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Synthetic and Mechanistic Investigations on the Rearrangement of 2,3-Unsaturated 1,4-Bis(alkylidene)carbenes to Enediynes

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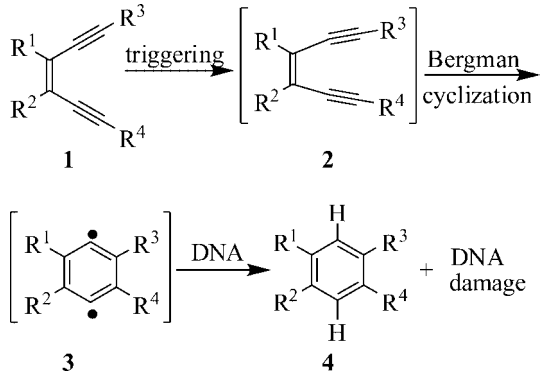
Dedicated to Professor Jayaraman Chandrasekhar on the occasion of his 55th birthday

Keywords: Vinylidenecarbene / Enediyne / Corey–Fuchs reaction / Bestmann–Ohira reagent / Enynes / Rearrangement

The synthesis of 3,4-ene-1,5-diynes, the key structural moiety present in several naturally occurring antitumor antibiotics, from 1,2-enedialdehydes under two different experimental conditions is reported. One method involves the dibromomethylenation of dialdehydes under Corey–Fuchs conditions (CBr_4, Ph_3P, and Zn) and treatment of the resulting tetrabromides with *n*BuLi or LDA to afford enediynes. The second method involves a base-mediated reaction of enedialdehydes with diethyl (1-diazo-2-oxopropyl)phosphonate (Bestmann–Ohira reagent) and subsequent transformation of the bis(diazo) compounds generated in situ to enediynes. While the transformation of bis(diazo) compounds to enediynes could take place exclusively through alkylidenecarbenes, generated in situ by geminal elimination of N_2, an alternative pathway, involving the vicinal elimination of HBr to afford an intermediate bromoalkyne and its subsequent metal-halogen exchange and protonation during workup, exists for the bis(dibromoalkylidenes). However, our deuterium-labeling experiments with a model substrate, deuterated *p*-methoxybenzylidene dibromide, established the predominance of the alkylidenecarbenes, generated in situ by metal-halogen exchange and elimination, for this substrate and, by analogy, for the tetrabromides as well. The scope of this novel methodology was extended to the synthesis of various heteroatom-based (S, Se, and P) enediynes by quenching the acetylides with suitable electrophiles.

Introduction

The irreversible cleavage of duplex DNA in tumor cells is central to combating cancer.[1] Although several natural[2] and synthetic[3] organic compounds exhibit DNA-cleavage activity, the application of many such compounds is severely limited by their scarcity, complexities associated with constructing their molecular structures, or generating the reactive species under biological conditions.[4] However, five different classes of natural products possessing a (*Z*)-3-hexen-1,5-diyne moiety, such as calicheamicin, esperamicin, dynemicin, kedarcidin, and C-1027 have attracted enormous attention due to their excellent DNA-cleaving ability.[5] These natural products operate through a four-stage mechanism, which involves (a) the recognition of and binding to DNA by a specific structural feature covalently bonded or complexed to the enediyne, (b) activation of the enediyne **1** towards Bergman cyclization[6] by a unique triggering mechanism, (c) Bergman cyclization to give 1,4-dehydroarene diradicals **3**, and (d) abstraction of hydrogen from DNA by the 1,4-dehydroarene diradicals **3**, thereby inflicting permanent damage on the genetic material (Scheme 1). The high potency shown by the structurally complex, natural, enediyne antibiotics motivated numerous groups to design and synthesize simpler functional analogs of these enediyne antibiotics.[5]



Scheme 1.

Construction of *Z*-enediyne subunits, in both linear and cyclic form, has been extensively carried out by various metal-mediated methods.[7–17] These include the Pd-catalyzed alkynylation[7] of 1,2-dihalides[7,8] or 1,2-ditri-

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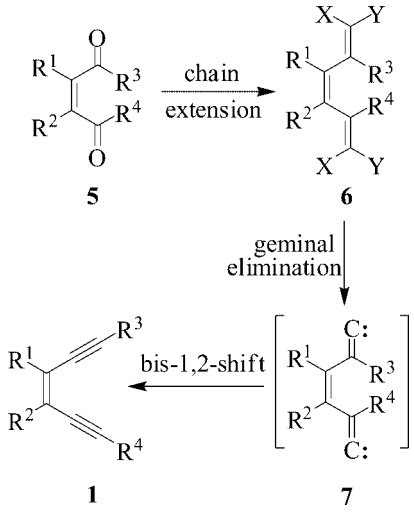
flates[9,10] and the coupling of vinyl/alkynyl stannanes,[11] boranes,[12] cuprates,[13] Li/Mg[14] and Zn[15] compounds, tellurides,[16] and carbenoids.[17] However, these procedures are often complicated by the cost and scarcity of 1,2-dihalides, the formation of complex mixtures in the case of triflates,[9] and the requirement of multistep reaction sequences and highly sensitive and often toxic organometallic reagents. Alternative strategies for the synthesis of enediynes, though limited in scope, focused on the generation of a double bond between and in conjugation with a 1,5-diyne.[18–20] Thermal (Diels–Alder),[18] photochemical (Norrish type II)[19] and various elimination[20] methods belong to this category.

We sought a methodology that is conceptually novel and operationally simple for the synthesis of functional analogs of the enediyne antibiotics. Our approach, which is based on the Fritsch–Buttenberg–Wiechell (FBW) rearrangement[21] of a vinylidenecarbene to its corresponding acetylene, does not require complex organometallic reagents and difficult reaction conditions. Although acetylenes [22] have been synthesized by the FBW rearrangement,[21,23–25] the synthesis of enediynes **1** from 1,2-enedialdehydes **5** by the 2,3-unsaturated bis(vinylidene)carbene **7** (Scheme 2)[26] remained an unexplored strategy until we recently reported our preliminary results.[27] This is despite the application of the FBW rearrangement to numerous systems in which the migrating group is an alkyl, aryl, or heteroaryl group.[28,29]

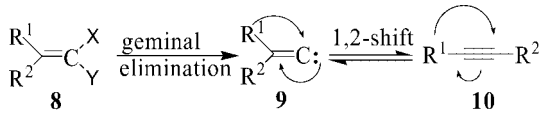


5 **6** **1** **7**

Scheme 2.

Results and Discussion

Since our approach relies on the rearrangement by a 1,2-shift of bis(vinylidene)carbene **7** to enediyne **1**, we needed efficient geminal elimination methods. Various such methods available in the literature for the generation of alkylidenecarbene **9** (Scheme 3)[23–24] include deprotonation–elimination from **8a**, desilylation–elimination from **8b**, metal-halogen exchange followed by elimination from **8c**[30] or **8d**,[23] extrusion of N_2 from **8e**,[31] and cycloelimination by pyrolysis from **8f**. Among these, the generation of an alkylidenecarbene from **8d** by metal-halogen exchange and elimination[23] appeared to be the most convenient method, as **8d** was easily accessible by the one-carbon elongation of corresponding aldehydes[32–34] or ketones[35] with the well-known Corey–Fuchs method of dihalomethylenation.[32]



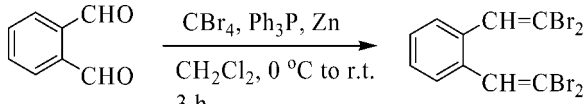
8 **9** **10**

8a: X = H, Y = Br, NH_2, OTf, N=NTs
8b: X = $SiMe_3$, Y = Cl, OTf, IPhOTf
8c: X = Cl, Y = S (O)Tol; **8d:** X = Y = Br
8e: XY = N_2; **8f**: XY = -$COOC(CH_3)_2OCO$-

Scheme 3.

At first, we used commercially available *o*-phthalaldehyde **11a** as the model substrate and subjected it to dibromomethylenation under the Corey–Fuchs conditions with CBr_4 and PPh_3 (Table 1). The desired product **12a** was isolated in low yield (42%) when stoichiometric amounts of CBr_4 were used in conjunction with 4 equiv. each of Ph_3P and Zn (Table 1, Entry 1). Although marginal improvement in the yield (56%) was noticed when the amounts of CBr_4, PPh_3, and Zn were increased 1.5-fold (Table 1, Entry 2), doubling the amounts of all the three reagents had a dramatic effect, providing the desired tetrabromide **12a** in 94% yield (Table 1, Entry 3). Entries 4 and 5 (Table 1) show that decreasing the amount of Zn or excluding it completely has a detrimental effect on the yield.

Table 1. Optimization of the reaction conditions for the dibromomethylenation of *o*-phthalaldehyde **11a**.



