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Steric buttressing in the Pauson–Khand reactions of aryl enynes

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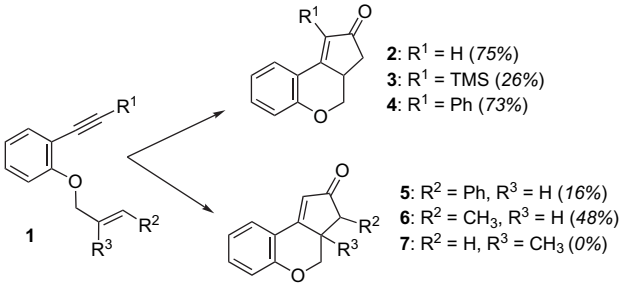
Abstract—A variety of aryl enynes have been constructed from *o*-iodophenol derivatives containing *ortho-tert*-butyl groups via O-alkylation and a Sonogashira cross-coupling reaction. These substrates undergo efficient thermal and oxidative intramolecular Pauson–Khand reactions leading to the formation of sterically congested cyclopentenones, as well as the formation of medium-sized rings, although in the latter case with unusual regioselectivity. Incorporation of a TMS moiety on the alkyne group in a higher homolog led to cyclization via the normal mode, albeit in relatively low yield.

1. Introduction

The Pauson–Khand (PK) reaction, the [2+2+1] co-cyclization of an alkene, alkyne (as the dicobalt hexacarbonyl complex), and carbon monoxide has evolved into an excellent method for the construction of cyclopentenones.[1,2] This reaction is known both inter- and intramolecularly, and can be mediated or catalyzed by a variety of metal complexes as well as by $Co_2(CO)_8$ as initially reported by Pauson and Khand.[1] In addition to developments with catalysts or mediators of this reaction, the reaction has been extended to a variety of substrates including allenes,[3] dienes,[4] and carbodiimides.[5] Despite these notable advances, there are several limitations with this cycloaddition that prevent the full realization of its synthetic potential. For example, the literature is replete with examples of the intramolecular variant leading to the formation of 5,5- and 5,6-fused systems,[6,7] but the generation of larger fused bicyclic systems is less well-known.[8,9] When this project was initiated there were no examples of medium-sized ring synthesis by this method[8] until the Krafft group[10] and shortly thereafter our own group disclosed some success in this area.[11] Although since these initial reports, several other studies have appeared in the literature.[11–13]

Our initial approach to this problem was to investigate the use of scaffolding elements that reduced the conformational degrees of freedom of the tethers containing the reactive functionality (olefin and alkyne). It was expected that this tactic should sufficiently reduce the entropic penalty associated with cycloaddition to allow the reaction to proceed. The first substrate that we selected for investigation was aromatic rings, an approach also employed by Krafft and co-workers.[10] The logic behind this selection was twofold: (a) the substrates should be rapidly constructed, and (b) there are several natural product targets, for example, the hamigerans[15,16] that in principle could be accessed through successful realization of this chemistry. Initial experiments along these lines were conducted using enynes derived from *o*-iodophenol via a Sonogashira cross-coupling and O-alkylation. When these substrates were subjected to cyclization under oxidative conditions (formation of the $Co_2(CO)_6$ complex and then treatment with *N*-methylmorpholine oxide, NMO),[17] cyclizations occurred with the simple allyl systems (R^2=R^3=H, Scheme 1), although the efficiency was attenuated with the TMS-substituted alkyne (R^1=TMS, Scheme 1).[14] It was also found that substitution on the olefin, or increase of the tether length (i.e., homoallyl) led to poor or no conversion to the cycloadduct.[14] As a result of these investigations, it became apparent that not only were medium-sized rings problematic, but also the formation of congested cyclopentenones via this method were difficult.



Scheme 1. See Ref. 14.

During the course of these initial studies, we became aware of a report from Sammes and co-workers describing the use of steric buttressing elements (*ortho* alkyl moiety) to coax recalcitrant intramolecular 1,3-dipole cycloadditions of

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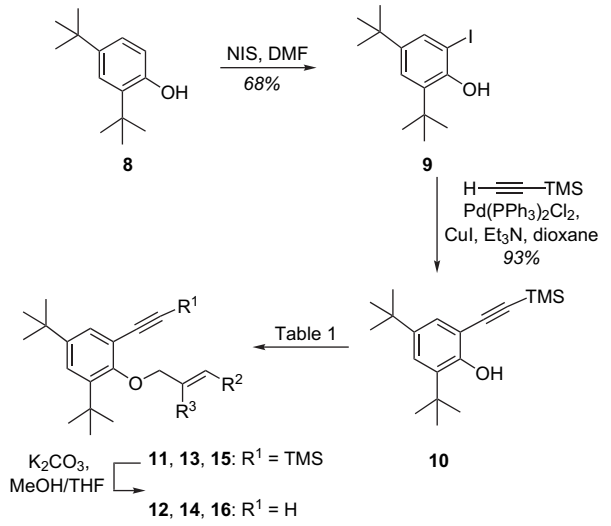
azides with pendant dipolarophiles into substantially more efficient reactions.[18] Indeed, the Sammes lab has reported several applications of steric buttressing to facilitate otherwise sluggish reactions.[18] Given the similarity of the situations, we became intrigued as to whether a similar approach might lead to enhancements of both the rates and efficiencies of PK cyclizations under investigation in our lab. It is the investigation of this tactic that is the subject of this paper.

2. Results and discussion

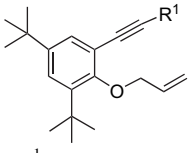
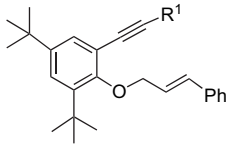
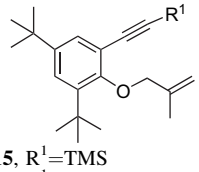
To explore this idea, 2,4-di-*tert*-butylphenol (**8**) was identified as a suitable precursor, as it provided both a suitable (and large) buttressing element, and the incorporation of an iodo moiety *ortho* to the hydroxy group was described in the literature.[19] It should be noted that the 4-*tert*-butyl substituent does not play any role in constraining the conformational mobility of the enyne, but it does block the 4-position toward electrophilic substitution, rendering the preparation of substrates more convenient. Simply treatment of the phenol with NIS or I_2/NaOH provided large quantities of the *o*-iodophenol in good yields (**9**, Scheme 2), which then served as the departure point for construction of the cyclization substrates.[19] Sonogashira reaction with the TMS-substituted acetylene provided the phenyl acetylene derivative **10** in excellent yield (Scheme 2).[20] Alkylation was achieved readily at this stage with allyl halide derivatives and base, or in the case of the cinnamyl moiety, this was incorporated via Mitsunobu chemistry (Table 1). In all cases, the expected products **11**, **13**, and **15** were obtained in excellent yields. Subsequent treatment of the alkylated products with methanolic K_2CO_3 provided the desilylated congeners **12**, **14**, and **16** in high yield.

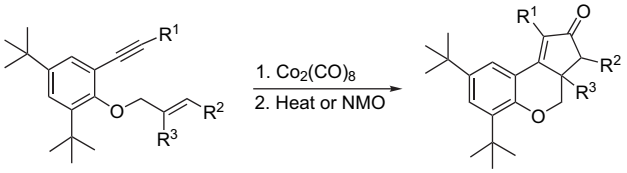


Scheme 2.

With this selection of enynes in hand, we began to investigate both their oxidative and thermal PK reactions. In order to establish the general viability of these substrates, the parent enyne **12** was converted into the corresponding $Co_2(CO)_6$ complex by treatment with a slight excess of $Co_2(CO)_8$ in CH_2Cl_2 and then treated with NMO. We immediately noted that this substrate underwent reaction substantially faster than **1** (R^2=R^3=H, Scheme 1), which lacks the

Table 1. Conditions and yields of alkylations of phenol **10**

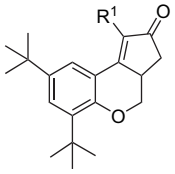
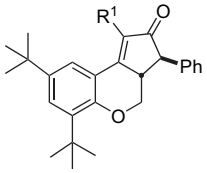
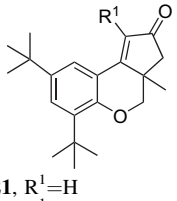
Entry	Conditions	Product	Yield (%)
	Br, K_2CO_3, DMF		
1		**11**, R^1=TMS	98
2		**12**, R^1=H	100
	HO, Ph, DEAD, PPh_3		
3		**13**, R^1=TMS	95
4		**14**, R^1=H	93
	Cl, K_2CO_3, NaI, DMF		
5		**15**, R^1=TMS	98
6		**16**, R^1=H	100



11-16 **17-22**

Scheme 3.

