

etrahedron. Author manuscript; available in PMC 2009 January 28.

Published in final edited form as:

Tetrahedron. 2008 January 28; 64(5): 915-925.

A benzannulation strategy for the synthesis of phenols and heteroaromatic compounds based on the reaction of (trialkylsilyl) vinylketenes with lithium ynolates

Wesley F. Austin, Yongjun Zhang, and Rick L. Danheiser*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA

Abstract

(Trialkylsilyl)vinylketenes react with lithium ynolates to generate 3-(oxido)dienylketenes which undergo rapid 6π -electrocyclization. The ultimate products of this benzannulation are highly substituted resorcinol monosilyl ethers which are formed via a [1,3] carbon to oxygen silyl group shift. Further transformations of the benzannulation products are described providing efficient access to *ortho*-benzoquinones and benzofuran, benzoxepine, and benzoxocine ring systems.

Keywords

(Trialkylsilyl)vinylketenes; Benzannulation; Ynolates; Electrocyclic ring closure

1. Introduction

The development of efficient strategies for the synthesis of highly substituted aromatic systems is a problem of considerable importance in organic chemistry. Classically, syntheses of highly substituted benzenoid compounds have most often been achieved by employing *linear substitution strategies* involving sequential electrophilic substitution and metalation-alkylation reactions. Frequently, however, a more effective approach involves the application of *benzannulation methods*: convergent strategies in which the aromatic ring system is assembled from two or more precursors in a single step, with all (or most) substituents in place. Benzannulation strategies enjoy significant advantages over conventional linear substitution strategies, especially when applied to the preparation of highly substituted target molecules. For example, benzannulation routes generally avoid the regiochemical ambiguities associated with aromatic substitution reactions, and their intrinsic convergent character facilitates the efficient assembly of highly substituted aromatic compounds that would require long, multistep routes using classical substitution methodology.

In this paper we report full details of our studies of a benzannulation strategy based on the reaction of lithium ynolates with (trialkylsilyl)vinylketenes ("TAS-vinylketenes"). 1 The utility of vinylketenes 2 in organic synthesis is well-established. Research in our laboratory has shown that [2+2] cycloadditions of vinylketenes can serve as triggering steps in powerful "pericyclic cascade" strategies for the synthesis of six- and eight-membered carbocyclic compounds. 3,4

^{*} Corresponding author. Tel.: 617 253 1842; fax: 617 252 1504; email: danheisr@mit.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

In related studies, we have demonstrated that (trialkylsilyl)vinylketenes are remarkably stable ketenes which exhibit reactivity complementary to other vinylketenes in many useful synthetic transformations. Silyl substitutents 5 suppress the tendency of vinylketenes to undergo dimerization and [2+2] cycloaddition, allowing them to express their underlying reactivity as electron-rich conjugated dienes in Diels-Alder reactions 6 and as reactive carbonyl compounds in [4+1] annulations leading to five-membered rings. 7,8 Herein we report the reaction of TAS-vinylketenes with lithium ynolates in a benzannulation process that provides access to highly substituted phenols and several classes of oxygen heteroaromatic compounds (Scheme 1).

2. Results and discussion

2.1 Synthesis of benzannulation reaction partners

Both reaction partners employed in the new benzannulation strategy are readily available via known chemistry. TAS-vinylketenes are conveniently prepared in two steps from α' -diazo- α,β -enones (5), which are themselves readily available from methyl ketones using the detrifluoroacetylative diazo transfer protocol developed in our laboratory. As outlined in Scheme 2, silylation of diazo ketones 5 furnish α' -silyl- α' -diazo- α,β -unsaturated ketones of type 6, which undergo photochemical Wolff rearrangement upon irradiation to provide the desired TAS-vinylketenes (7). As expected, these ketenes are remarkably stable substances as compared to other vinylketenes. Triisopropyl derivatives such as 7 are recovered unchanged after heating for several days at 80 °C, and these ketenes can be purified by conventional silica gel chromatography without detectable decomposition.

"Ynolate anions" serve as intermediates in a number of useful synthetic transformations, and several reliable methods have been developed for their preparation. ¹¹ For the generation of the lithium ynolates employed in our benzannulation studies, we focused our attention on the cleavage of siloxy alkynes ("silyl ynol ethers") with methyllithium. This method, first described by Kowalski, ¹² is a variant of the well known strategy for the regiospecific generation of enolates introduced by Stork and Hudrlik. ¹³ For our purposes, this process offered the attraction that it takes place under mild conditions and produces only inert tetraalkylsilanes as byproducts. As shown in Scheme 3, the siloxy alkyne ynolate precursors can be conveniently prepared in one step either from esters via the Kowalski reaction ¹² (10a–d), or from readily available alkynes by the method of Julia ¹⁴ (10e–k, 11). As noted previously, TIPS ynol ethers can be purified by distillation or careful chromatography, and can be stored in solution at 0 °C for extended periods with minimal decomposition.