11a **12a**

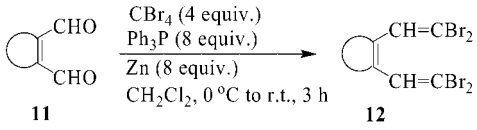
Entry	CBr_4 (equiv.)	PPh_3 (equiv.)	Zn (equiv.)	Yield (%)[a]
1	2	4	4	42
2	3	6	6	56
3	4	8	8	94
4	4	8	7	89
5	4	8	0	68

[a] Isolated yield after purification by silica gel column chromatography.

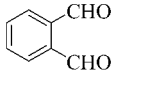
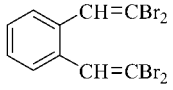
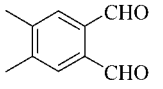
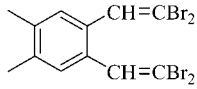
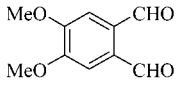
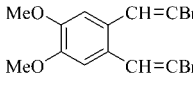
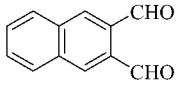
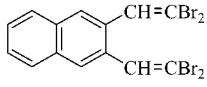
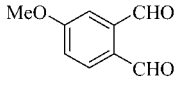
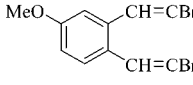
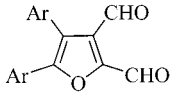
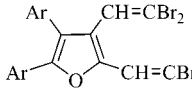
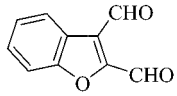
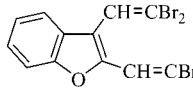
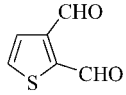
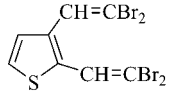
Under the optimized conditions described above, we subjected a variety of 2,3-unsaturated 1,4-dicarbonyl compounds, namely 1,2-enedialdehydes **11b**–**h**, to the dibromomethylenation conditions (Table 2). The desired tetrabromides **12b**–**h** were isolated in good to excellent yields (Table 2, Entries 2–8).

The transformation of tetrabromides **12a**–**h** to enediynes **13a**–**h** was performed under two different conditions, *n*BuLi or LDA. At first, the experimental conditions for the *n*BuLi-mediated reaction were optimized with tetrabromide **12a** as the model substrate (Table 3). The yields were 14%

Table 2. Conversion of various 1,2-enedialdehydes **11** to tetrabromides **12**.



11 **12**

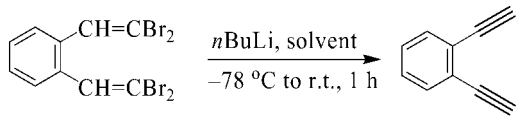
Entry	11	Dialdehydes **11**[a]	Tetrabromides **12**	Yield (%)[b] of **12**
1	**11a**[c]			94
2	**11b**			62
3	**11c**			46
4	**11d**			88
5	**11e**			66
6	**11f**[d]			80
7	**11g**			73
8	**11h**			95

[a] The dialdehydes **11a** and **11h** were commercially available. All other dialdehydes (**11b**–**g**) were prepared in the laboratory following published procedures; see ref.[36]. [b] Isolated yield after purification by silica gel column chromatography. [c] **12a**, reported in ref.,[37] was prepared by a procedure similar to the one we recently reported; see ref.[27] [d] Ar = 4-OMe-Ph.

and 55% when 2 equiv. and 4 equiv. of *n*BuLi in *n*-hexane, respectively, were used (Table 3, Entries 1 and 2). However, with 5 equiv. and 6 equiv. of *n*BuLi in *n*-hexane, tetrabromide **12a** afforded the desired enediyne **13a** in excellent yield (96% and 93%, respectively, Table 3, Entries 3 and 4). The yields were much lower when the reaction was carried out with the same amount of *n*BuLi (5 equiv.) in other solvents such as THF, toluene, or a benzene/toluene mixture (Table 3, Entries 5–7).

Under the optimized conditions described above (5 equiv. of *n*BuLi in *n*-hexane at –78 °C), tetrabromides **12b**–**h** were subsequently subjected to the *n*BuLi-mediated transformation to enediynes **13b**–**h** (Table 4, Entries 2–8). Although tetrabromides **12b**–**f** provided their corresponding enediynes **13b**–**f** in very high yields (Table 4, Entries 2–6), complex mixtures were isolated in the cases of tetrabromides **12g** and **12h** due to poor stability of the parent enediynes under these experimental conditions. The enediynes

Table 3. Optimization of the reaction conditions for the *n*BuLi-mediated transformation of tetrabromide **12a** to enediyne **13a**.



12a **13a**

Entry	*n*BuLi (equiv.)	Solvent	Yield (%)[a] of **13a**
1	2	*n*-hexane	14
2	4	*n*-hexane	55
3	5	*n*-hexane	96[b]
4	6	*n*-hexane	93
5	5	THF	23
6	5	toluene	78
7	5	benzene/toluene	57

[a] Isolated yield after purification by silica gel column chromatography. [b] 5 equiv. of *n*BuLi were required to obtain the best yields even upon scale up of the reaction (from 1 mmol to 5 mmol).

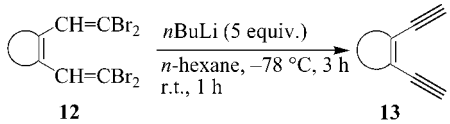
were subsequently isolated as their bis(trimethylsilyl) derivatives **13g** and **13h** (R = TMS) by quenching the reaction mixtures with TMSCl (Table 4, Entries 7–8).

In a parallel strategy, tetrabromides **12a**–**h** were treated with LDA. Optimization of the LDA-mediated transformation of tetrabromide **12a** to enediyne **13a** was carried out by screening different solvents and by varying the amount of LDA (Table 5). Although stoichiometric amounts of LDA were insufficient to obtain the desired enediyne in a considerable amount (Table 5, Entry 1), increasing the amount of LDA in toluene led to a gradual increase in the yield of **13a** (Table 5, Entries 2–5). The best yield of **13a** (88%) was obtained when excess (6 equiv.) LDA in toluene was used (Table 5, Entry 4). When the same amount of LDA was used in other solvents such as THF, *n*-hexane, or toluene, the yields were only moderate (Table 5, Entries 6–8).

The optimized conditions described above (6 equiv. of LDA in toluene at –78 °C) were employed for the conversion of tetrabromides **12b**–**h** to enediynes **13b**–**h** (Table 6). As in the case of the *n*BuLi-mediated reactions of **12g** and **12h** (Table 4, Entries 7–8), the parent enediynes were transformed in situ into their TMS derivatives for convenient isolation and characterization (Table 6, Entries 7–8).

The strategy developed for the synthesis of enediynes **13** from enedialdehydes **11** through bis(alkylidene dibromides) **12** involved two steps requiring isolation and purification of the intermediate **12**. Furthermore, the transformation of **12** to enediynes **13** required strong bases such as *n*BuLi or LDA. Therefore, we embarked on the idea of developing another strategy, which involved a one-pot transformation of enedialdehydes **11** to enediynes **13** through bis(diazo) compounds. Although dialkyl (diazomethyl)phosphonate (**14**, Seyferth–Colvin–Gilbert reagent, DAMP) has been reacted with ketones,[31] and its synthetic equivalent dialkyl (1-diazo-2-oxopropyl)phosphonate (**15**, Bestmann–Ohira reagent, BOR) has been reacted with aldehydes[44] for the synthesis of acetylenes,[45] the synthesis of enediynes **13**

Table 4. *n*BuLi-mediated transformation of tetrabromides **12** to enediynes **13**.

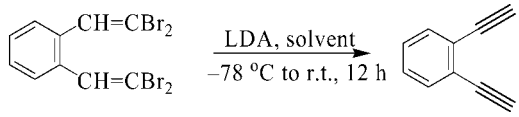


12 **13**

Entry	Tetrabromide **12**	Enediyne **13**, yield (%)[a]	
1	**12a**	**13a**	96
2	**12b**	**13b**	84
3	**12c**	**13c**	71
4	**12d**	**13d**	67
5	**12e**	**13e**	91
6	**12f**[b]	**13f**[b]	70
7	**12g**	**13g**	33[c]
8	**12h**	**13h**	43[c]

[a] Isolated yield after purification by silica gel column chromatography; **13a**–**e** and **13h** are known compounds; see ref.[38–43] [b] Ar = 4-OMe-Ph. [c] The parent enediyne (R = H), due to its instability under these experimental conditions, was isolated as its bis(trimethylsilyl) derivative (R = TMS).

Table 5. Optimization of the reaction conditions for the LDA-mediated transformation of tetrabromide **12a** to enediyne **13a**.