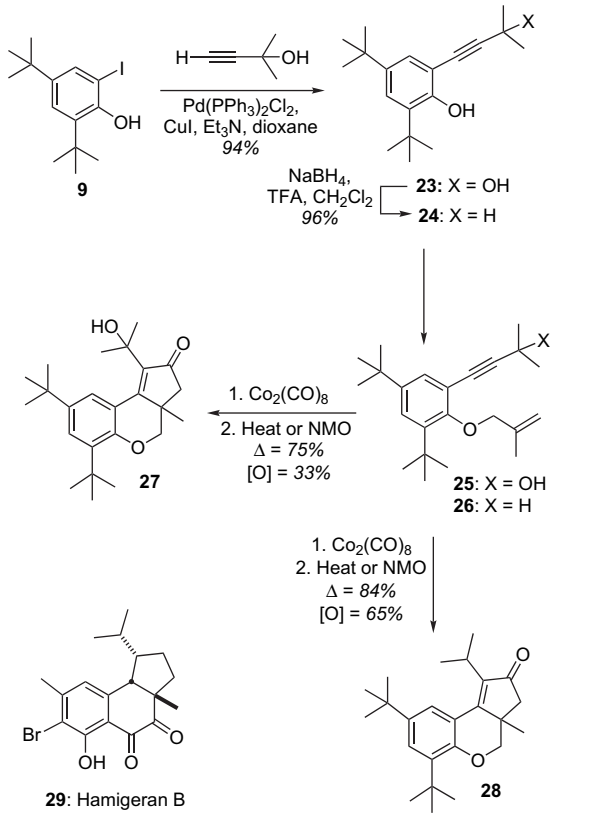
Table 2. PK-cyclization yields under thermal and oxidative conditions

Entry	Product	Conditions	
		Thermal (%)	Oxidative (%)
			
1	**17**, R^1=H	91	80
2	**18**, R^1=TMS	93	96
			
3	**19**, R^1=H	73	91
4	**20**, R^1=TMS	71	81
			
5	**21**, R^1=H	91	81
6	**22**, R^1=TMS	92	97

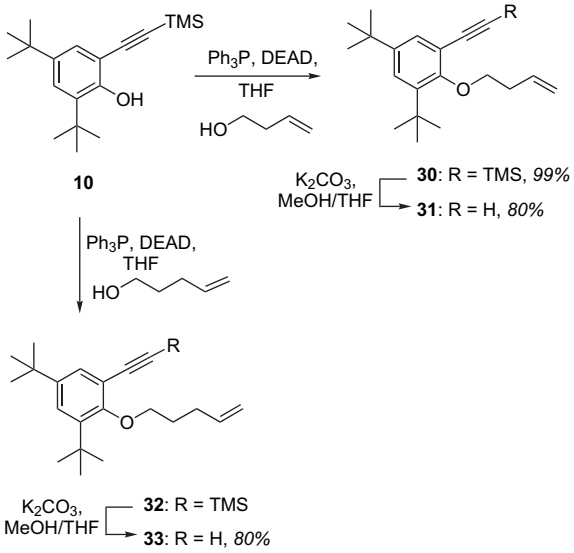
ortho-tert-butyl moiety, as the complex rapidly disappeared by TLC analysis. On work up and purification we were delighted to find that the expected cycloadduct had been formed in 80% yield (entry 1, Table 2). In our initial study,[11] we reported that this substrate did not engage in the cycloaddition on thermal activation, when in fact this substrate does engage in the PK reaction under thermal activation in PhMe, provided that the temperature is maintained at ~70 °C (our previous reactions were conducted at reflux temperatures).[21] In this case the cycloadduct was obtained in 91% yield. As the parent substrate engaged effectively in the cycloaddition, our attention turned to cyclizations of more substituted derivatives (Scheme 3). Two general types of derivative were investigated, those containing substituted allyl derivatives (entries 3 and 5, Table 2) and those with TMS-substituted moiety (entries 2, 4, and 6, Table 2). As can be seen in Table 2, all of these derivatives engage in the cycloaddition reaction under both thermal or oxidative conditions, leading to the expected adduct in excellent yield, uniformly higher than the parent substrate lacking the *tert*-butyl groups. Of particular note is **15** (providing **22**), which contains both a TMS and methyl moiety and in the corresponding enyne that lacks steric buttressing elements (**1**, R^1=TMS, R^2=H, R^3=Me, Scheme 1), no cyclization occurs, but in the presence of a *tert*-butyl group, the reaction proceeds in high efficiency.

A major aim of this investigation was to establish the utility of this reaction for the assembly of complex natural products. Although not widespread in nature, there are several examples of naturally occurring molecules that contain aryl rings with a pendant five-membered ring. The hamigerans and tintinnadiol are among these.[22,23] As a preliminary evaluation of the PK reaction as a viable approach to the former of these targets (e.g., hamigeran B (**29**), Scheme 4), enynes **25** and **26** were constructed from iodophenol **9** through Sonogashira chemistry with the butynol derivative[24] and either allylation (**23**→**25**) or reduction and then allylation (**23**→**26**). Subjection of either enyne **25** or **26** to a thermal PK reaction led to an efficient cyclization reaction, providing the corresponding cyclopentanone derivative (**27** or **28**) in good yields. When the cyclization PK reaction of the alcohol derivative was performed under oxidative conditions, the expected cycloadduct was obtained but in lower efficiency. The thus formed tricyclic derivatives **27** and **28** bear some resemblance to the hamigerans (albeit an oxa analog).

As indicated in the introduction, one of the long-term goals of this project was to extend the scope of the intramolecular PK reaction to include the construction of rings larger than 5- and 6-membered. Toward this end, the higher homologs **31** and **33** were prepared using similar protocols as described above, although it should be noted that in the case the alkylations were carried out under Mitsunobu conditions as attempts to employ the corresponding halides were compromised by low yields (Scheme 5). The terminal trimethylsilyl moieties were removed on treatment with base. With these substrates (**31** and **33**) in hand, they were converted to their cobalt complexes and subjected to the PK cyclization under both oxidative and thermal conditions. As can be seen in Schemes 6 and 7, each of the substrates provided cycloadducts, but there is clearly some dependence on both the substrate and reaction conditions.

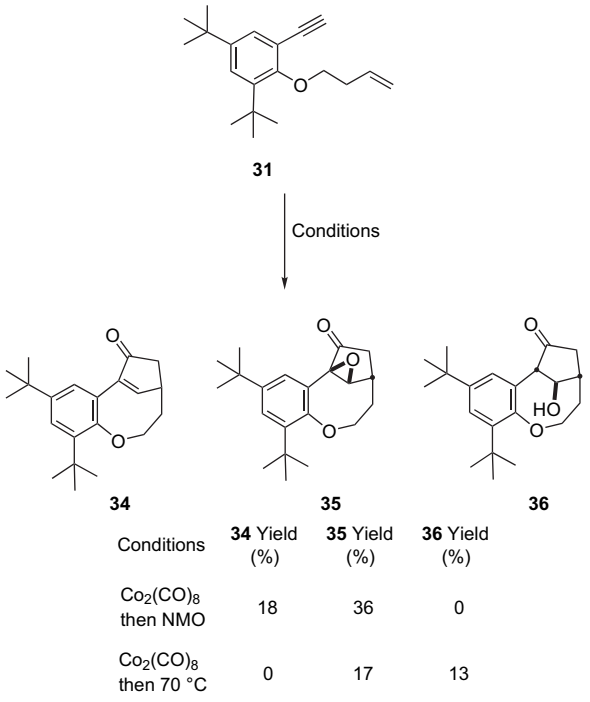


Scheme 4.



Scheme 5.

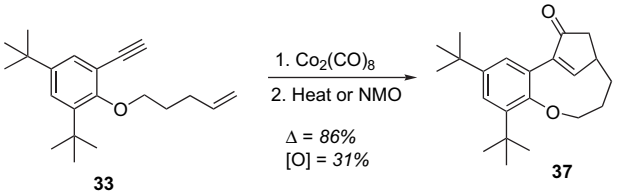
In the case of the parent butenyl-containing substrate **31**, under oxidative conditions two products were obtained, both of which were initially unanticipated. The major product was the epoxy ketone **35** (confirmed by X-ray analysis) along with the enone **34**,[11] interestingly, both products result as a consequence of 'abnormal' regiochemistry arising from insertion of the CO moiety adjacent to the aryl ring and previously unobserved orientation of the olefin (see Scheme 8).[2] When the same substrate was subjected to cyclization under



Conditions	**34** Yield (%)	**35** Yield (%)	**36** Yield (%)
$Co_2(CO)_8$ then NMO	18	36	0
$Co_2(CO)_8$ then 70 °C	0	17	13

Scheme 6.

thermal conditions, a reaction also occurred leading to the formation of the β-hydroxy ketone **36** and the epoxy ketone **35**. The β-hydroxy ketone results from the Michael addition of water to the enone **34** as demonstrated by a control reaction in which the enone is treated with water in toluene at reflux. Although we have no direct evidence, we believe that the epoxide results from the intermediacy of cobalt oxo species that are formed during the course of the reaction. Krafft and co-workers have demonstrated that the normal PK reaction takes a different course in the presence of oxygen, leading to the so-called interrupted PK reaction resulting in the formation of a non-cyclic enone.[2,25] When the reaction of the cobalt complex of **31** was conducted in an oxygen atmosphere, the yield of the epoxide **35** increased to 63%. Whereas attempts to convert enone **34** to the epoxide **35** under either the oxidative or thermal PK conditions were unsuccessful, suggesting that the enone is not an intermediate.[26] The higher homolog **33** also underwent cyclization under both oxidative and thermal conditions (Scheme 7), providing a similar type of unusual enone in 30% and 86% yield, respectively (the structure of **37** was confirmed by X-ray crystallography).[11] Interestingly, it is only with the butenyl substrate that these abnormal products are obtained, a molecular model suggests that the olefin moiety