2.2. Benzannulation studies

At the outset of our studies, the feasibility of the proposed benzannulation was far from certain. As outlined in Scheme 4, we envisaged that the reaction of lithium ynolates with TAS-vinylketenes would lead initially to dienylketene intermediates of type 12. Importantly, we expected that addition would occur anti to the bulky trialkylsilyl group, thus resulting in the stereoselective formation of the indicated (Z)-enolate. At this point several modes of ring closure are conceivable (in addition to intermolecular processes leading to dimeric and oligomeric products). For example, the addition of ynolates to aldehydes and ketones is well known and leads to the formation of β -lactone enolates, 11 and an analogous reaction in this case would give rise to products of type 14. An alternative mode of ring closure would generate the four-membered carbocycle 15, an enolate derivative of a substituted 1,3-cyclobutanedione. Our expectation, however, was that intermediate 12 would most likely undergo facile 6π electrocyclic ring closure 15,16 to afford the desired cyclohexadienone 13. Favoring this mode of cyclization is the (Z)-enolate geometry of 12, which enforces close proximity between the C-1 and C-6 carbon atoms at which bond formation is desired to occur. Also important is the

significant increase in charge stabilization that should develop in the transition state leading to the 1,3-dicarbonyl enolate system in 13. It was our expectation that these factors would suffice to favor the desired mode of ring closure over alternative cyclization pathways and intermolecular condensation reactions. The possibility that the cyclohexadiene intermediate 13 might form via a concerted [4+2] cycloaddition of the ynolate to the ketene cannot be excluded; however, previous research in our laboratory has demonstrated that TAS-vinylketenes behave as electron-rich dienes in Diels-Alder cycloadditions and generally require *electron-deficient* dienophiles for successful reaction. Consistent with this is the observation that no reaction was observed to take place upon heating a solution of TAS-vinylketene 7a with siloxy alkyne 10f in toluene at reflux for 8 h.

The initial investigation of the feasibility of the benzannulation was conducted using TAS-vinylketene **7a** and the lithium ynolate derived from siloxy alkyne **10f**. Cleavage of the silyl ether took place smoothly upon exposure of the siloxy alkyne to 1 equiv of methyllithium in THF at room temperature, with TLC analysis indicating complete consumption of the silyl ynol ether within 3.5 h. Addition of ketene **7a** then resulted in a gold-colored mixture, and TLC analysis showed the formation of a single new aromatic product which was obtained in 62% yield following purification by silica gel chromatography. Interestingly, however, ¹H NMR data for this compound was not consistent with that expected for the resorcinol derivative with a hexasubstituted benzene ring that would result from protonation of a benzannulation product of type **16**. In particular, two downfield singlets were observed at 6.19 and 4.71ppm, with only the latter exhibiting exchange with D₂O. Further analysis suggested that a migration of the trialkylsilyl group from carbon to oxygen had taken place, and the benzannulation product was in fact the silyl ether **26** (Table 1, entry 1). Additional support for this structure was obtained by NOE studies of the related annulation product **31** (Figure 1), which allowed unequivocal assignment of the regiochemistry as that shown.

Evidence that the silyl ether benzannulation products are formed via an *intramolecular* silyl shift was obtained by the crossover experiment summarized in Scheme 5. Thus, reaction of a 1:1 mixture of TAS-vinylketenes **7b** and **17** with 1 equiv of ynolate **18** led to the formation of two phenolic products assigned by NMR and GC-MS analysis as **19** and **20**. Neither of the phenols **21** and **22** that would result from intermolecular silyl group transfer could be detected in the crude product of the reaction.

As outlined in Scheme 6, we propose that the observed silyl group migration takes place via a 1,3 carbon—oxygen shift involving a 6-silyl-2,4-cyclohexadienone intermediate of type 24. 1,3-Silyl shifts in α -silyl ketones to form silyl enol ethers are well known processes, ¹⁷ and related rearrangements involving silylcyclohexadienones have been observed in our laboratory ^{6b} and others. ¹⁸ We speculate that 24 is generated by tautomerization of 23, which is itself derived from the initial electrocyclization product 13 via tautomerization to 16 followed by a series of (reversible) proton transfer steps. The small difference in pK_{a1} and pK_{a2} values for the hydroxyl groups in resorcinol (9.2 and 10.9 in water ¹⁹) suggests that interconversion of the monolithium salts 16 and 23 may proceed via disproportionation to form a mixture of the corresponding resorcinol and its dilithium derivative. Once 23 forms, tautomerization can produce the 6-silyl-2,4-cyclohexadienone 24 which then aromatizes via irreversible 1,3 silyl shift.