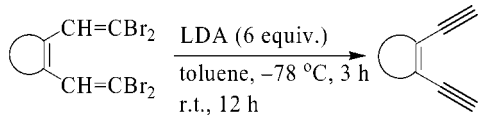


12a **13a**

Entry	LDA (equiv.)	Solvent	Yield (%)[a] of **13a**
1	2	toluene	<5
2	4	toluene	41
3	5	toluene	79
4	6	toluene	88
5	7	toluene	84
6	6	THF	60
7	6	*n*-hexane	66
8	6	benzene/toluene (1:1)	61

[a] Isolated yield after purification by silica gel column chromatography.

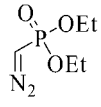
Table 6. LDA-mediated transformation of tetrabromide **12** to enediyne **13**.



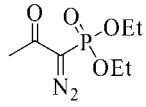
12 **13**

Entry	Tetrabromide **12**	Enediyne **13**	Yield (%)[a]
1	**12a**	**13a**	88
2	**12b**	**13b**	68
3	**12c**[b]	**13c**	84
4	**12d**	**13d**	44
5	**12e**	**13e**	87
6	**12f**	**13f**	61
7	**12g**	**13g**	26[c]
8	**12h**	**13h**	31[c]

[a] Isolated yield after purification by silica gel column chromatography. [b] Heated at 70 °C for 4 h. [c] The parent enediyne, due to its instability under these experimental conditions, was isolated as its bis(trimethylsilyl) derivative (R = TMS).



14
(DAMP)



15
(BOR)

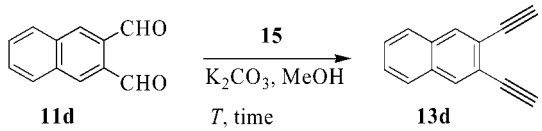
from enedialdehydes **11** with either of these reagents remains unreported heretofore.

Initially, the efficacy of DAMP (**14**) was investigated for the transformation of enedialdehydes **11** to enediynes **13** with phthalaldehyde **11a** as the model substrate. However, the desired enediyne **13a** was isolated only in low yield (15%) even with an excess (6 equiv.) of DAMP (**14**) in the presence of *t*BuOK as the base at low temperature (–78 °C) for 12 h. The problems associated with the multi-step preparation of the reagent, its poor storability, the requirement of a strong base such as *t*BuOK, and prolonged maintenance of low temperature (for 12 h) prompted us to employ an alternative reagent such as BOR (**15**),[44,45] which can be prepared conveniently on a multi-gram scale in a single step from commercially available diethyl (2-oxopropyl)phosphonate and stored without any appreciable decomposition. More importantly, only mild conditions are required for the key step.

The reaction of naphthalene-1,2-dicarbaldehyde (**11d**) with BOR (**15**, 3 equiv.) mediated by K_2CO_3 (4 equiv.) at room temperature provided the desired enediyne **13d** in 38% yield (Table 7, Entry 1). Increasing the amount of the reagent (to 4 equiv.) improved the yield considerably (Table 7, Entry 2). However, a strong improvement in the yield of **13d** (84%) was noticed when the reaction mixture

was maintained at 0 °C initially for a period of 30 min (Table 7, Entry 3). A further increase in the amount of reagents had only a marginal effect (Table 7, Entry 4).

Table 7. Optimization of the reaction conditions for the transformation of dialdehyde **11d** to enediyne **13d** with BOR (**15**).



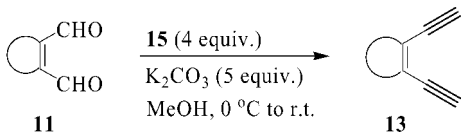
11d **13d**

Entry	**15** (equiv.)	K_2CO_3 (equiv.)	Temp [°C]	Time [h]	Yield (%)[a] of **13d**
1	3	4	room temp.	8	38
2	4	5	room temp.	7	53
3	4	5	0 °C to room temp.	0.5–11	84
4	5	6	0 °C to room temp.	0.5–11	82

[a] Isolated yield after purification by silica gel column chromatography.

Under the optimized conditions described above, we transformed a variety of 1,2-dialdehydes **11a**–**b**, **d**–**f**, and **g**–**h** to their corresponding enediynes in good yields (Table 8).

Table 8. Conversion of dialdehydes **11** to enediynes **13** with BOR.



11 **13**

Entry	Aldehyde **11**	Enediyne **13**	Time [h]	Yield (%)[a] of **13**
1	**11a**	**13a**	11.5	72
2	**11b**	**13b**	7.5	79
3	**11d**	**13d**	11	84
4	**11e**	**13e**	15.5	76
5	**11f**	**13f**	6.5	64
6	**11g**	**13g**[b]	15	[c]
7	**11h**	**13h**[b]	8	45

[a] Isolated yield after purification by silica gel column chromatography. [b] R = H. [c] Decomposition on silica gel.

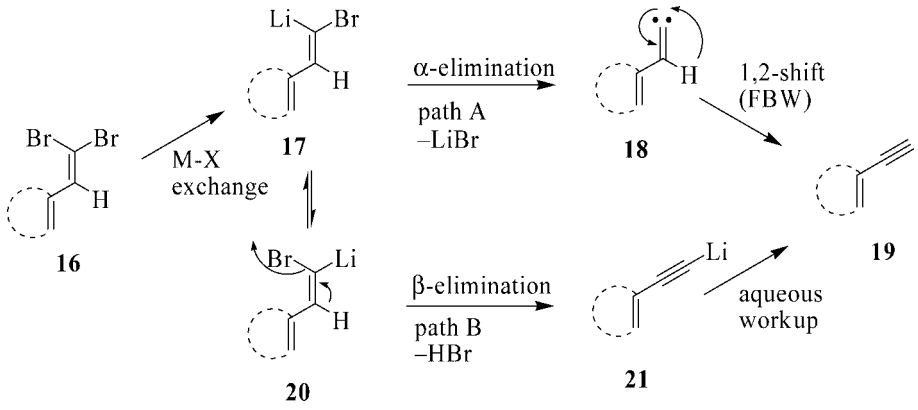
Mechanistic Studies

It is well documented in the literature that 1,1-dihaloalkenes (e.g. **8**, X, Y = halogen, Scheme 3), on treatment with a strong base such as *n*BuLi or LDA, produce acetylenes (vide supra). In the case of 2,2-disubstituted 1,1-dihaloalkenes (**8**, X = Y = halogen; R^1 and $R^2 \neq$ H, Scheme 3), metal-halogen exchange followed by a geminal elimination to generate alkylidenecarbenes/carbenoids **9**, which are converted to acetylenes **10** by a 1,2-shift of one of the β-substituents (FBW rearrangement), are the mechanistic steps.[23,28] For instance, the transformation of 1,1-dihalo-2,2-diarylethylenes (**8**, X = Y = halogen; $R^1 = R^2$ = Ar, Scheme 3) to diarylacetylenes (**10**, $R^1 = R^2$ = Ar, Scheme 3) involves a carbenoid as an intermediate.[46] However, in the case of 1,1-dihaloalkenes possessing a β-hydrogen (**8**, X = Y = halogen; R^1 or R^2 = H, Scheme 3), a β-elimination and subsequent metal-halogen exchange of a haloacetylene (**10**, R^1 or R^2 = halogen, Scheme 3) is assumed to be the mechanistic pathway.[47] While the carbene/carbenoid pathway, apparently the only pathway available, has been widely accepted for the former,[23] the β-elimination pathway for the latter remained speculative. This ambiguity exists for the transformation of 1-haloalkenes possessing a β-hydrogen (e.g. **8**, X = halogen, Y = H; R^1 or R^2 = H, Scheme 3) to the corresponding acetylenes (**10**, R^1 or R^2 = H, Scheme 3) as well. For instance, an alkylidenecarbene was suggested as an intermediate in the formation of phenylacetylene from β-styryl bromide in the presence of PhLi.[48] From stereochemical study and low-temperature experiments, a carbenoid was found to be the intermediate in the conversion of 1-halo-2-arylpropene to the corresponding acetylene.[49] However, Schlosser and coworkers ruled out the involvement of any alkylidenecarbene in the reaction of β-chlorostyrene with organolithium, which produced the corresponding acetylene.[50] Based on their labeling experiments, an alternate mechanism (E_2C_B) was proposed.