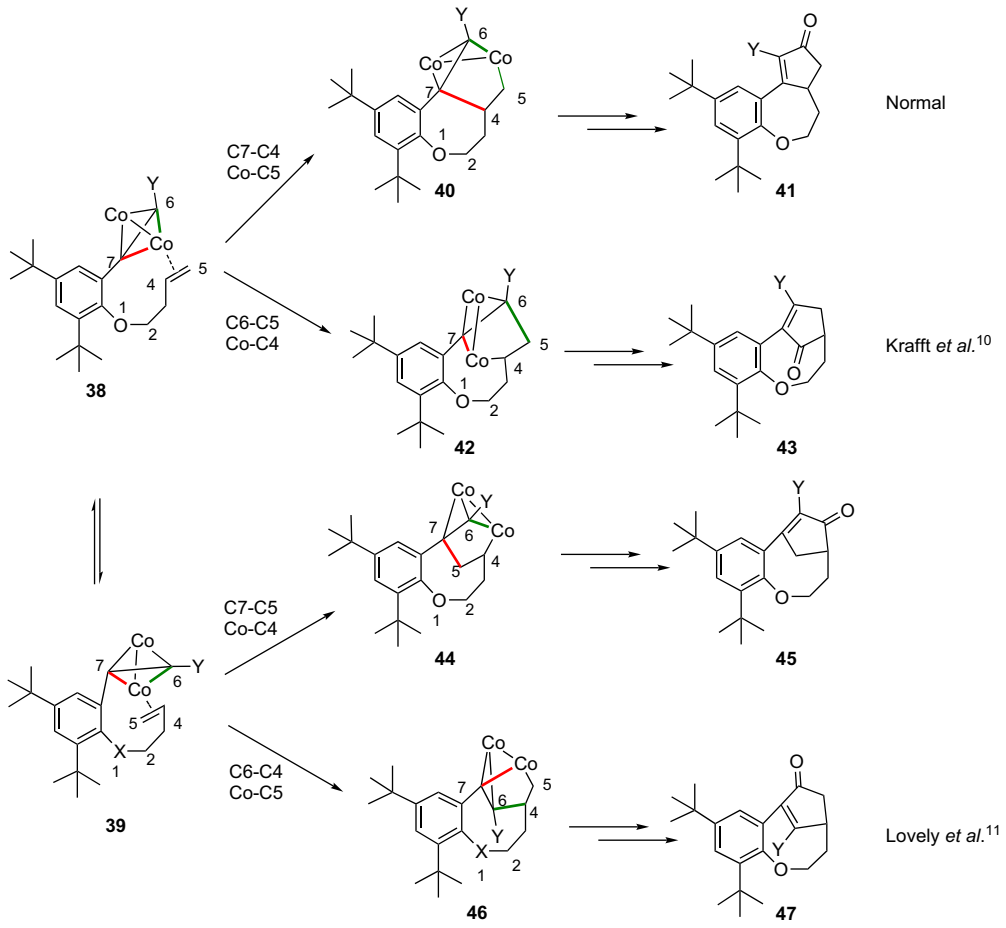
Scheme 7.

is rather strained, and reaction at the double bond relieves this strain.

Several selectivity aspects of these cyclization reactions of the higher homologs warrant further discussion. In general, intermolecular PK reactions are regioselective with respect to the alkyne component, with the larger substituent placed adjacent to the carbonyl moiety. This observation has been interpreted in terms of steric factors, with this mode of cycloaddition leading to a reduction of non-bonded interactions between the alkyne substituent and the cobalt cluster. Electronic factors also play a role,[27] with the more electron rich substituent placed adjacent to the carbonyl moiety. Regioselectivity in the olefinic moiety tends to be lower unless there are directing groups,[28] or the reaction is conducted intramolecularly. In intramolecular variants of the PK reaction, the regiochemistry of the carbonyl insertion appears to depend on the tether length. For substrates, which lead to 5,5-, 5,6-bicyclic, and for most 5,7-systems, the CO moiety inserts between the two terminii of the enyne. However, for systems that lead to larger rings, there is the possibility that insertion can occur at either the terminii or the internal positions. Indeed, our own results[11] and those from the Krafft group amply demonstrate this possibility.[10] This apparent change in selectivity can be interpreted as a reversion to intermolecular selectivity (carbonyl adjacent to the larger substituent) as a result of a more flexible tether in the larger rings. However, the mode of cyclization observed with **31** and **33** appears to be unique to the systems under investigation in this work. The mode of CO insertion, adjacent to the aryl moiety, is consistent with the normal selectivities observed in intermolecular variants, i.e., adjacent the largest and most electron rich substituent. The olefin regiochemistry is unusual, but is most likely a consequence of the structural features of the substituted aromatic ring (vide infra).

There are four possible modes of cyclization (leading to **41**, **43**, **45**, and **47**, Scheme 8) in the intramolecular PK reaction that are distinguished by the relative orientation of the two reacting moieties and the locus of CO insertion. Three of these modes of cycloaddition have now been observed experimentally (**41**, **43**, and **47**). We propose that in the present case, the *ortho-tert*-butyl moiety forces the olefin moiety to adopt a conformation such that the terminus of the olefin is placed proximal to the internal carbon of the acetylene. When insertion takes place to form the metallocycle, it occurs through this conformation, subsequent CO insertion and reductive elimination leads to the formation of the observed products. Although a detailed rationalization of this observation is still under investigation, the regiochemistry of alkyne insertion is consistent with both the steric (bulkiest substituent α to carbonyl) and electronic (most electron rich substituent α to carbonyl) effects observed in the intermolecular version of this reaction. Therefore, this outcome may be simply a result of the larger tether, which allows normal steric and electronic biases to operate[27] that are otherwise geometrically prohibitive with smaller tethers, e.g., in substrates **11**–**16** and **25**–**26**.

As these larger systems participated in the cycloaddition reaction, albeit with unexpected selectivity, we decided to probe the scope of this reaction with the TMS-containing substrates. Our motivation here was to investigate whether

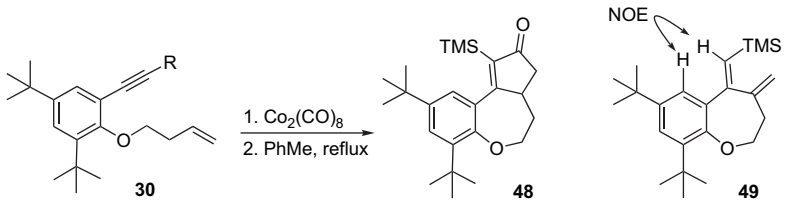


Scheme 8.

the regiochemistry of the cyclization may change with the introduction of a bulky substituent on the terminus of the alkyne. Under oxidative conditions, cyclization did not occur, but under thermal conditions a reaction did take place (Scheme 9). Two products were obtained from this reaction when it was conducted under standard conditions under a nitrogen atmosphere the expected enone was isolated in 14% yield, however, the major product was the diene, which was obtained in 75% yield.[29] Assignment of the stereochemistry at the TMS-substituted diene was determined by a NOESY experiment, the indicated NOE (Scheme 9) was particularly diagnostic. Repeating this reaction under a CO atmosphere led to a slight improvement in the yield of the enone but no diene was observed.

3. Conclusion

In summary, we have explored the use of steric buttressing elements in the intramolecular PK reaction. This investigation suggests that very crowded cyclopentenones can be constructed in excellent yields under either oxidative or thermal activation. In a second application, access to medium-sized rings is demonstrated, leading in some cases to a bridged ring system previously unobserved in the intramolecular PK reaction. An initial experiment with a internal alkyne leads to cycloaddition via the 'normal' mode, but providing the cyclopentenone in low yields. Current efforts in our labs are focused on improving the efficiency of this last example, along with the investigation of temporary buttressing elements.



Conditions	**48** Yield (%)	**49** Yield (%)
N_2	14	75
CO	22	0

Scheme 9.

4. Experimental

4.1. General

For general considerations see Ref. 30. All NMR spectra were acquired in $CDCl_3$ unless otherwise indicated.

4.1.1. 4,6-Di-*tert*-butyl-2-trimethylsilylethynylphenol (10). To a stirred solution of **9** (3.54 g, 10.7 mmol) and Et_3N (5.9 mL) in dioxane (5.9 mL), (trimethylsilyl)acetylene (1.37 g, 13.9 mmol), $PdCl_2(PPh_3)_2$ (78 mg, 0.12 mmol), and CuI (41 mg, 0.24 mmol) were added. The reaction mixture was stirred at 55 °C (bath temperature) under N_2 for 5 h. Et_2O (50 mL) and 1 M HCl (20 mL) were added, and the organic layer was separated, neutralized with a saturated $NaHCO_3$ (30 mL) solution, washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane) to afford **10** (3.03 g, 93%) as a solid, mp 114–116 °C. ^1H NMR (500 MHz): δ=7.27 (d, J=2.4 Hz, 1H), 7.20 (d, J=2.4 Hz, 1H), 6.08 (s, 1H), 1.39 (s, 9H), 1.39 (s, 9H), 0.27 (s, 9H); ^{13}C NMR (125 MHz): δ=153.6, 142.1, 134.8, 125.7, 125.6, 109.2, 76.8, 35.0, 34.3, 31.5, 29.5, 0.1; IR (KBr, cm^{-1}): 3494, 2959, 2143, 1467, 1122, 758, 657; EIMS: 57, 73, 286 (100%), 302 (M^+). Anal. Calcd for $C_{19}H_{30}OSi$: C, 75.43; H, 9.99. Found: C, 75.32; H, 10.01.