Table 1 delineates the scope of the TAS-vinylketene-ynolate benzannulation reaction. Optimal conditions were found to involve the generation of the ynolate using 1 equiv of methyllithium; low yields of benzannulation products were obtained when TBAF, TBAT, or KOEt²⁰ were employed in place of MeLi for the reaction. Addition of the ynolate to TAS-vinylketenes was observed to take place within 30–60 min at room temperature, and the benzannulation products **26–36** were obtained in fair to good yield following aqueous workup and chromatographic

purification. Direct analysis of the reaction mixture prior to workup showed the presence of only silyl ether benzannulation products, suggesting that the silyl shift is not occurring during isolation or purification. As noted above, direct reaction of siloxy alkynes with TAS-vinylketenes did not take place at 25 °C or at elevated temperatures, and attempts to promote benzannulation with Lewis or Brønsted acids (ZnI₂, TiCl₄, AgNTf₂, HNTf₂) were unsuccessful, resulting only in complex mixtures of products.

A wide variety of siloxy alkynes participate in the benzannulation (Table 1). Primary, secondary, and tertiary alkyl substituents on the siloxy alkyne are all well tolerated, and alkenyl and aryl derivatives react albeit in somewhat diminished yield. A low yield of the desired benzannulation product was obtained in the case of the allyl-substituted acetylene 10g, apparently due to competitive metalation at the methylene carbon by MeLi during the ynolate generation step. ²¹ This problem is easily circumvented, however, by substituting the TBDMS ynol ether 11 for the TIPS derivative 10g as the ynolate precursor. Cleavage of this more reactive siloxy alkyne is complete within minutes, and upon reaction with TAS-vinylketene 7b the desired benzannulation product 35 is obtained in good yield. In general, however, the use of triisopropylsiloxy alkynes is preferred due to their increased stability towards purification and storage. With respect to the TAS-vinylketene annulation partner, the only limitation identified to date is that TAS-aryl and TAS-heteroarylketenes do not undergo benzannulation, producing only complex mixtures of unidentifiable products. In these cases the 6π electrocyclic ring closure would require disruption of aromaticity, which may retard the rate of this cyclization step and permit the alternative processes outlined in Scheme 4 to become competitive.

Interesting results were obtained when the t-butyldimethylsilyl-substituted ynolate derived from **10k** was employed in the benzannulation. In this case a 3:2 mixture of two phenols was produced in a combined yield of ca. 40–60%. 22 Spectroscopic analysis identified the minor product as **38** and the major product as either **37a** or the isomeric silyl ether **37b**. Unfortunately, to date we have been unable to ambiguously distinguish between these two structures for the major product. Upon heating in chloroform or benzene, **38** underwent carbon to oxygen 1,3-silyl shift in near quantitative yield to afford **39**, the structure of which was confirmed by desilylation to produce the corresponding resorcinol. 23 , 24 In contrast, **37** was largely unchanged after heating in toluene at reflux for 14 h. We believe that annulation product **38** is generated via the usual mechanism as outlined in Scheme 6 (where $R^1 = t$ -butyldimethylsilyl), while **37a** and **37b** can arise from tautomeric forms of intermediates **16** and **23**, respectively.

2.3. Transformations of Benzannulation Products

The regiocontrolled benzannulation strategy described herein provides access to *ortho*-substituted phenols that can participate in a variety of useful synthetic transformations. Scheme 8 outlines several straightforward functional group manipulations. Desilylation of **26** is readily accomplished with TBAF to afford the expected resorcinol, and oxidation of **26** with Fremy's salt furnishes the *ortho*-quinone **41** in good yield. Of particular synthetic utility are benzannulation products bearing unsaturated *ortho* substituents such as **31**, **32**, **34**, and **35**, which are useful substrates in cyclizations leading to a variety of benzofused oxygen heterocycles. For example, exposure of the *ortho*-allyl phenol **35** to catalytic PdCl₂(MeCN)₂ in the presence of LiCl and benzoquinone provides tetrahydronaphthofuran **42** in good yield (Scheme 9), ²⁶ while the vinyl-substituted benzannulation product **34** can be converted to the tetracyclic benzofuran **43** using the general method of Lattanzi (Scheme 10).