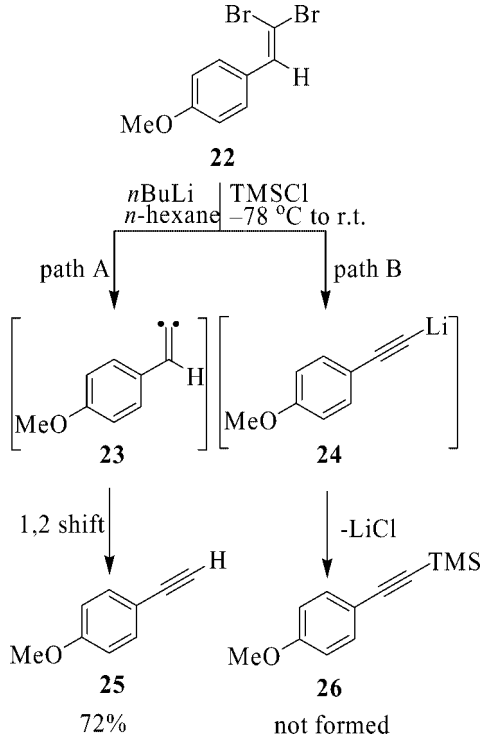
In view of the above, we considered two alternative mechanistic pathways for the formation of enediynes **13**, i.e. the carbene pathway and the β-elimination pathway and proposed to establish the pathway that is operative by taking 2-aryl 1,1-dibromoethylene **16** as the model substrate (Scheme 4). In dibromide **16**, the more sterically hindered bromine[51] is likely to undergo metal-halogen exchange to provide carbenoid **17**. Carbenoid **17** or its α-elimination product vinylidenecarbene **18** (path A) would undergo a 1,2-shift (FBW rearrangement) to afford acetylene **19**.[52] Alternatively, carbenoid **17** could isomerize to give **20**,[53] which is poised to undergo HBr elimination rather than α-elimination since Br and the β-H are *trans* to each other, affording the acetylide **21**, which would furnish acetylene **19** upon aqueous workup.

In order to ascertain the mechanism which is operative in the conversion of alkylidene dibromide **16** to acetylene **19** (and by analogy tetrabromide **12** to enediyne **13**), we performed a preliminary experiment as shown in Scheme 5. Thus, alkylidene dibromide **22** was prepared from *p*-methoxybenzaldehyde in 64% yield.[54] Dibromide **22** was then treated with *n*BuLi (2 equiv.) under conditions similar to those employed for the desired transformation of tetrabromides **12** to enediynes **13**.[55] The reaction mixture was quenched with excess TMSCl (3 equiv.) in anticipation that if the carbene mechanism were operative (Scheme 4, path A), the product would be **25**, which is expected to form by metal-halogen exchange to form the vinylidenecarbene **23**, followed by an intramolecular 1,2-shift. No incorporation of an external electrophile is expected. On the other hand, path B, which involves a deprotonation step, would provide TMS-acetylene **26**. Analysis of the product by ^{1}H NMR revealed that only alkyne **25** was formed (72%).[56] There was no evidence for the formation of TMS-acetylene **26**.

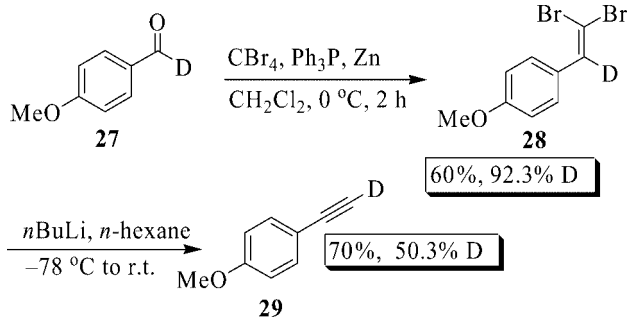
Encouraged by the above observation, though inconclusive, we desired to gather more corroborative evidence by a deuterium-labeling experiment (Scheme 6). To this end,



Scheme 4. Proposed mechanistic pathways for the conversion of tetrabromides **12** to enediynes **13** with **16** as the model substrate.



Scheme 5. Treatment of dibromide **22** with *n*BuLi and quenching the reaction mixture with TMSCl.



Scheme 6. Mechanistic evaluation of the base-mediated transformation of alkylidene dibromide **28** into the acetylene **29** by a deuterium-labeling experiment.

deuterated *p*-methoxybenzaldehyde **27** was prepared following literature procedure.[57] Aldehyde **27** was then converted to the corresponding dibromide **28** (60% yield, 92.3% D, ^{1}H NMR). Dibromide **28** was subsequently treated with *n*BuLi (2 equiv.) as in the case of **22**. The reaction mixture was analyzed by ^{1}H NMR after an aqueous workup. The ^{1}H NMR analysis indicated that the product acetylene **29**[58] contained 50.3% of D (70% yield, see also the Supporting Information).

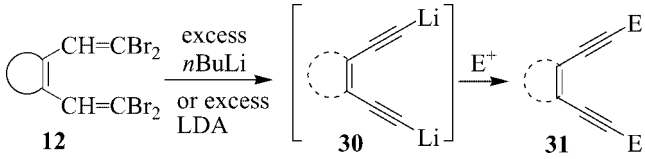
The formation of acetylene **29** possessing 50.3% D from dibromide **28** possessing 92.3% D suggested an overall retention of 54.5% D by a 1,2-shift (FBW rearrangement). This confirms that the carbene pathway (path A, Scheme 4 and Scheme 5) is the predominant pathway because of the preference for α-elimination (path A, Scheme 4 and Scheme 5) over β-elimination (path B). However, a substantial amount of non-deuterated acetylene **25** (45.5%) is formed by the β-elimination pathway (path B, Scheme 4) and, by analogy, in enediyne **13**.[59]

One-Pot Synthesis of Heteroatom-Based Enediynes

The critical *c*,*d* distance (distance between the two acetylene moieties) in enediynes is an important parameter in the Bergman cyclization.[60] Structural perturbations of enediynes can affect the critical *c*,*d* distance and allow the enediyne to cyclize even at room temperature.[61] The effect of substituents[62,63] or metal-ion complexation[64,65] on Bergman cyclization kinetics has been investigated. However, existing methods for the synthesis of structurally modified enediynes involve multistep protocols.[5] More importantly, the direct insertion of heteroatoms such as S, Se, and P, which are capable of chelating with metal ions, on the terminal acetylenic moieties of enediyne appears to be an attractive objective for facilitating the Bergman cyclization and exploring the biological properties of heteroatom-based enediynes.[66]

Our methodology, especially the one involving the bis(dibromoalkylidene) compound **12**, appeared suitable for the synthesis of heteroatom-based enediynes. Since conversion of dibromide **12** to the corresponding enediyne **13** in high yield required excess base (5 equiv. of *n*BuLi or 6 equiv. of

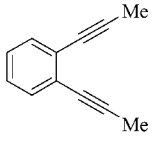
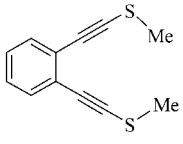
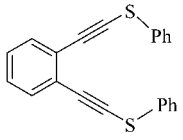
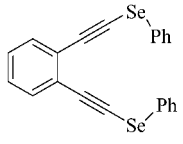
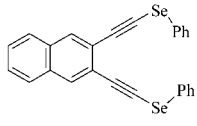
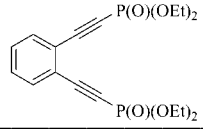
LDA, Table 4, Table 6), we envisioned that the diacetylide **30** should be amenable for trapping in situ with different electrophiles (Scheme 7).[67] Therefore, such an approach would provide a convenient entry into substituted enediynes in general and heteroatom-substituted enediynes in particular.



Scheme 7.

To test the viability of the proposed methodology, we converted the tetrabromide **12a** to its corresponding enediyne **13a** under the conditions of Method A (5 equiv. of *n*BuLi, *n*-hexane, Table 3 and Table 4) and quenched the reaction mixture with MeI. This provided a complex mixture from which the substituted enediyne **31a** could not be isolated. However, we have succeeded in synthesizing **31a** in one pot in 62% yield by employing Method B (LDA, toluene, Table 5 and Table 6) for the generation of enediyne **13a** and the trapping of its corresponding bis(acetylide) with MeI (Table 9, Entry 1). Encouraged by this result, we turned our attention to the introduction of heteroatoms such as S, Se, and P. Thus, representative examples of heteroatom-substituted enediynes **31b–f** were prepared in moderate to good yield with tetrabromides and commercially available electrophiles such as Me_2S_2, Ph_2S_2, PhSeBr, and $P(O)(OEt)_2Cl$ (Table 9, Entries 2–6).

Table 9. Generation of diacetylides **30** from tetrabromides **12** with LDA and their trapping with different electrophiles.