4.1.2. 4,6-Di-*tert*-butyl-2-trimethylsilylethynyl-(2-propenyl-oxy)benzene (11). Allyl bromide (1.35 g, 14.9 mmol) was added to a suspension of K_2CO_3 (2.06 g, 14.9 mmol) and **10** (1.50 g, 4.97 mmol) in DMF (20 mL). The reaction mixture was stirred at room temperature for 8 h. This was then quenched with water (100 mL) and extracted with CH_2Cl_2, the organic layer was then separated, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was then purified by flash chromatography (hexane/EtOAc, 91:9) to furnish **11** (1.74 g, 98%) as a light yellow liquid. ^1H NMR (300 MHz, $CDCl_3$): δ=7.30 (d, J=2.4 Hz, 1H), 7.28 (d, J=2.4 Hz, 1H), 6.07 (ddt, J=17.2, 10.7, 5.2 Hz, 1H), 5.41 (dd, J=17.2, 1.7 Hz, 1H), 5.22 (dd, J=10.7, 1.4 Hz, 1H), 4.77 (dd, J=5.2, 1.4 Hz, 2H), 1.37 (s, 9H), 1.28 (s, 9H), 0.24 (s, 9H,); ^{13}C NMR (75 MHz, $CDCl_3$): δ=157.5, 145.2, 142.0, 134.4, 129.2, 125.3, 116.6, 116.4, 103.2, 98.5, 73.2, 35.3, 34.5, 30.5, 30.7, 0.1; IR (neat, cm^{-1}): 3082, 2963, 2864, 2151, 1466, 1361, 1303, 1229, 1203, 1123, 959, 843; HRMS: calcd for $C_{22}H_{35}OSi$ $(M+H)^+$ 343.2452, found 343.2446.

4.1.3. 4,6-Di-*tert*-butyl-2-ethynyl-(2-propenyloxy)benzene (12). K_2CO_3 (0.49 g, 3.55 mmol) was added to a solution of **11** (0.62 g, 1.74 mmol) in MeOH/THF (10 mL, 1:1). The mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and filtered through a plug of silica gel (EtOAc). The residue was purified by flash chromatography (hexane/ether, 83:17) to furnish **12** (0.50 g, quantitative) as a colorless liquid. ^1H NMR (500 MHz): δ=7.38 (d, 1H, J=2.5 Hz), 7.36 (d, 1H, J=2.5 Hz), 6.17 (m, 1H), 5.49 (dd, 1H, J=1.3, 10.4 Hz), 5.29 (dd, 1H, J=1.3, 17.2 Hz), 4.81 (d, 2H, J=5.3 Hz), 3.31 (s, 1H), 1.42 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (125 MHz): δ=157.7, 145.4, 142.2, 134.2, 129.5, 125.6, 116.8, 115.5, 81.9, 81.5, 73.6, 35.3, 34.5, 31.4, 30.7; IR (neat, cm^{-1}): 3311, 2962, 2106, 1647, 1437, 1122, 742, 650. Anal. Calcd for $C_{19}H_{26}O$: C, 84.39; H, 9.69. Found: C, 84.34; H, 9.53.

4.1.4. 4,6-Di-*tert*-butyl-2-trimethylsilylethynyl-(3-phenyl-2-propenyloxy)benzene (13). DEAD (3.46 g, 19.9 mmol) in THF (10 mL) was added dropwise to a solution of **10** (2.00 g, 6.60 mmol), cinnamyl alcohol (1.78 g, 13.3 mmol), and PPh_3 (5.21 g, 19.9 mmol) in THF (20 mL) and stirred at 0 °C for 6 h. The solvent was removed in vacuum and the crude product was purified by flash chromatography (hexane) to give the product as a white solid (2.70 g, 95%). Mp 123–125 °C; ^1H NMR (500 MHz): δ=7.45 (d, J=7.3 Hz, 2H), 7.33–7.36 (m, 4H), 7.25–7.28 (m, 1H), 6.82 (d, J=15.9 Hz, 1H), 6.50 (dt, J=15.9, 5.7 Hz, 1H), 4.97 (dd, J=5.7, 1.8 Hz, 2H), 1.42 (s, 9H), 1.31 (s, 9H), 0.27 (s, 9H); ^{13}C NMR (125 MHz): δ=157.5, 145.3, 142.1, 137.0, 132.0, 129.3, 128.6, 127.7, 126.6, 125.8, 125.4, 116.5, 103.3, 98.7, 73.2, 35.3, 34.5, 31.5, 30.8, 0.2; IR (neat, cm^{-1}): 3109, 2960, 2152, 1434, 1371, 1229, 1120; LRMS (ESI): 419 (M+H), 441 (M+Na); HRMS: calcd for $C_{28}H_{39}OSi$ $(M+H)^+$ 419.2765, found 419.2767: calcd for $C_{28}H_{39}NaOSi$ $(M+Na)^+$ 441.2584, found 441.2589.

4.1.5. 4,6-Di-*tert*-butyl-2-ethynyl-(3-phenyl-2-propenyloxy)-benzene (14). K_2CO_3 (1.32 g, 9.57 mmol) was added to a solution of **13** (1.00 g, 2.39 mmol) in MeOH/THF (10 mL, 1:1). The mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and filtered through a plug of silica gel (EtOAc). The residue was purified by flash chromatography (hexane/ether, 83:17) to furnish **14** (0.77 g, 93%) as a colorless liquid: ^1H NMR (500 MHz): δ=7.45 (d, J=7.3 Hz, 2H), 7.24–7.38 (m, 5H), 6.78 (d, J=15.8 Hz, 1H), 6.51 (dt, J=15.8, 5.8 Hz, 1H), 4.94 (dd, J=5.8, 1.8, Hz, 2H), 3.34 (s, 1H), 1.42 (s, 9H), 1.31 (s, 9H); ^{13}C NMR (125 MHz): δ=157.8, 145.5, 142.3, 137.0, 132.2, 129.5, 128.6, 127.8, 126.7, 125.7, 125.6, 115.6, 82.0, 81.6, 73.6, 35.3, 34.5, 31.5, 30.8; IR (neat, cm^{-1}): 3298, 2959, 2103, 1658, 1578, 1435, 1368, 1230, 1121; LRMS (ESI): 347 (M+H), 369 (M+Na). Anal. Calcd for $C_{25}H_{30}O$: C, 86.66; H, 8.73. Found: C, 86.40; H, 8.86.

4.1.6. 4,6-Di-*tert*-butyl-2-trimethylsilylethynyl-(2-methylallyloxy)benzene (15). 3-Chloro-2-methylpropene (1.35 g, 14.9 mmol) was added to a suspension of K_2CO_3 (2.06 g, 14.9 mmol), NaI (2.34 g, 14.9 mmol), and **10** (1.50 g, 4.97 mmol) in DMF (20 mL). The reaction mixture was stirred for 12 h. This was then quenched with water (100 mL) and extracted with CH_2Cl_2, the organic layer was then separated, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was then purified by flash chromatography (hexane/EtOAc, 91:9) to furnish **15** (1.74 g, 98%) as a yellow liquid. ^1H NMR (500 MHz): δ=7.32 (d, J=2.3 Hz, 1H), 7.30 (d, J=2.8 Hz, 1H), 5.20 (s, 1H), 4.97 (s, 1H), 4.69 (s, 2H), 1.86 (s, 3H), 1.37 (s, 9H), 1.29 (s, 9H), 0.24 (s, 9H); ^{13}C NMR (125 MHz): δ=157.4, 145.2, 142.1, 141.5, 129.4, 125.3, 116.4, 111.1, 103.2, 98.6, 75.5, 35.2, 34.5, 31.4, 30.7, 19.7, 0.02; IR (neat, cm^{-1}): 2961, 2151, 1436, 1249, 960; HRMS: calcd for $C_{23}H_{37}OSi$ $(M+H)^+$ 357.2608, found 357.2613.

4.1.7. 4,6-Di-*tert*-butyl-2-ethynyl-(2-methylallyloxy)benzene (16). K_2CO_3 (0.49 g, 3.55 mmol) was added to a solution

of **15** (0.62 g, 1.74 mmol) in MeOH/THF (10 mL, 1:1). The mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and filtered through a plug of silica gel (EtOAc). The residue was purified by flash chromatography (hexane/ether, 83:17) to furnish **16** (0.50 g, quantitative) as a yellow liquid. ^{1}H NMR (300 MHz): δ=7.38 (d, J=2.4 Hz, 1H), 7.36 (d, J=2.4 Hz, 1H), 5.20 (s, 1H), 5.00 (s, 1H), 4.70 (s, 2H), 3.30 (s, 1H), 1.90 (s, 3H), 1.41 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (75 MHz): δ=157.7, 145.3, 142.2, 141.7, 129.6, 125.6, 115.5, 111.8, 81.9, 81.6, 76.0, 35.3, 34.5, 31.5, 30.7, 19.8; IR (neat, cm^{-1}): 3313, 3108, 2974, 2107, 1658, 1438, 1233, 1165, 1123, 1042; HRMS: calcd for $C_{20}H_{28}ONa$ (M+Na)$^+$ 307.2032, found 307.2037, and calcd for $C_{20}H_{29}O$ for (M+H)$^+$ 285.2213, found 285.2211.