A variety of benzofused oxygen heterocyclic systems are also available from the benzannulation products through the application of ring closing metathesis. Scheme 11 illustrates this strategy as applied to the synthesis of the benzoxocine 46 and benzoxepine 47.

3. Conclusions

We have shown that TAS-vinylketenes react with lithium ynolates in a regiocontrolled benzannulation process that provides efficient access to highly substituted phenols. In conjunction with transition-metal catalyzed cyclization reactions, this strategy can be employed for the synthesis of a variety of benzofused oxygen heterocycles, including benzofurans, benzo[b]oxocines, and benzo[b]oxepines.

4. Experimental

4.1. General

All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at ca. 20 mmHg and then at ca. 0.1 mmHg (vacuum pump) unless otherwise indicated. Thin layer chromatography was performed on Merck precoated glass-backed silica gel 60 F-254 0.25 mm plates. Column chromatography was performed on Silicycle silica gel 60 (230–400 mesh) or Sorbent silica gel 60A (32–63 μ m).

4.2. Materials

Commercial grade reagents and solvents were used without further purification except as indicated below. Triisopropylsilyl trifluoromethanesulfonate, 1,1,1,3,3,3-hexamethyldisilazane, benzene, and diisopropylethylamine were distilled under argon from calcium hydride. Dichloromethane, diethyl ether, and tetrahydrofuran were purified by pressure filtration through activated alumina. Toluene was purified by pressure filtration through activated alumina and copper(II) oxide. Anhydrous *tert*-butyl hydroperoxide in toluene was prepared from the aqueous solution as described by Sharpless. Phethyllithium was obtained from either Aldrich Chemical Co. (1.6 M in Et₂O, 0.05 M halide content) or Alfa Aesar (1–2 M in Et₂O, "low halide"). In some cases decreased yields were observed when aged methyllithium was used in the benzannulation. Methyllithium and *n*-butyllithium were titrated according to the Watson-Eastham method using BHT in THF with 1,10-phenanthroline as an indicator. Previously reported methods were employed for the preparation of TAS-vinylketenes 7a,6b 7b,6b 7c,1 and 7d.1 Several known siloxy alkynes were prepared according to the previously described procedures either using the method of Kowalski (10a,12 10b,31 10c,1 10d,12) or the method of Julia (10e,32 10f,33 10g,1 10h,1 10i,14 10j,34 and 11¹; the preparation of the new siloxy alkyne 10k is described below.

4.3. Instrumentation

Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were measured with a Varian Inova 500 MHz spectrometer or a Varian 300 MHz spectrometer. ^1H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the CHCl₃ peak at 7.27 ppm or the residual benzene peak at 7.16 ppm used as a standard). ^{13}C NMR spectra chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of CDCl₃ at 77.23 ppm or the C_6D_6 peak at 128.06 used as a standard). High resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEX II 3 tesla Fourier transform mass spectrometer or a Bruker Daltonics APEX IV 4.7 tesla Fourier transform ion cyclotron resonance mass spectrometer.

4.4. 2-(tert-Butyldimethylsilyl)-(E)-2-(1-methyl-1-propenyl)ketene (17)

A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with a solution of 1-diazo-3-methyl-3-penten-2-one^{9a} (0.500 g, 4.0 mmol) in 20 mL of 1:1 Et₂O-hexanes and cooled at 0 °C while i-Pr₂EtN (0.71 mL, 0.53 g, 4.1 mmol) was added dropwise over 1 min. After 3 min, t-BuMe₂SiOTf (0.93 mL, 1.1 g, 4.1 mmol) was added dropwise over 1 min, and the resulting solution was allowed to slowly warm to 10 °C over 2.5 h, and then stirred at rt for an additional 30 min. The reaction mixture was filtered through Celite with the aid of 10 mL of hexanes, and the filtrate was concentrated to afford 1.048 g of an orange oil. Column chromatography on 60 g of silica gel (elution with 2% EtOAc-1% Et₃N-hexanes) provided 0.716 g (75%) of 1-(tert-Butyldimethylsilyl)-1-diazo-3-methyl-1-(E)-3-penten-2-one as a yellow oil: IR (neat) 2929, 2858, 2066, 1615 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.13 (qq, J = 6.9, 1.4 Hz, 1 H), 1.81 (app quint, J = 1.1 Hz, 3 H), 1.76 (dq, J = 6.7, 1.1 Hz, 3 H), 0.94 (s, 9 H), 0.23 (s, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 196.4, 136.7, 130.5, 51.6, 26.9, 19.3, 13.9, 13.3, -6.0. A solution of this silylated diazo ketone (0.693 g, 2.91 mmol) in 30 mL of benzene was distributed evenly between two 30-cm quartz tubes fitted with rubber septa. A second rubber septum (inverted) was secured with vinyl tape to each tube to ensure a good seal, and the reaction mixtures were degassed (three freeze-pump-thaw cycles at -196 °C, <0.5 mmHg) and then irradiated with 300 nm light in a Rayonet reactor for 3 h. The resulting solutions were combined and concentrated at reduced pressure to afford 0.513 g of a yellow oil. Column chromatography on 30 g of silica gel (elution with hexanes) provided 0.393 g (64%) of ketene 17 as a yellow oil: IR (neat) 2930, 2859, 2077, 1647 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.22 (qq, J = 7.0, 1.3 Hz, 1 H), 1.80 (app quintet, J = 1.1 Hz, 3 H), 1.62 (dq, J = 6.7, 1.0 Hz, 3 H), 0.93 (s, 9 H), 0.18 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 184.6, 124.1, 120.3, 27.0, 25.3, 19.3, 19.2, 14.2, -4.3.