Entry	Tetrabromides **12**	Electrophiles[a]	Enediynes **31**, yield (%)[b]	
1	**12a**	MeI	**31a**	 62[c]
2	**12a**	Me_2S_2	**31b**	 65
3	**12a**	Ph_2S_2	**31c**	 78
4	**12a**	PhSeBr	**31d**	 54
5	**12d**	PhSeBr	**31e**	 53
6	**12a**	$P(O)(OEt)_2Cl$	**31f**	 48

[a] Attempted trapping of the diacetylides with ethylene 1,2-dibromide provided only a complex mixture. [b] Isolated yield after purification by silica gel column chromatography. [c] **31a** is a known compound, see ref.[68]

Conclusion

Two simple and efficient methodologies for the synthesis of enediyne analogs from 1,2-enedialdehydes have been developed. While one methodology involves the synthesis of bis(alkylidene dibromides) from 1,2-enedialdehydes under Corey–Fuchs conditions and subsequent treatment of the tetrabromides with *n*BuLi or LDA, the second one involves a one-pot transformation of 1,2-enedialdehydes into enediynes with diethyl (1-diazo-2-oxopropyl)phosphonate (BOR) in the presence of K_2CO_3. The intermediacy of a bis(alkylidene)carbene in the conversion bis(alkylidene dibromides) to enediynes has been confirmed by deuterium-labeling experiments. The scope of our methodology has been expanded by trapping the bis(acetylides) with different electrophiles, which provides a simple yet novel class of heteroatom-substituted enediynes.

Experimental Section

General Procedure for Dibromomethylenation of Dialdehydes 11: To a stirred suspension of activated Zn dust (0.520 g, 8 mmol) in dry CH_2Cl_2 (20 mL) under N_2 was added triphenylphosphane (2.09 g, 8 mmol). The reaction mixture was cooled to 0 °C, and carbon tetrabromide (1.342 g, 4 mmol) dissolved in dry CH_2Cl_2 (5 mL) was added over 15 min, which resulted in an intense yellow color. At the same temperature, 1,2-dialdehyde **11** (1 mmol) dissolved in CH_2Cl_2 (10 mL) was added dropwise to the reaction mixture, and the reaction mixture was brought to room temp. It was allowed to stir until the completion of the reaction, which was confirmed by TLC analysis (ca. 3 h). The reaction mixture was diluted with water (30 mL), the layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried (anhydrous Na_2SO_4) and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (*n*-hexane or *n*-hexane/ethyl acetate mixture, gradient elution) to afford pure alkylidenetetrabromide **12**.

1,2-Bis(2,2-dibromovinyl)benzene (12a):[37] Yellow liquid. Yield 94% (0.415 g). IR (neat): $\tilde{\nu}$ = 3061 (m), 3013 (m), 2924 (m), 1596 (s), 1459 (m), 1263 (m), 861 (s), 811 (m), 749 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41 (s, 2 H), 7.34–7.39 & 7.49–7.54 (AA′BB′, J = 5.9, 3.3 Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 93.2 (s), 128.4 (d), 128.8 (d), 134.5 (s), 135.3 (d) ppm. MS (DCI, CH_4): *m/z* (%) = 448, (4) $[M + 6]^+$, 446, (6) $[M + 4]^+$, 444 (4) $[M + 2]^+$, 367 (25), 365 (25), 288 (45), 286 (100), 284 (54), 195 (11), 193 (11), 126 (29). HRMS (DCI, CH_4): calcd. for $C_{10}H_6{}^{79}Br_3{}^{81}Br$ $[M + 2]^+$ 443.7182; found 443.7175. These data are in agreement with literature data.[37]

1,2-Bis(2,2-dibromovinyl)4,5-dimethylbenzene (12b): Colorless solid. Yield 62% (0.290 g). M.p. 95 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 2922 (m), 1595 (m), 1447 (m), 1265 (s), 895 (m), 741 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 6 H), 7.28 (s, 2 H), 7.35 (s, 2 H) ppm. ^{13}C

NMR (75 MHz, $CDCl_3$): δ = 19.8 (q), 92.3 (s), 129.8 (d), 132.0 (s), 135.5 (d), 137.2 (s) ppm. MS (DCI, CH_4): *m/z* (%) = 476 (10) [M + 6]$^+$, 474 (13) [M + 4]$^+$, 472 (9) [M + 2]$^+$, 395 (21), 393 (21), 316 (52), 314 (100), 312 (53), 235 (12), 233 (11), 153 (14). HRMS (DCI, CH_4): calcd. for $C_{12}H_{10}{}^{79}Br_2{}^{81}Br_2$ [M + 4]$^+$ 473.7475; found 473.7471.

1,2-Bis(2,2-dibromovinyl)4,5-dimethoxybenzene (12c): White solid. Yield; 46% (0.230 g). M.p. 128–129 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 2960 (s), 2931 (s), 1599 (m), 1502 (s), 1459 (s), 1293 (s), 1210 (s), 1101 (s), 875 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.90 (s, 6 H), 7.07 (s, 2 H), 7.38 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.2 (q), 92.2 (s), 111.4 (d), 127.5 (s), 135.2 (d), 148.8 (s) ppm. MS (DCI, CH_4): *m/z* (%) = 510 (6) [M + 8]$^+$, 508 (17) [M + 6]$^+$, 506 (23) [M + 4]$^+$, 504 (22) [M + 2]$^+$, 502 (5) [M]$^+$, 348 (46), 346 (100), 344 (58), 149 (100). HRMS (DCI, CH_4): calcd. for $C_{12}H_{10}O_2{}^{79}Br_3{}^{81}Br$ [M + 2]$^+$ 503.7394; found 503.7368.

2,3-Bis(2,2-dibromovinyl)naphthalene (12d): Light yellow solid. Yield 88% (0.432 g). M.p. 135–137 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 3068 (m), 3005 (m), 1588 (s), 1276 (m), 904 (s), 843 (m), 788 (m), 679 (w), 608 (w) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (m, 4 H), 7.84 (m, 2 H), 7.99 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 93.1 (s), 127.1 (d), 128.0 (d), 128.5 (d), 132.1 (s), 132.5 (s), 135.3 (d) ppm. MS (DCI, CH_4): *m/z* (%) = 498 (13) [M + 6]$^+$, 496 (19) [M + 4]$^+$, 494 (13) [M + 2]$^+$, 492 (3) [M]$^+$, 338 (48), 336 (100), 334 (50), 245 (36), 243 (38), 176 (51). HRMS (DCI, CH_4): calcd. for $C_{14}H_8{}^{79}Br_2{}^{81}Br_2$ [M + 4]$^+$ 495.7319; found 495.7320.

1,2-Bis(2,2-dibromovinyl)-4-methoxybenzene (12e): Light yellow liquid. Yield 66% (0.310 g). IR (neat): $\tilde{\nu}$ = 3006 (m), 2931 (m), 2835 (m), 1601 (s), 1563 (s), 1289 (s), 1240 (s), 1036 (s), 868 (s), 754 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 3 H), 6.89 (dd, *J* = 8.7, 2.6 Hz, 1 H), 7.03 (d, *J* = 2.6 Hz, 1 H), 7.34 (s, 1 H), 7.39 (s, 1 H), 7.49 (d, *J* = 8.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.6 (q), 91.8 (s), 93.3 (s), 113.9 (d), 114.1 (d), 126.9 (s), 130.0 (d), 134.8 (d), 135.2 (d), 135.9 (s), 159.1 (s) ppm. MS (DCI, CH_4): *m/z* (%) = 480 (4) [M + 8]$^+$, 478 (16) [M + 6]$^+$, 476 (26) [M + 4]$^+$, 474 (19) [M + 2]$^+$, 472 (5) [M]$^+$, 446 (29), 317 (65), 316 (100), 314 (65), 272 (40), 225 (44), 223 (44), 113 (52). HRMS (DCI, CH_4): calcd. for $C_{11}H_8O^{79}Br_2{}^{81}Br_2$ [M + 4]$^+$ 475.7268; found 475.7255.

2,3-Bis(2,2-dibromovinyl)-4,5-bis(4-methoxyphenyl)furan (12f): Yellow solid. Yield 80% (0.514 g). M.p. 119–121 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 2963 (w), 2840 (w), 1606 (m), 1519 (m), 1492 (w), 1265 (s), 1178 (m), 1032 (w), 761 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78 (s, 3 H), 3.86 (s, 3 H), 6.79 (d, *J* = 9.1 Hz, 2 H), 6.90 (s, 1 H), 6.94 (d, *J* = 8.8 Hz, 2 H), 7.19 (d, *J* = 9.1 Hz, 2 H), 7.26 (s, 1 H), 7.45 (d, *J* = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.2 (2 × q), 87.1 (s), 94.9 (s), 114.0 (d), 114.4 (d), 120.9 (s), 122.8 (s), 124.1 (s), 124.4 (d), 125.3 (d), 127.2 (d), 129.2 (s), 130.9 (d), 143.2 (s), 149.6 (s), 159.3 (s), 159.5 (s) ppm. MS (MALDI): *m/z* (%) = 651 (2) [(M – H) + 8], 649 (6) [(M – H) + 6], 647 (9) [(M – H) + 4], 645 (6) [(M – H) + 2], 643 (2) [M – H], 379 (30), 190 (100).