Oxidative Pauson–Khand method (procedure A): the enyne was dissolved in CH_2Cl_2 under N_2 and 1.1 equiv of $Co_2(CO)_8$ was added and stirred at room temperature for 5 h. It was cooled to 0 °C before NMO (8–10 equiv total) was added in three approximately equal portions at 30 min intervals and then left to stir for 2 h. The reaction mixture was then filtered through a pad of Celite and SiO_2, and washed with EtOAc. The filtrate was concentrated and then the product was the purified by flash chromatography using the indicated eluant.

Thermal Pauson–Khand method (procedure B): the enyne was dissolved in toluene under N_2 and 1.1 equiv of $Co_2(CO)_8$ was added and stirred at room temperature for 5 h. It was then heated under N_2 at 70 °C until the reaction was complete. The reaction mixture was then filtered through a pad of Celite and SiO_2, washed with hexane to remove the alkyne–$Co_2(CO)_6$ remaining, and then washed with ethyl acetate to get the cyclized product. The crude product was then purified by flash chromatography using the indicated eluant.

4.1.8. 6,8-Di-*tert*-butyl-3a,4-dihydro-3*H*-cyclopenta[*c*]-chro-men-2-one (17). Cyclization following the general procedure A utilizing **12** (180 mg, 0.63 mmol), $Co_2(CO)_8$ (0.24 g, 0.64 mmol), and NMO (0.64 g, 5.50 mmol) in CH_2Cl_2 (mL) or procedure B utilizing **12** (100 mg, 0.37 mmol), toluene (5 mL), and $Co_2(CO)_8$ (140 mg, 0.41 mmol) followed by flash chromatography (hexane/EtOAc, 90:10) afforded **17** (133 mg, 80% or 100 mg, 91%, respectively) as a solid. Mp 179–180 °C; ^{1}H NMR (500 MHz): δ=7.44 (d, J=2.4 Hz, 1H), 7.39 (d, J=2.4 Hz, 1H), 6.35 (d, J=1.7 Hz, 1H), 4.64 (dd, J=10.7, 5.5 Hz, 1H), 3.80 (dd, J=13.4, 10.3 Hz, 1H), 3.28 (m, 1H), 2.67 (dd, J=17.9, 6.9 Hz, 1H), 2.04 (dd, J=17.9, 4.1 Hz, 1H), 1.39 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (125 MHz): δ=206.3, 170.6, 153.1, 143.3, 138.5, 128.5, 121.4, 121.2, 117.1, 69.8, 38.1, 36.5, 34.5, 35.3, 31.4, 29.7; IR (KBr, cm^{-1}): 2962, 1698, 1599, 1479, 1189, 860, 680. Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.50; H, 9.00.

4.1.9. 6,8-Di-*tert*-butyl-1-trimethylsilyl-3a,4-dihydro-3*H*-cyclopenta[*c*]chromen-2-one (18). Cyclization following the general procedure B utilizing **11** (100 mg, 0.29 mmol), toluene (5 mL), and $Co_2(CO)_8$ (110 mg, 0.32 mmol) followed by flash chromatography (hexane/EtOAc; 90:10) to afford **18** (100 mg, 93%) as a light yellow liquid, which solidified on standing. Mp 132–134 °C; ^{1}H NMR (500 MHz): δ=7.41 (d, J=2.4 Hz, 1H), 7.28 (d, J=2.4 Hz, 1H), 4.67 (dd, J=10.4, 5.7 Hz, 1H), 3.87 (dd, J=10.4, 13.4 Hz, 1H), 3.15 (m, 1H), 2.62 (dd, J=17.8, 7.0 Hz, 1H), 1.95 (dd, J=17.8, 4.5 Hz, 1H), 1.39 (s, 9H), 1.31 (s, 9H), 0.33 (s, 9H); ^{13}C NMR (125 MHz): δ=210.7, 177.3, 152.5, 141.1, 137.4, 133.3, 128.0, 124.5, 119.0, 70.2, 38.2, 37.2, 35.3, 34.7, 31.6, 29.8, 0.1; IR (neat, cm^{-1}): 2960, 1693, 1578, 1440, 1248, 844. Anal. Calcd for $C_{23}H_{34}O_2Si$: C, 74.54; H, 9.25. Found: C, 74.13; H, 9.33; HRMS: calcd for $C_{23}H_{35}O_2Si$ (M+H)$^+$ 371.2401, found 371.2402.

4.1.10. 6,8-Di-*tert*-butyl-3-phenyl-3a,4-dihydro-3*H*-cyclopenta[*c*]chromen-2-one (19). Cyclization following the general procedures A and B utilizing **14** (200 mg, 0.58 mmol), CH_2Cl_2 (10 mL) for procedure A and toluene (10 mL) for procedure B, $Co_2(CO)_8$ (220 mg, 0.64 mmol), and NMO (740 mg, 6.40 mmol) followed by flash chromatography (hexane/EtOAc, 90:10) to afford **19** (200 mg, 91% for procedure A and 160 mg, 73% for procedure B) as a light yellow solid. Mp 155–157 °C; ^{1}H NMR (500 MHz): δ=7.49 (d, J=2.3 Hz, 1H), 7.47 (d, J=2.3 Hz, 1H), 7.36 (t, J=7.3 Hz, 2H), 7.30 (d, J=7.3 Hz, 1H), 7.21 (d, J=7.3 Hz, 2H), 6.47 (d, J=1.8 Hz, 1H), 4.74 (dd, J=5.5, 10.5 Hz, 1H), 3.96 (dd, J=10.5, 13.3 Hz, 1H), 3.36 (ddt, J=1.8, 5.5, 11.5 Hz, 1H), 3.26 (d, J=4.6 Hz, 1H), 1.39 (s, 9H), 1.35 (s, 9H); ^{13}C NMR (125 MHz): δ=205.6, 168.2, 153.4, 143.5, 138.7, 137.9, 129.0, 128.8, 128.6, 127.4, 121.3, 119.9, 116.8, 69.2, 56.0, 45.6, 35.3, 34.5, 30.4, 29.7; IR (neat, cm^{-1}): 3105, 2959, 2864, 1712, 1607, 1476, 1214, 1151, 1005; LRMS (ESI): 413 [M+K], 397 [M+Na], 375 [M+H]. Anal. Calcd for $C_{26}H_{30}O_2$: C, 83.38; H, 8.07. Found: C, 83.25; H, 8.18.

4.1.11. 6,8-Di-*tert*-butyl-3-phenyl-1-trimethylsilyl-3a,4-dihydro-3*H*-cyclopenta[*c*]chromen-2-one (20). Cyclization following the general procedures A and B utilizing **14** (200 mg, 0.48 mmol) and the appropriate solvent (10 mL), $Co_2(CO)_8$ (180 mg, 0.53 mmol), and NMO (620 mg, 5.26 mmol) followed by flash chromatography (hexane/EtOAc, 90:10) to afford **20** (170 mg, 81% for procedure A and 150 mg, 71% for procedure B) as a light yellow solid. Mp 129–131 °C; ^{1}H NMR (500 MHz): δ=7.46 (d, J=2.3 Hz, 1H), 7.42 (d, J=2.3 Hz, 1H), 7.34 (t, J=7.3 Hz, 2H), 7.28 (d, J=7.3 Hz, 1H), 7.19 (d, J=6.9 Hz, 2H), 4.77 (dd, J=5.5, 10.5 Hz, 1H), 4.01 (dd, J=10.5, 13.3 Hz, 1H), 3.30 (dt, J=5.5, 12.8 Hz, 1H), 3.14 (d, J=5.0 Hz, 1H), 1.39 (s, 9H), 1.36 (s, 9H), 0.39 (s, 9H); ^{13}C NMR (125 MHz): δ=209.5, 174.7, 153.0, 141.5, 138.2, 137.7, 132.2, 128.9, 128.7, 128.3, 127.2, 124.7, 118.7, 69.6, 56.1, 46.2, 35.4, 34.8, 31.7, 29.8, 0.1; IR (neat, cm^{-1}): 3106, 2961, 1687, 1581, 1441, 1249, 1007, 939; ESI-MS: 447 [M+H], 469 [M+Na]; HRMS: calcd for $C_{29}H_{38}SiO_2Na$ (M+Na)$^+$ 469.2533, found 469.2579.

