71 (m, 1 H, H^{Ar}), 7.82−7.84 (m, 1 H, H^{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 19.7 (s), 24.3 (s), 33.0 (s), 74.3 (q), 76.1 (q_q), 96.2 (q), 96.7 (q), 115.9 (s), 116.7 (s), 122.0 (t), 122.7 (q), 123.3 (t), 124.9 (t), 125.7 (q), 125.8 (t), 131.5 (t), 136.9 (t), 138.1 (q), 139.0 (q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3077, 2980, 2920, 2224, 1641, 1458, 1433, 1415, 1363, 1320, 1286, 1217, 1160, 1108, 1067, 1016, 990, 916, 759, 731, 643. MS (EI, 70 eV), *m*/*z*: 276 (100, M^+), 235.0 (82), 234.0 (50), 221.0 (11), 208 (15), 202 (32), 43.0 (31). HRMS (*m*/*z*): calcd for $C_{19}H_{16}S$ $[M]^+$ 276.0973, found 276.0969.

General Procedure for the RCM Experiments for Diolefins 10, 15, and 16. Conditions a, c: To a solution of diolefin (20.0 μmol) in dry DCM (10.0 mL) or toluene (10.0 mL) in a 20 mL vial was added Grubbs II or Hoveyda−Grubbs II catalyst (7, 10, 20, or 30 mol %). The reaction vial was sealed, evacuated, flushed with Ar several times, and heated in a steel monoblock at 45 °C (for DCM) and at 115 °C (for toluene) for 14 h, which afforded only the starting diolefins **10**, **15**, and **16** in the reaction mixture according to TLC monitoring.

Conditions b: To a degassed solution of diolefin **10** (40.0 μmol, 10.5 mg) in dry DCM (20.0 mL) was added Grubbs II (7 mol %). The reaction mixture was heated under reflux in a stream of Ar for 14 h that afforded only the starting diolefin **10** in the reaction mixture according to TLC monitoring.

Mixture of $Co_2(CO)_6$ Complexes of 3-(Hex-5-en-1-ynyl)-2-(pent-4-en-1-ynyl)benzo[*b*]thiophene 34 and 35. To a stirred solution of diolefin **16** (0.230 mmol, 64.0 mg) in anhydrous THF (8.0 mL) was added $Co_2(CO)_8$ (0.60 mmol, 205 mg) in one portion in a stream of Ar. The reaction mixture was stirred under Ar at room temperature over 1.5 h. Then the solvent was removed under reduced pressure at room temperature, and the residue was purified by column chromatography using petroleum ether as the eluent to give 110 mg (85%) of the mixture of complexes **34** and **35** in molar ratio (5:1) according to ^{1}H NMR. Analytic data for the $Co_2(CO)_6$-complex **34**.[5S] ^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.41−2.46 (m, 2H, CH_2^b), 2.61 (t, ^3J = 7.1, 2H, CH_2^a), 3.33 (d, ^3J = 7.1 Hz, 2H, CH_2^c), 5.09−5.19 (m, 3H, CH^B, CH^A, $CH^{B\prime}$), 5.27−5.32 (m, 1H, $CH^{A\prime}$), 5.88−5.98 (m, 1H, CH^X) 6.06−6.16 (m, 1H, $CH^{X\prime}$), 7.35−7.42 (m, 2H, H^{Ar}), 7.69−7.70 (m, 1H, H^{Ar}), 7.83−7.85 (m, 1H, H^{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 20.0, 32.7, 39.4, 75.5, 79.0, 99.7, 99.9, 116.0, 117.5, 118.4, 122.0, 123.0, 125.0, 125.5, 136.0, 136.8, 138.5, 141.2, 144.8, 199.1. IR (neat) ν_{max} (cm^{-1}): 2917, 2087, 2047, 2006, 1639, 1571, 1488, 1426, 1315, 1196, 1103, 990, 916, 758, 729, 650, 511. MS (EI, 70 eV), *m*/*z*: 562 (16, M^+), 506 (17), 478 (84), 450 (29), 422 (98), 394 (97), 352 (100). HRMS (FAB): calcd for $C_{25}H_{16}O_6Co_2S$ $[M]^+$ 561.9326, found 561.9326.

$Co_2(CO)_6$ Complex of (8*Z*)-Benzo[*b*]thieno[3,4-*b*]-cycloundeca-3,8-diene-1,5-diyne (36). To a solution of the mixture of $Co_2(CO)_6$ complexes **34** and **35** (5:1, 0.178 mmol, 100 mg) in dry DCM (178 mL, thoroughly flushed with argon) was added Grubbs II catalyst (0.071 mmol, 60.0 mg). The reaction mixture was heated at reflux for 5 h under static pressure of Ar from a balloon. After cooling, ethyl vinyl ether (0.200 mL) was added to the reaction mixture, and the solvent was evaporated under reduced pressure to yield the crude product. Purification by column chromatography on silica gel using pentane as the eluent gave 15.0 mg of macrocyclic Co complex **36** (16%) as a dark red-purple crystals and 6 mg of recovered pure acyclic Co complex **34** (conversion 93%). Mp > 200 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.59 (br s, 4H, $2CH_2$), 3.60 (br s, 1H, CH), 4.50 (br s, 1H, CH), 5.49−5.55 (m, 1H, CH), 5.84−5.91 (m, 1H, CH), 7.33−7.29 (m, 2H, H^{Ar}), 7.69 (d, ^3J = 7.3 Hz,1H, H^{Ar}), 7.79 (d, ^3J = 7.3 Hz,1H, H^{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 20.0, 26.1, 34.1, 76.3, 78.5, 97.7, 99.2, 116.4, 122.1, 123.3, 125.1, 125.5, 125.8, 132.5, 139.4, 140.0, 147.7, 199.1. MS (EI, 70 eV), *m*/*z*: 534 (15, M^+), 478 (62), 450 (43), 422 (67), 394 (82), 366 (100). HRMS (FAB): calcd for $C_{23}H_{12}O_6Co_2S$ $[M]^+$ 533.9013, found 533.9014. The single crystals of $C_{23}H_{12}O_6Co_2S$ compound **36** were grown from pentane by slow evaporation of the solvent until dryness. A suitable crystal was selected and studied on a diffractometer at T = 100(2) K. Crystal Data: $C_{23}H_{12}O_6Co_2S$, M = 534.25, orthorhombic, space group *Pbca*, a = 11.4350(5) Å, b = 13.7734(4) Å, c = 27.2118(17) Å, V = 4285.8(3) Å^3, Z = 8, μ(Mo Kα) = 1.683 mm^{-1}, 9924 reflections measured, 4401 unique (R_{int} = 0.0481) which were used in all calculations. The final wR_2 was 0.0820 (all data), and R_1 was 0.0431 (> 2σ(I)). Crystallographic data for the structure reported in this work have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1011257.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H NMR spectra for all compounds synthesized; copies of ^{1}H, ^{13}C NMR and DEPT spectra for all new compounds; copies of COSY spectra for compounds **10**,**15**, and **16**; copies of HRMS and GCMS chromatograms for macrocycle **4**. Details for the variable-temperature NMR experiment for $Co_2(CO)_6$ complex **36**; details of conditions optimization for the synthesis of terminal diolefins **15** and **16**; X-ray data for the complex **36**; all computational details; and the comparison of X-ray diffraction data obtained for compound **36** with structural data obtained by calculations. X-ray data (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00409.

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Notes

The authors declare no competing financial interest.

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(55) It was impossible to separate this mixture by column chromatography because of close retention factors of both complexes. The pure complex **34** for analytical data was recovered from the next macrocyclization step.

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