2,3-Bis(2,2-dibromovinyl)benzofuran (12g): Colorless solid. Yield 73% (0.351 g). M.p. 136–138 °C. IR (KBr): $\tilde{\nu}$ = 2922 (m), 2856 (w), 1608 (w), 1517 (w), 1444 (w), 1345 (w), 1256 (m), 1185 (m), 1123 (m), 1005 (w), 929 (w), 801 (s), 745 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.57 (m, 4 H), 7.36 (s, 1 H), 7.37 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 91.9 (s), 95.6 (s), 111.7 (d), 117.6 (s), 121.0 (d), 123.5 (d), 124.8 (d), 125.8 (s), 126.2 (d), 127.7 (d), 147.4 (s), 154.2 (s) ppm. MS (DCI, CH_4): *m/z* (%) = 490 (3) [M + 8]$^+$, 488 (15) [M + 6]$^+$, 486 (24) [M + 4]$^+$, 484 (17) [M + 2]$^+$, 446 (65), 328 (47), 326 (100), 324 (45), 166 (18), 138 (15), 137 (10). HRMS (DCI, CH_4): calcd. for $C_{12}H_6O^{79}Br^{81}Br_3$ [M + 6]$^+$ 487.7091; found 487.7102.

2,3-Bis(2,2-dibromovinyl)thiophene (12h): Yellow liquid. Yield 95% (0.424 g). IR (KBr): $\tilde{\nu}$ = 2955 (m), 2924 (s), 2853 (m), 1682 (w), 1459 (w), 1270 (m), 1091 (w), 840 (m), 808 (s), 751 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (ABq, *J* = 2.6 Hz, 2 H), 7.54 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 89.6 (s), 92.9 (s), 126.2 (d), 126.7 (d), 128.8 (d), 130.6 (d), 135.4 (s), 136.4 (s) ppm. MS (DCI, CH_4): *m/z* (%) = 456 (11) [M + 8]$^+$, 454 (37) [M + 6]$^+$, 452 (54) [M + 4]$^+$, 450 (40) [M + 2]$^+$, 448 (10) [M]$^+$, 447 (11), 446 (35), 294 (53), 292 (100), 290 (55), 211 (12), 132 (34), 97 (19), 85 (25), 83 (19), 71 (22), 69 (15). HRMS (DCI, CH_4): calcd. for $C_8H_4S^{79}Br_2{}^{81}Br_2$ [M + 4]$^+$ 451.6726; found 451.6748.

General Procedures for the Conversion of Dialdehydes 11 to Enediynes 13

Reaction of Bis(dibromoalkylidene) Compounds 12 with *n*BuLi. Method A: To a stirred solution of tetrabromide **12** (0.95 mmol) in dry *n*-hexane (30 mL) at –78 °C under N_2 was added dropwise *n*BuLi (1.9 mL, 4.75 mmol, 5 equiv., 2.5 M solution in hexanes) over 20 min. Stirring was continued at the same temperature for another 3 h. The reaction mixture was then brought to room temp. over 1 h. After confirming the completion of the reaction (by TLC), the reaction mixture was poured into cold saturated aqueous NH_4Cl (10 mL). The layers were separated, and the organic layer was washed with water (2 × 10 mL) and brine (10 mL), dried (anhydrous Na_2SO_4), and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (*n*-hexane or *n*-hexane/ethyl acetate mixture, gradient elution) to afford pure enediyne **13**. See also Tables 3 and 4.

Reaction of Bis(dibromoalkylidene) Compounds 12 with LDA. Method B: To a stirred solution of dry diisopropylamine (0.8 mL, 5.82 mmol) in dry toluene (10 mL) at 0 °C under N_2 was added dropwise *n*BuLi (2.24 mL, 5.6 mmol, 2.5 M solution in hexanes) over 20 min. Stirring was continued at the same temperature for another 2.5 h. The reaction mixture was then diluted with dry toluene (25 mL) and cooled to –78 °C. To the cooled solution was added tetrabromide **12** (0.95 mmol) in toluene (5 mL), during which time the solution turned yellow. The resulting solution was stirred at the same temperature for another 3 h and gradually brought to room temperature while being stirred overnight. The reaction mixture was then poured into ice-cold dilute HCl (2%, 10 mL). The layers were separated, and the aqueous layer was further extracted with toluene (2 × 20 mL). The combined organic layers were washed with water (2 × 10 mL) and brine (10 mL), dried (anhydrous Na_2SO_4), and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (*n*-hexane or *n*-hexane/ethyl acetate mixture, gradient elution) to afford pure enediyne **13**. See also Tables 5 and 6.

Reaction with 15. Method C: To a stirred solution of 1,2-dialdehyde **11** (1 mmol) and K_2CO_3 (828 mg, 6 mmol) in dry MeOH (5 mL) was added reagent **15** (880 mg, 4 mmol) at 0 °C. The reaction mixture was maintained at 0 °C for 30 min and was gradually brought to room temp. and stirred until the reaction was complete (monitored by TLC, see Table 8). The reaction mixture was diluted with water (15 mL), neutralized with dilute HCl (5%, 5 mL), and extracted with dichloromethane (3 × 15 mL). The combined organic layers were then washed with brine (2 × 10 mL), dried (anhydrous Na_2SO_4), and then concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, *n*-hexane) to afford pure enediynes **13**. See also Tables 7 and 8.

1,2-Diethynylbenzene (13a):[38] Yellow liquid. Yield 96% (0.114 g) (Method A), 88% (0.105 g) (Method B), 72% (0.090 g) (Method

C). IR (neat): $\tilde{\nu}$ = 3291 (s), 3063 (w), 2925 (m), 2854 (w), 2109 (w), 1476 (m), 1439 (m), 1258 (m), 761 (s), 649 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.34 (s, 2 H), 7.27–7.35 & 7.48–7.56 (AA′BB′, J = 5.9, 3.3 Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 81.2 (d), 81.9 (s), 125.1 (s), 128.6 (d), 132.7 (d) ppm. MS (EI): m/z (%) = 126 (100) $[M]^+$, 98 (9), 74 (20), 63 (30). These data are in agreement with literature data.[38a,38e]

1,2-Diethynyl-4,5-dimethylbenzene (13b):[39] Light yellow viscous liquid. Yield 84% (0.122 g) (Method A), 68% (0.099 g) (Method B), 79% (0.121 g) (Method C). IR ($CHCl_3$): $\tilde{\nu}$ = 3302 (s), 3026 (m), 2927 (m), 2868 (w), 2111 (w), 1611 (w), 1452 (m), 1218 (s), 1025 (m), 907 (m), 769 (s), 670 (m), 620 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.20 (s, 6 H), 3.27 (s, 2 H), 7.29 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7 (q), 80.2 (d), 82.3 (s), 122.4 (s), 133.8 (d), 137.9 (s) ppm. MS (DCI, CH_4): m/z (%) = 310 (100) [2 (M + H)]$^+$, 154 (10) $[M]^+$, 141 (29), 115 (19), 91 (33). HRMS (DCI, CH_4): calcd. for $C_{24}H_{22}$ [2 (M + H)]$^+$ 310.1723; found 310.1836. No experimental data were available in the literature.

1,2-Diethynyl-4,5-dimethoxybenzene (13c):[40] Colorless solid. Yield 71% (0.125 g) (Method A), 84% (0.148 g) (Method B). M.p. 120–122 °C. IR (KBr): $\tilde{\nu}$ = 3302 (s), 2927 (m), 2868 (w), 2104 (w), 1604 (w), 1506 (m), 1466 (w), 1262 (m), 1229 (m), 1104 (w), 911 (s), 737 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.28 (s, 2 H), 3.89 (s, 6 H), 6.97 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.1 (q), 79.8 (d), 82.1 (s), 114.7 (d), 118.1 (s), 149.4 (s) ppm. MS (DCI, CH_4): m/z (%) = 186 (100) $[M]^+$, 143 (8), 115 (10), 84 (16). HRMS (DCI, CH_4): calcd. for $C_{12}H_{10}O_2$ $[M]^+$ 186.0681; found 186.0660. These data are in agreement with literature data.[40c]