4.1.12. 6,8-Di-*tert*-butyl-3a-methyl-3a,4-dihydro-3*H*-cyclopenta[*c*]chromen-2-one (21). Cyclization following the general procedure A utilizing **16** (180 mg, 0.63 mmol), $Co_2(CO)_8$ (0.24 g, 0.70 mmol), and NMO (0.73 g, 6.3 mmol) in CH_2Cl_2 (10 mL) or procedure B utilizing **16** (110 mg, 0.39 mmol), toluene (5 mL), and $Co_2(CO)_8$ (130 mg, 0.38 mmol) followed by flash chromatography (hexane/EtOAc, 90:10) to afford **21** (160 mg, 81% and 110 mg, 91%) as a solid, mp 130–132 °C. ^{1}H NMR

(300 MHz): δ=7.43 (d, J=2.4 Hz, 1H), 7.36 (d, J=2.1 Hz, 1H), 6.23 (s, 1H), 4.33 (d, J=10.4 Hz, 1H), 3.87 (d, J=10.7 Hz, 1H), 2.39 (d, J=17.5 Hz, 1H), 2.20 (d, J=17.5 Hz, 1H), 1.40 (s, 9H), 1.31 (s, 9H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=205.8, 174.9, 151.7, 143.2, 138.3, 128.4, 121.5, 120.0, 116.2, 73.9, 47.0, 38.8, 35.2, 34.4, 31.4, 29.7, 23.8; IR (neat, cm^{-1}): 3098, 2962, 1700, 1594, 1463, 1183, 1011; HRMS: calcd for $C_{21}H_{29}O_2$ (M+H)$^+$ 313.2162, found 313.2164.

4.1.13. 6,8-Di-*tert*-butyl-1-trimethylsilyl-3a-methyl-4-hydro-3*H*-cyclopenta[*c*]chromen-2-one (22). Cyclization following the general procedures B utilizing **15** (240 mg, 0.64 mmol), toluene (10 mL), and $Co_2(CO)_8$ (240 mg, 0.74 mmol) followed by flash chromatography (hexane/EtOAc, 90:10) to afford **22** (240 mg, 92%) as a solid, mp 156–157 °C. ^{1}H NMR (500 MHz): δ=0.30 (s, 9H), 1.19 (s, 3H), 1.32 (s, 9H), 1.39 (s, 9H), 2.02 (d, J=17.5 Hz, 1H), 2.31 (d, J=17.2 Hz, 1H), 3.96 (d, J=10.7 Hz, 1H), 4.32 (d, J=10.7 Hz, 1H), 6.23 (s, 1H), 7.24 (d, J=2.3 Hz, 1H), 7.40 (d, J=2.3 Hz, 1H); ^{13}C NMR (125 MHz): δ=210.1, 181.4, 151.3, 141.2, 137.1, 132.1, 127.9, 124.8, 117.8, 74.6, 47.3, 39.0, 35.2, 34.6, 31.6, 29.7, 22.9, 0.2; IR (neat, cm^{-1}): 2959, 1691, 1529, 1255, 1028, 938. Anal. Calcd for $C_{24}H_{36}O_2Si$: C, 74.94; H, 9.43. Found: C, 74.77; H, 9.23; HRMS: calcd for $C_{24}H_{37}O_2Si$ (M+H)$^+$ 385.2557, found 385.2559.

4.1.14. 2,4-Di-*tert*-butyl-6-(3-hydroxy-3-methylbut-1-ynyl)-phenol (23). To a stirred solution of **9** (2.82 g, 8.50 mmol) and Et_3N (5.9 mL) in dioxane (5.9 mL), 2-hydroxy-2-methylbut-1-yne (2.14 g, 25.5 mmol), $PdCl_2(PPh_3)_2$ (0.30 g, 0.43 mmol), and CuI (0.16 g, 0.84 mmol) were added. The reaction mixture was stirred at 55 °C (bath temperature) under N_2 for 5 h. Et_2O (50 mL) and 1 M HCl (20 mL) were added, and the organic layer was separated, neutralized with a saturated $NaHCO_3$ (30 mL) solution, washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, hexane) to afford **23** (2.30 g, 94%), as a golden yellow solid. Mp 97–99 °C; ^{1}H NMR (300 MHz): δ=7.27 (d, J=2.4 Hz, 1H), 7.18 (d, J=2.4 Hz, 1H), 6.02 (s, 1H), 2.31 (s, 1H), 1.66 (s, 6H), 1.40 (s, 9H), 1.28 (s, 9H); ^{13}C NMR (75 MHz): δ=153.0, 142.1, 134.9, 125.8, 125.3, 108.6, 100.7, 66.0, 35.0, 34.3, 31.7, 31.5, 29.5; IR (neat, cm^{-1}): 3358, 2959, 2223, 1443, 1415, 1363, 1197; HRMS: calcd for $C_{19}H_{28}O_2Na$ (M+Na)$^+$ 311.1982, found 311.1985.

4.1.15. 2,4-Di-*tert*-butyl-6-(3-methylbut-1-ynyl)phenol (24). To a stirred solution of **23** (0.10 g, 0.35 mmol) and $NaBH_4$ (0.13 g, 3.50 mmol) in CH_2Cl_2 (5 mL), at 0 °C was added TFA (3 mL) over a period of 10 min. The reaction mixture was then decanted into iced water (100 mL) and extracted with CH_2Cl_2 (20 mL), and the organic layer was separated, neutralized with a saturated $NaHCO_3$ (30 mL) solution, washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane) to afford **24** (0.09 g, 96%) as a golden yellow oil. ^{1}H NMR (500 MHz): δ=7.23 (d, J=2.8 Hz, 1H), 7.17 (d, J=2.8 Hz, 1H), 6.03 (s, 1H), 1.28 (s, 9H), 2.86 (sept, J=6.9 Hz, 1H), 1.40 (s, 9H), 1.30 (d, J=6.9 Hz, 6H); ^{13}C NMR (125 MHz): δ=152.8, 141.9, 134.5, 125.6, 124.4, 109.9, 102.8, 74.8, 35.0, 34.9, 34.3, 31.6, 29.5, 23.3, 21.5; IR (neat, cm^{-1}): 3497, 2959, 1443, 1363, 1234, 880; HRMS: calcd for $C_{19}H_{29}O$ (M+H)$^+$ 273.2213, found 273.2221.

4.1.16. 4,6-Di-*tert*-butyl-2-(2-methylbut-3-yn-2-ol)-(2-methyl-allyloxy)benzene (25). 3-Chloro-2-methylpropene (1.26 g, 13.9 mmol) was added to a suspension of K_2CO_3 (1.92 g, 13.9 mmol), NaI (2.08 g, 13.9 mmol), and **23** (1.00 g, 3.47 mmol) in DMF (20 mL). The reaction mixture was stirred for 12 h. This was then quenched with water (100 mL) and extracted with CH_2Cl_2, the organic layer was then separated, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was then purified by flash chromatography (hexane/EtOAc, 91:9) to furnish **25** (0.88 g, 74%) as a light yellow solid, mp 91–93 °C. ^{1}H NMR (300 MHz): δ=7.31 (d, J=2.7 Hz, 1H), 7.25 (d, J=2.7 Hz, 1H), 5.25 (app. t, J=1.0 Hz, 1H), 4.99 (app. t, J=1.4 Hz, 1H), 4.63 (s, 2H), 2.12 (s, 1H), 1.85 (s, 3H), 1.60 (s, 6H), 1.38 (s, 9H), 1.29 (s, 9H). ^{13}C NMR (75 MHz): δ=157.0, 145.3, 142.1, 141.9, 128.8, 125.0, 116.1, 110.7, 97.9, 80.1, 75.5, 65.8, 35.3, 34.5, 31.7, 31.4, 30.7, 29.7, 19.7; IR (neat, cm^{-1}): 3331, 2956, 2866, 1657, 1467, 1436, 1410, 1361, 1316, 1229, 1200, 1166, 1125, 1038; HRMS: calcd for $C_{23}H_{34}O_2Na$ (M+Na)$^+$ 365.2451, found 365.2450.

4.1.17. 4,6-Di-*tert*-butyl-2-(2-methylbut-3-ynyl)-(2-methyl-allyloxy)benzene (26). 3-Chloro-2-methylpropene (0.15 g, 1.7 mmol) was added to a suspension of K_2CO_3 (0.11 g, 0.81 mmol), NaI (0.25 g, 1.7 mmol), and **24** (0.11 g, 0.40 mmol) in DMF (20 mL). The reaction mixture was stirred for 12 h. This was then quenched with water (100 mL) and extracted with CH_2Cl_2, the organic layer was then separated, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was then purified by flash chromatography (hexane/EtOAc, 91:9) to furnish **26** (0.12 g, 92%) as a light yellow oil. ^{1}H NMR (300 MHz): δ=7.27 (d, J=2.7 Hz, 1H), 7.24 (d, J=2.7 Hz, 1H), 5.21 (app. t, J=1.0 Hz, 1H), 4.98 (app. t, J=1.4 Hz, 1H), 4.67 (s, 2H), 2.74–2.88 (h, J=6.9 Hz, 1H), 1.87 (s, 3H), 1.38 (s, 9H), 1.29 (s, 9H), 1.26 (d, J=7.2 Hz, 6H); ^{13}C NMR (75 MHz): δ=156.8, 145.1, 141.9, 141.7, 128.9, 124.2, 117.2, 110.9, 99.9, 75.2, 35.2, 34.5, 31.5, 30.7, 29.4, 23.0, 21.6, 19.7; IR (neat, cm^{-1}): 2956, 2866, 1657, 1467, 1436, 1410, 1361, 1316, 1229, 1200, 1166, 1125, 1038; HRMS: calcd for $C_{23}H_{34}O$ (M+H)$^+$ 326.2604, found 326.2585.

4.1.18. 6,8-Di-*tert*-butyl-1-(1-hydroxy-1-methylethyl)-3a-methyl-3a,4-dihydro-3*H*-cyclopenta[*c*]chromen-2-one (27). Cyclization following the general procedures A and B utilizing **25** (110 mg, 0.32 mmol) and 5 mL of appropriate solvent, $Co_2(CO)_8$ (120 mg, 0.35 mmol), and NMO (410 mg, 3.51 mmol) followed by flash chromatography (hexane/EtOAc, 90:10) to afford **27** (40 mg, 33% for procedure A and 91 mg, 75% for procedure B) as a yellow liquid; ^{1}H NMR (300 MHz): δ=7.39 (d, J=2.4 Hz, 1H), 7.37 (d, J=2.4 Hz, 1H), 4.72 (s, 1H), 4.32 (d, J=10.7 Hz, 1H), 3.96 (d, J=11.0 Hz, 1H), 2.38 (d, J=18.2 Hz, 1H), 2.16 (d, J=18.2 Hz, 1H), 1.69 (s, 3H), 1.56 (s, 3H), 1.38 (s, 9H), 1.31 (s, 9H), 1.16 (s, 3H); ^{13}C NMR (75 MHz): δ=207.9, 166.4, 151.1, 141.0, 138.5, 136.7, 127.4, 125.8, 116.6, 74.7, 71.4, 46.0, 36.2, 35.2, 34.5, 31.5, 31.4, 29.6, 27.8, 22.6; IR (neat, cm^{-1}): 3393, 2956, 2869, 1680, 1603,

1467, 1438, 1025; HRMS: calcd for $C_{24}H_{35}O_3$ $(M+H)^+$ 371.2581 found 371.2587.

4.1.19. 6,8-Di-*tert*-butyl-1-isopropyl-3a-methyl-3a,4-dihydro-3*H*-cyclopenta[*c*]chromen-2-one (28). Cyclization following the general procedures B utilizing **26** (110 mg, 0.34 mmol), toluene (5 mL), and $Co_2(CO)_8$ (130 mg, 0.37 mmol) followed by flash chromatography (hexane/EtOAc, 90:10) to afford **28** (100 mg, 84%) as a solid. Mp 147–149 °C; ^{1}H NMR (300 MHz): δ=7.40 (d, J=2.3 Hz, 1H), 7.34 (d, J=2.3 Hz, 1H), 4.31 (d, J=10.5 Hz, 1H), 3.90 (d, J=10.5 Hz, 1H), 3.14 (m, 1H), 2.28 (d, J=17.9 Hz, 1H), 2.04 (d, J=17.9 Hz, 1H), 1.40 (s, 9H), 1.38 (d, J=6.8 Hz, 3H), 1.32 (s, 9H), 1.26 (d, J=6.8 Hz, 3H), 1.19 (s, 3H); ^{13}C NMR (75 MHz): δ=206.2, 164.9, 19.7; 150.9, 142.0, 138.8, 137.3, 126.9, 123.0, 117.1, 74.9, 46.2, 35.8, 35.3, 34.4, 31.5, 29.6, 25.9, 22.9, 20.6; IR (neat, cm^{-1}): 3375, 2962, 1698, 1611, 1474, 1386, 1363, 1307, 1231, 1166, 1129, 1021; HRMS: calcd for $C_{24}H_{35}O_2$ $(M+H)^+$ 355.2632, found 355.2635.

4.1.20. 4,6-Di-*tert*-butyl-2-trimethylsilylethynyl-(3-butenyloxy)benzene (30). DEAD (3.46 g, 19.9 mmol) in THF (20 mL) was added dropwise to a solution of **10** (2.0 g, 6.62 mmol), 3-buten-1-ol (0.96 g, 13.3 mmol), and PPh_3 (5.22 g, 19.9 mmol) in THF (50 mL) and stirred at 0 °C for 6 h. The solvent was removed by rotary evaporation and the crude product was purified by flash chromatography (hexane) to give **30** as a clear liquid (2.35 g, 99%). ^{1}H NMR (300 MHz): δ=7.31 (d, J=1.2 Hz, 2H), 5.92 (m, 1H), 5.15 (dd, J=17.2, 2.1 Hz, 1H), 5.09 (dd, J=17.2, 2.1 Hz, 1H), 4.29 (app. t, J=6.9 Hz, 2H), 2.61 (dd, J=7.2, 6.9 Hz, 2H), 1.38 (s, 9H), 1.29 (s, 9H), 0.27 (s, 9H); ^{13}C NMR (75 MHz): δ=157.8, 145.0, 141.9, 134.9, 135.4, 129.4, 125.3, 116.8, 116.4, 103.5, 98.3, 71.8, 35.3. 34.7, 34.5, 31.5, 30.8, 0.1; IR (neat, cm^{-1}): 3106, 2959, 2151, 1437, 1235, 1123, 960, 912; HRMS: calcd for $C_{23}H_{37}OSi$ $(M+H)^+$ 357.2608, found 357.2613.

4.1.21. 4,6-Di-*tert*-butyl-2-ethynyl-(3-butenyloxy)benzene (31). K_2CO_3 (1.13 g, 8.2 mmol) was added to a solution of **30** (1.41 g, 4.1 mmol) in MeOH/THF (10 mL, 1:1). The mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and filtered through a plug of silica gel (EtOAc). The residue was purified by flash chromatography (silica gel, 83:17 *n*-hexane/ether) to furnish **31** (0.75 g, 80%) as a colorless liquid. ^{1}H NMR (500 MHz): δ=7.34 (d, J=2.4 Hz, 1H), 7.33 (d, J=2.4 Hz, 1H), 5.98 (ddt, J=17.0, 10.3, 6.8 Hz, 1H), 5.16–5.20 (m, 1H), 5.09–5.11 (m, 1H), 4.30 (app. t, J=7.0 Hz, 2H), 3.30 (s, 1H), 2.62–2.67 (m, 2H), 1.39 (s, 9H), 1.29 (s, 9H); ^{13}C NMR (125 MHz): δ=158.1, 145.1, 142.0, 134.9, 129.5, 125.5, 116.8, 115.4, 82.1, 81.3, 72.2, 35.3, 34.8, 34.5, 31.5, 30.8; IR (neat, cm^{-1}): 3304, 2959, 2107, 1656, 1122, 727; EIMS: 57, 171, 215 (100%), 269, 284 (M^+). Anal. Calcd for $C_{20}H_{28}O$: C, 84.45; H, 9.92. Found: C, 84.48; H, 10.03.

4.1.22. 4,6-Di-*tert*-2-ethynyl-(4-pentenyloxy)benzene (33). DEAD (0.78 g, 4.5 mmol) in THF (15 mL) was added dropwise to a solution of **10** (0.44 g, 1.5 mmol), 4-penten-1-ol (0.25 g, 3.0 mmol), and PPh_3 (1.18 g, 3.0 mmol) in THF (50 mL). The reaction mixture was stirred at 0 °C for 2 h. The solvent was removed by rotary evaporation, dissolved in pentane, washed with 10% aq KOH (30 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in 1:1 MeOH/THF (15 mL) and K_2CO_3 (0.42 g, 3.0 mmol) was added to it, followed by stirring overnight. The reaction mixture was concentrated, dissolved in EtOAc, filtered through a plug of silica gel, and the filtrate was concentrated. The residue was purified by flash chromatography (hexane) to provide **33** (0.36 g, 83%) as a pale yellow liquid. ^{1}H NMR (500 MHz): δ=7.33 (d, J=2.6 Hz, 1H), 7.32 (d, J=2.6 Hz, 1H), 5.89 (ddt, J=17.0, 10.1, 6.6 Hz, 1H), 5.06–5.10 (m, 1H), 4.98–5.00 (m, 1H), 4.24 (t, J=6.8 Hz, 2H), 3.28 (s, 1H), 2.27 (app. dt, J=7.3, 6.6 Hz, 2H), 1.97 (m, 2H), 1.38 (s, 9H), 1.28 (s, 9H); ^{13}C NMR (125 MHz): δ=158.2, 145.1, 142.0, 138.4, 129.5, 125.5, 115.4, 114.8, 82.1, 81.2, 72.6, 35.3, 34.5, 31.4, 30.8, 30.3, 29.5; IR (neat, cm^{-1}): 3301, 2857, 2103, 1641, 1122, 730; EIMS (*m*/*z*): 298 (M^+), 282 (100%), 214, 57. Anal. Calcd for $C_{21}H_{30}O$: C, 84.51; H, 10.13. Found: C, 84.58; H, 10.51.

4.2. Oxidative cyclization of 31

Cyclization of **31** (113 mg, 0.40 mmol) utilizing general procedure A provided after purification by flash chromatography (hexane/EtOAc/Et_3N, 87.4:12.5:0.1) **35** (47 mg, 36%) and **34** (22 mg, 18%), both as colorless solids.