2,3-Diethynylnaphthalene (13d):[41] Yellow crystalline solid. Yield 67% (0.112 g) (Method A), 44% (0.073 g) (Method B), 84% (0.147 g) (Method C). M.p. 119–120 °C. IR (KBr): $\tilde{\nu}$ = 3306 (s), 3284 (s), 3059 (m), 2922 (m), 2849 (m), 2116 (w), 1584 (m), 1488 (m), 1244 (m), 956 (m), 902 (s), 801 (m), 750 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.35 (s, 2 H), 7.48–7.56 & 7.74–7.82 (AA′BB′, J = 6.2, 3.3 Hz, 4 H), 8.10 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 80.7 (d), 82.1 (s), 121.2 (s), 127.7 (2 × d), 132.5 (s), 133.1 (d) ppm. MS (DCI, CH_4): m/z (%) = 176 (77) $[M]^+$, 150 (10), 131 (25), 119 (23), 84 (16), 69 (100). HRMS (DCI, CH_4): calcd. for $C_{14}H_8$ $[M]^+$ 176.0626; found 176.0587. These data are in agreement with literature data.[41b]

1,2-Diethynyl-4-methoxybenzene (13e):[42] Yellow liquid. Yield 91% (0.135 g) (Method A), 87% (0.129 g) (Method B), 76% (0.118 g) (Method C). IR (neat): $\tilde{\nu}$ = 3287 (s), 2945 (m), 2844 (m), 2110 (s), 1606 (s), 1565 (s), 1489 (s), 1316 (s), 1255 (s), 1041 (s), 832 (m), 639 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.25 (s, 1 H), 3.33 (s, 1 H), 3.82 (s, 3 H), 6.86 (dd, J = 8.7, 2.7 Hz, 1 H), 7.02 (d, J = 2.7 Hz, 1 H), 7.43 (d, J = 8.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.4 (q), 79.6 (d), 80.9 (d), 81.8 (2 × s), 115.5 (d), 117.32 (d), 117.44 (s), 126.3 (s), 134.0 (d), 159.4 (s) ppm. MS (EI): m/z (%) = 156 (100) $[M]^+$, 141 (29), 113 (60), 63 (25). HRMS (DCI, CH_4): calcd. for $C_{11}H_8O$ $[M]^+$ 156.0575; found 156.0549. These data are in agreement with literature data.[42b]

2,3-Diethynyl-4,5-bis(4-methoxyphenyl)furan (13f): Dark brown viscous liquid. Yield 70% (0.218 g) (Method A), 61% (0.190 g) (Method B), 64% (0.209 g) (Method C). IR (neat): $\tilde{\nu}$ = 3300 (s), 2928 (s), 2852 (m), 2305 (w), 1613 (s), 1520 (m), 1265 (s), 1177 (s), 761 (s), 741 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.12 (s, 1 H), 3.75 (s, 1 H), 3.78 (s, 3 H), 3.84 (s, 3 H), 6.80 (d, J = 8.7 Hz, 2 H), 6.93 (d, J = 8.9 Hz, 2 H), 7.35 (d, J = 8.7 Hz, 2 H), 7.41 (d, J = 8.9 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.18 (q), 55.21 (q), 74.1 (d), 74.3 (d), 84.3 (s), 86.0 (s), 113.0 (d), 114.0 (d), 115.6 (s), 122.0 (s), 122.3 (s), 123.6 (s), 127.8 (d), 130.7 (d), 138.1 (s), 149.7 (s), 159.2 (s), 159.6 (s) ppm. MS (ESI, Ar): m/z (%) = 329 (100) $[M + H]^+$, 214 (4), 158 (9). HRMS (ESI, Ar): calcd. for $C_{22}H_{17}O_3$ $[M + H]^+$ 329.1178; found 329.1188.

2,3-Bis[2-(trimethylsilyl)ethynyl]benzofuran (13g, R = TMS): Yellow liquid. Yield 33% (0.097 g) (Method A), 26% (0.076 g) (Method B). IR (neat): $\tilde{\nu}$ = 2961 (s), 2160 (s), 1449 (m), 1368 (w), 1252 (s), 1183 (m), 1125 (s), 845 (s), 751 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.30 (s, 9 H), 0.31 (s, 9 H), 7.26–7.42 (m, 3 H), 7.62 (dt, J = 8.0, 0.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.3 (q), 0.1 (q), 93.1 (s), 94.2 (s), 103.5 (s), 106.8 (s), 111.5 (d), 120.9 (d), 123.8 (d), 126.7 (d), 127.5 (2 × s), 142.0 (s), 153.9 (s) ppm. MS (DCI, CH_4): m/z (%) = 310 (100) $[M]^+$, 296 (10), 295 (16), 280 (5), 267 (7), 73 (22). HRMS (DCI, CH_4): calcd. for $C_{18}H_{22}OSi_2$ $[M]^+$ 310.1209; found 310.1220.

2,3-Diethynylthiophene (13h, R = TMS):[43] Yellow liquid. Yield 43% (0.112 g) (Method A), 31% (0.081 g) (Method B). IR (neat): $\tilde{\nu}$ = 3291 (w), 3109 (w), 2960 (s), 2162 (s), 2152 (s), 1250 (s), 970 (m), 842 (s), 759 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.25 (s, 9 H), 0.26 (s, 9 H), 6.97 (d, J = 5.3 Hz, 1 H), 7.10 (d, J = 5.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –0.2 (q), –0.4 (q), 96.2 (s), 98.7 (s), 98.8 (s), 103.5 (s), 125.7 (d), 127.2 (s), 127.5 (s), 129.3 (d) ppm. MS (EI): m/z (%) = 277 (25) $[M + H]^+$, 237 (100), 164 (19). HRMS (ESI, Ar): calcd. for $C_{14}H_{21}SSi_2$ $[M + H]^+$ 277.0903, found 277.0902. No experimental data were available in the literature.

2,3-Diethynylthiophene (13h, R = H):[43] Light yellow viscous liquid. Yield 45% (0.059 g) (Method C). IR (neat): $\tilde{\nu}$ = 3303 (s), 2926 (m), 2855 (w), 2112 (m), 1654 (m), 1461 (m), 1378 (m), 1091 (m), 910 (s), 736 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.32 (s, 1 H), 3.61 (s, 1 H), 7.03 (d, J = 5.1 Hz, 1 H), 7.17 (d, J = 5.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 75.7 (s), 77.6 (s), 81.3 (d), 85.5 (d), 126.4 (s), 126.6 (d), 126.7 (s), 130.0 (d) ppm. MS (ESI, Ar): m/z (%) = 133 (3) $[M + H]^+$, 102 (11), 77 (11), 73 (76). HRMS (ESI, Ar): calcd. for C_8H_5S $[M + H]^+$ 133.0112; found 133.0014. No experimental data were available in the literature.

[D]1-(2,2-Dibromovinyl)-4-methoxybenzene (28): To a stirred suspension of activated Zn dust (0.260 g, 4 mmol) in dry CH_2Cl_2 (15 mL) under N_2 was added triphenylphosphane (1.04 g, 4 mmol). The reaction mixture was cooled to 0 °C, and carbon tetrabromide (0.670 g, 2 mmol) dissolved in dry CH_2Cl_2 (2 mL) was added over 15 min, which resulted in an intense yellow color. At the same temperature, [D]4-methoxybenzaldehyde **27** (0.137 g, 1 mmol, 95.6% D by ^1H NMR, average of 3 integrations) dissolved in CH_2Cl_2 (2 mL) was added dropwise to the reaction mixture, and the reaction mixture was brought to room temp. over a period of 4 h. The reaction mixture was then diluted with CH_2Cl_2 (10 mL), washed with water (20 mL), dried (anhydrous Na_2SO_4), and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (*n*-hexane as the eluent) to afford pure dibromide **28**. Yellow solid. Yield 60% (0.175 g). M.p. 48–50 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 2960 (m), 1602 (m), 1505 (m), 1450 (m), 1258 (s), 1176 (m), 1029 (s), 834 (s), 803 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 3 H), 6.88 (d, J = 8.8 Hz, 2 H), 7.50 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.2 (q), 87.1 (s), 113.8 (d), 127.7 (s), 129.8 (d), 136.2 (t, $J_{C\text{-}D}$ = 23.7 Hz), 159.7 (s) ppm. MS (DCI, CH_4): m/z (%) = 295 (70) $[M + 4]^+$, 293 (100) $[M + 2]^+$, 291 (58) $[M]^+$, 278 (25), 213 (10), 171 (13), 133 (50). HRMS (ESI, Ar): calcd. for $C_9H_9{}^{81}Br_2O$ $[M + 4]^+$ 294.8979; found 294.8974. Deuterium incorporation in **28** was determined to be 92.3% by ^1H NMR (average of 3 integrations, a singlet at δ = 7.40 ppm with an integration value of < 0.1 H corresponds to the olefinic proton of the minor non-deuterated compound, see the Supporting Information).