4.2.1. Epoxy ketone 35. Mp 216–219 °C; ^{1}H NMR (500 MHz): δ=7.39 (d, J=2.4 Hz, 1H), 7.35 (d, J=2.4 Hz, 1H), 4.45 (app. d, J=13.9 Hz, 1H), 4.04 (s, 1H), 3.40 (app. t, J=13.0 Hz, 1H), 2.93–2.95 (m, 1H), 2.76 (dd, J=6.3, 18.1 Hz, 1H), 2.53–2.50 (m, 1H), 1.98 (app. d, J=18.1 Hz, 1H), 1.94 (app. d, J=15.6 Hz, 1H), 1.32 (s, 9H), 1.31 (s, 9H); ^{13}C NMR (125 MHz): δ=207.0, 157.7, 145.5, 141.3, 125.4, 125.0, 70.1, 67.5, 56.8, 36.6, 35.2, 34.7, 32.4, 31.5, 30.7; IR (KBr, cm^{-1}): 2954, 1744, 1435, 1113, 737, 647; EIMS (*m*/*z*): 328 (M^+), 299 (100%). Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.59; H, 8.59. Found: C, 76.92; H, 8.79.

4.2.2. Ketone 34. Mp 236–238 °C; ^{1}H NMR (500 MHz): δ=8.25 (s, 1H), 7.26 (s, 1H), 7.24 (s, 1H), 4.11 (app. d, J=13.9 Hz, 1H), 3.41 (br s, 1H), 3.33 (app. t, J=13.0 Hz, 1H), 2.77 (dd, J=5.0, 17.8 Hz, 1H), 2.64 (app. t, J=13.6, 1H), 2.28 (app. d, J=17.8 Hz, 1H), 2.04 (app. d, J=15.4 Hz, 1H), 1.35 (s, 9H), 1.31 (s, 9H); ^{13}C NMR (125 MHz): δ=208.2, 176.0, 158.1, 145.4, 141.3, 125.5, 125.1, 125.0, 67.5, 56.8, 36.6, 35.2, 34.7, 32.4, 31.6, 30.7; IR (KBr, cm^{-1}): 2955, 1701, 1637, 1477, 1112, 836, 737, 747; EIMS (*m*/*z*): 312 (M^+), 297 (100%).

4.3. Thermal cyclization of 3-butenyloxy-4,6-di-*tert*-butylethynylbenzene (31)

Cyclization followed the general procedure utilizing **31** (200 mg, 0.70 mmol), toluene (5 mL), and $Co_2(CO)_8$ (270 mg, 0.78 mmol), and refluxed to afford the epoxide **35** (40 mg, 17%) and Michael product **36** (30 mg, 13%) as a colorless solid after purification by flash chromatography (hexane/EtOAc, 87:13).

4.3.1. 4′6′-Di-*tert*-butyl-14-hydroxy-8-oxa-tricyclo-[9.2.1.0]-tetradeca-2,4,6-triene-13-one (36). Mp 192–194 °C;

^{1}H NMR (500 MHz): δ=7.23 (d, J=2.3 Hz, 1H), 7.07 (d, J=2.3 Hz, 1H), 4.18 (d, J=11.9 Hz, 1H), 3.51 (t, J=10.5 Hz, 1H), 3.27 (s, 1H), 3.06 (dd, J=8.7, 18.3 Hz, 1H), 2.66 (s, 1H), 1.31 (s, 9H), 1.33 (s, 9H), 1.72 (d, J=14.7 Hz, 1H), 1.96 (s, 1H), 2.38 (m, 1H), 2.16 (d, J=18.3 Hz, 1H); ^{13}C NMR (125 MHz): δ=219.2, 145.5, 142.0, 129.0, 123.4, 71.1, 63.0, 43.0, 41.2, 35.5, 35.2, 34.5, 31.6, 31.2; IR (Neat, cm^{-1}): 3396, 2957, 1734; ESI-MS: 353 [M+Na]$^+$, 365. Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.17; H, 9.31.

4.4. Oxidative cyclization of 3-butenyloxy-4,6-di-*tert*-butylethynylbenzene (31) under oxygen atmosphere

The enyne **31** (300 mg, 1.06 mmol) was dissolved in CH_2Cl_2 (10 mL) and $Co_2(CO)_8$ (400 mg, 1.16 mmol) was added under N_2 and stirred for 2 h. The reaction mixture was then purged with O_2 and then NMO (1.24 g, 10.6 mmol) was added in three portions at 0 °C and the reaction was left to stir to room temperature under an oxygen atmosphere. The reaction was worked up as indicated in the general procedure. The crude product was purified by flash chromatography (hexane/EtOAc, 90:10) to afford only the epoxide **35** (220 mg, 63%).

4.4.1. 4′6′-Di-*tert*-butyl-8-oxa-tricyclo[10.2.1.0]pentadeca-1(14),2,4,6-tetraene-14-one (37). Cyclization employing the oxidative method utilizing the enyne **33** (121 mg, 0.41 mmol), CH_2Cl_2 (20 mL), $Co_2(CO)_8$ (278 mg, 0.81 mmol), and NMO (569 mg, 4.86 mmol) or the thermal method, utilizing the enyne (130 mg, 0.44 mmol) in toluene (10 mL) and $Co_2(CO)_8$ (164 mg, 0.48 mmol), and then heated at 70 °C provided **37** in 41 mg, 31% and 120 mg, 86%, respectively, as a colorless solid after flash chromatography (hexane/EtOAc, 90:10). Mp 191–192 °C; ^{1}H NMR (300 MHz): δ=7.28 (d, J=2.5 Hz, 1H), 7.52 (s, 1H), 7.07 (d, J=2.5 Hz, 1H), 4.37 (app. t, J=10.3 Hz, 1H), 3.34–3.35 (m, 1H), 3.20–3.22 (m, 1H), 2.67 (dd, J=5.8, 18.0 Hz, 1H), 2.27 (app. d, J=18.0 Hz, 1H), 1.93–2.04 (m, 1H), 1.80–1.89 (m, 1H), 1.42–1.47 (m, 1H), 1.34 (s, 9H), 1.30 (s, 9H); ^{13}C NMR (75 MHz): δ=208.5, 166.5, 153.3, 145.3, 141.5, 141.1, 127.8, 123.9, 123.6, 76.3, 40.5, 39.3, 35.0, 34.6, 33.7, 31.6, 31.2, 25.6; IR (KBr, cm^{-1}): 2956, 1706, 1594, 1441, 1110, 750; HRMS: calcd for $C_{22}H_{30}O_2Na$ (m/z) 349.2138, found 349.2159.

4.5. Thermal cyclization of 30

Cyclization followed the general procedure utilizing **30** (0.20 g, 0.56 mmol), toluene (10 mL), and $Co_2(CO)_8$ (0.21 g, 0.62 mmol), and refluxed under N_2 to afford the expected PK product **48** (30 mg, 14%) and the diene **49** (150 mg, 75%) as a yellow solid after flash chromatography (hexane/EtOAc, 87:13). When the above reaction was carried out under CO (1 atm, balloon) afforded **48** (47 mg, 22%).

4.5.1. 7,9-Di-*tert*-butyl-1-trimethylsilyl-4,4a-dihydro-3*H*,5*H*-6-oxabenzo[*f*]azulen-2-one (48). ^{1}H NMR (300 MHz): δ=7.33 (d, J=3.0 Hz, 1H), 6.90 (d, J=2.4 Hz, 1H), 4.37 (dt, J=9.0, 3.3 Hz, 1H), 3.76 (dt, J=11.4, 1.2 Hz, 1H), 2.98 (quin, J=5.1 Hz, 1H), 2.70 (dd, J=18.6, 6.6 Hz, 1H), 2.18 (m, 1H), 2.12 (dd, J=18.6, 1.8 Hz, 1H), 1.76 (qd, J=10.2, 3.0 Hz, 1H), 1.39 (s, 9H), 1.30 (s, 9H), −0.03 (s, 9H); ^{13}C NMR (75 MHz): δ=212.5, 189.4, 154.6, 144.7, 141.5, 132.6, 125.5, 125.2, 125.2, 72.7, 43.8, 43.7, 35.2, 31.6, 34.7, 31.6, 30.4, −0.7; IR (neat, cm^{-1}): 2954, 1692, 1587, 1560, 1432, 1360, 1248, 1224, 1123, 1068, 1025, 936; HRMS: calcd for $C_{24}H_{36}O_2SiNa$ (M+Na)$^+$ 407.2377, found 407.2397.

4.5.2. (7,6-Di-*tert*-butyl-4-methylene-3,4-dihydro-2*H*-benzo[*b*]oxepin-5-ylidenemethyl)trimethylsilane (49). Mp 105–107 °C. ^{1}H NMR (500 MHz): δ=7.23 (d, J=1.8 Hz, 1H), 7.19 (d, J=1.8 Hz, 1H), 5.77 (s, 1H), 4.94 (d, J=6.4 Hz, 2H), 4.16 (t, J=5.1 Hz, 2H), 2.76 (t, J=5.1 Hz, 2H), 1.37 (s, 9H), 1.32 (s, 9H), 0.50 (s, 9H); ^{13}C NMR (125 MHz): δ=159.1, 153.5, 148.9, 144.4, 139.7, 134.9, 130.5, 123.5, 123.4, 111.8, 70.4, 39.8, 35.3, 34.6, 31.7, 30.6, 0.6; IR (neat, cm^{-1}): 2955, 1639, 1571, 1468, 1433, 1361, 1245, 1166; HRMS: calcd for $C_{23}H_{36}OSi$ 356.2530, found 356.2533.

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