Procedure for the *n*BuLi-Mediated Transformation of Dibromide 28 to Acetylene 29. D-Labeling Experiment: To a stirred solution of dibromide **28** (310 mg, 1.05 mmol, 92.3% D) in *n*-hexane (6 mL) was added *n*BuLi (1.3 mL, 2.1 mmol, 2.0 equiv., 1.6 M solution in hexanes) dropwise at –78 °C over a period of 20 min. Stirring was continued at the same temperature for another 3 h. The reaction mixture was then brought to room temp. over 1 h and was poured into cold saturated aqueous NH_4Cl (10 mL). The layers were separated, and the organic layer was washed with water (2 × 10 mL) and brine (10 mL), dried (anhydrous Na_2SO_4), and concentrated in vacuo. The crude residue was passed through a plug of silica gel and eluted with hexanes to afford acetylene **29**. Light yellow liquid. Yield 70% (0.097 g). IR (neat): $\tilde{\nu}$ = 3290 (s), 2957 (m), 2931 (m), 2582 (s), 2106 (w), 1607 (s), 1507 (s), 1291 (m), 1251 (s), 1171 (m), 1032 (s), 833 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.79 (s, 3 H), 6.83 (d, J = 8.8 Hz, 2 H), 7.42 (d, J = 8.8 Hz, 2 H) ppm. D incorporation in **29** is 50.3% (average of 3 integrations, a singlet at δ = 3.0 ppm with an integration value of about 0.5 H corresponds to the acetylenic proton of the minor non-deuterated compound, see the Supporting Information).[56,58]

General Procedure for the Quenching of Acetylide 30 with Different Electrophiles: To a stirred solution of dry diisopropylamine (0.62 mL, 5.0 mmol) in dry toluene (10 mL) at 0 °C under N_2 was added dropwise *n*BuLi (2.8 mL, 4.6 mmol, 1.6 M solution in hexanes) over 20 min. Stirring was continued at the same temperature for another 2.5 h. The reaction mixture was then diluted with dry toluene (25 mL) and cooled to –78 °C. At the same temperature, tetrabromide **12** (0.77 mmol) in toluene (4 mL) was added dropwise over a period of 15 min. Low temperature was maintained for 3 h, and then the reaction mixture was gradually warmed to –40 °C. At this temperature, the reaction mixture was quenched with the electrophile (1.7 mmol, 2.2 equiv., see Table 9) in toluene or THF (2 mL). The resulting brown mixture was stirred overnight and subsequently quenched with saturated aqueous NH_4Cl (5 mL). The layers were separated, and the aqueous layer was further extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed with water (2 × 10 mL) and brine (10 mL), dried (anhydrous Na_2SO_4), and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (*n*-hexane or *n*-hexane/ethyl acetate mixture, gradient elution) to afford pure substituted enediynes **31**.

1,2-Di(prop-1-ynyl)benzene (31a):[68] Colorless liquid. Yield 62% (0.073 g). IR (neat): $\tilde{\nu}$ = 3052 (s), 2982 (m), 2917 (s), 2851 (m), 2236 (m), 1481 (m), 1441 (m), 1265 (s), 745 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.12 (s, 6 H), 7.18 (shielded half of AA′XX′, J = 9.1, 2.5 Hz, 2 H), 7.37 (deshielded half of AA′XX′, J = 9.3, 2.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 4.6 (q), 78.6 (s), 89.5 (s), 126.1 (s), 127.2 (d), 131.9 (d) ppm. MS (EI): m/z (%) = 154 (100) $[M]^+$, 152 (70), 128 (10), 115 (8), 76 (20). These data are in agreement with literature data.[68b]

1,2-Bis[2-(methylthio)ethynyl]benzene (31b): Yellow liquid. Yield 65% (0.109 g). IR (neat): $\tilde{\nu}$ = 2929 (m), 2157 (s), 1472 (m), 1440 (m), 1265 (s), 740 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.51 (s, 6 H), 7.19 (shielded half of AA′XX′, J = 5.5, 3.4 Hz, 2 H), 7.36 (deshielded half of AA′XX′, J = 5.8, 3.3 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6 (q), 85.4 (s), 90.8 (s), 125.4 (s), 127.4 (d), 130.9 (d) ppm. MS (ESI, Ar): m/z (%) = 219 (19) $[M + H]^+$. HRMS (ESI, Ar): calcd. for $C_{12}H_{11}S_2$ $[M + H]^+$ 219.0302; found 219.0307.

1,2-Bis[2-(phenylthio)ethynyl]benzene (31c): Yellow liquid. Yield 78% (0.205 g). IR (neat): $\tilde{\nu}$ = 3058 (w), 2925 (w), 2157 (m), 1582 (s), 1478 (s), 1441 (s), 1024 (s), 757 (m), 736 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.07–7.20 (m, 2 H), 7.25–7.35 (m, 6 H), 7.45–7.55 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 80.0 (s), 96.8 (s), 125.0 (s), 126.0 (d), 126.4 (d), 128.1 (d), 129.4 (d), 131.7 (d), 132.4 (s) ppm. MS (ESI, Ar): m/z (%) = 343 (100) $[M]^+$, 306 (50), 264 (48), 234 (32), 224 (14), 158 (12), 141 (10). HRMS (ESI, Ar): calcd. for $C_{22}H_{15}S_2$ $[M]^+$ 343.0615; found 343.0618.

1,2-Bis[2-(phenylselanyl)ethynyl]benzene (31d): Brown viscous liquid. Yield 54% (0.182 g). IR (neat): $\tilde{\nu}$ = 3056 (m), 2921 (m), 2155 (m), 1577 (m), 1477 (s), 1439 (m), 1021 (m), 734 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.31 (m, 8 H), 7.48 (dd, J = 5.8, 3.5 Hz, 2 H), 7.55–7.60 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 74.0 (s), 101.8 (s), 125.4 (s), 127.0 (d), 128.0 (d), 128.7 (s), 128.8 (d), 129.6 (d), 131.9 (d) ppm. ^{77}Se NMR (57 MHz, $CDCl_3$): δ = 273.9 ppm. MS (ESI): m/z (%) = 439 (10) $[M + H]^+$, 413 (100), 374 (12), 338 (15), 322 (30), 258 (13), 189 (35), 149 (50), 129 (17). HRMS (ESI, Ar): calcd. for $C_{22}H_{15}Se_2$ $[M + H]^+$, 438.9504; found 438.9485.

2,3-Bis[2-(phenylselanyl)ethynyl]naphthalene (31e): Brown solid. Yield 53% (0.199 g). M.p. 110–111 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 3054 (m), 3020 (m), 2985 (m), 2305 (m), 1422 (m), 1266 (s), 1217 (s), 1063 (m), 896 (m), 741 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.31 (m, 6 H), 7.48 (shielded half of AA′XX′, J = 6.2, 3.1 Hz, 2 H), 7.62–7.64 (m, 4 H), 7.75 (deshielded half of AA′XX′, J = 6.0, 3.3 Hz, 2 H), 8.00 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 73.4 (s), 101.9 (s), 122.0 (s), 127.0 (d), 127.4 (d), 127.6 (d), 128.8 (s), 128.9 (d), 129.6 (d), 132.0 (d), 132.3 (s) ppm. ^{77}Se NMR (57 MHz, $CDCl_3$): δ = 274.4 ppm. MS (ESI): m/z (%) = 527 (2) $[M + K]^+$, 525 (10), 342 (18), 298 (7), 255 (8), 212 (25). HRMS (ESI, Ar): calcd. for $C_{26}H_{16}KSe_2$ $[M + K]^+$, 526.9219; found 526.9257.

1,2-Bis[2-(diethoxyphosphoryl)ethynyl]benzene (31f): Colorless liquid. Yield 48% (0.147 g). IR (neat): $\tilde{\nu}$ = 3056 (m), 2986 (s), 2962 (m), 2933 (m), 2190 (s), 1734 (s), 1444 (w), 1374 (m), 1266 (s), 1046 (s), 742 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.42 (t, J = 7.1 Hz, 12 H), 4.24–4.28 (m, 8 H), 7.48, 7.64 (AA′XX′, J = 5.8, 3.3 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1 (d, J = 6.8 Hz), 63.5 (d, J = 5.4 Hz), 83.0 (d, J = 292.9 Hz), 95.5 (d, J = 51.9 Hz), 123.1 (d, J = 2.3 Hz), 130.4 (d), 133.4 (d, J = 2.3 Hz) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ = –8.6 (s) ppm. MS (ESI, Ar): m/z (%) = 421 (38) $[(M – 1) + Na]^+$, 399 (100) $[M]^+$, 243 (25), 177 (11), 124 (9). HRMS (ESI, Ar): calcd. for $C_{18}H_{25}O_6P_2$ $[M]^+$ 399.1126; found 399.1125.

Supporting Information (see also the footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra for all new compounds and some of the known compounds for which experimental data are not available in the literature and ^{31}P and ^{79}Se NMR spectra, wherever applicable.

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