4.5. 2-tert-Butyldimethylsilyl-1-(triisopropylsiloxy)ethyne (10k)

A 100-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of tert-butyldimethylsilylacetylene (0.86 mL, 0.65 g, 4.6 mmol) in 15 mL of THF and cooled at -78 °C while 5.5 mL of LiHMDS solution (1.0 M in THF, 5.5 mmol)³⁵ was added rapidly dropwise over 30 s. A 50-mL, two-necked, roundbottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of tert-butyl hydroperoxide (4.0 M in toluene, 1.4 mL, 5.6 mmol) in 10 mL of THF and cooled at -78 °C while 6.0 mL of LiHMDS solution (1.0 M in THF, 6.0 mmol) was added rapidly dropwise over 30 s. The resulting solution was transferred into the solution of lithium acetylide via cannula over 3 min, the dry ice-acetone bath was replaced with an ice-water bath, and the reaction mixture was stirred for 2.5 h at 0 °C. The reaction mixture was then recooled to -78 °C, and TIPSOTf (1.6 mL, 1.8 g, 6.0 mmol) was added in one portion. The resulting mixture was stirred for 45 min at -78 °C and then at 0 °C for 45 min. The mixture was recooled to -78 °C, diluted with 50 mL of hexanes, and then poured into a separatory funnel containing 40 mL of satd aqueous NaHCO₃ solution. The aqueous phase was separated and extracted with two 25-mL portions of hexanes, and the combined organic phases were washed with 75 mL of water and 75 mL of satd aqueous NaCl solution, dried over Na₂SO₄, filtered, and concentrated (0.25 mmHg, 2 h) to yield 1.549 g of an orange oil. Bulb-to-bulb distillation (105– 110 °C oven temperature, 0.25 mmHg) provided 0.937 g (65%) of siloxy alkyne 10k as a colorless oil with spectral characteristics identical to those previously reported: ³⁶ IR (neat) 2184 cm^{-1} ; ¹H NMR (300 MHz, CDCl₃) δ 1.20–1.30 (m, 3 H), 1.13 (d, J = 6.8 Hz, 18 H), 0.90 (s, 9 H), 0.03 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 107.9, 27.8, 26.4, 17.5, 17.0, 12.1, -3.6.

4.6. Benzannulation

Experimental procedures and characterization data for benzannulation products **26**, **27**, **30**, **31**, **33**, **34**, and **36** have been reported previously. ¹

4.6.1. General procedure: illustrated with preparation of 2-(3-propenyl)-5,6,7,8tetrahydro-3-(triisopropylsiloxy)-1-naphthol (35)—A 25-mL, two-necked, roundbottomed flask equipped with a rubber septum and argon inlet adapter was charged with siloxyalkyne 10g (0.890 g, 4.53 mmol) and 6 mL of THF. MeLi solution (1.53 M in Et₂O, 3.0 mL, 4.6 mmol) was added dropwise via syringe over 10 s, and the resulting solution was stirred at room temperature for 30 min. A solution of ketene 7b (1.267 g, 4.551 mmol) in 3 mL of THF was added via cannula in one portion (the flask was rinsed with 1 mL of THF), and the resulting solution was stirred for an additional 70 min. The reaction mixture was poured into 20 mL of satd aqueous NH₄Cl solution, the aqueous phase was separated and extracted with two 10-mL portions of Et₂O, and the combined organic phases were washed with 20 mL of water and 20 mL of satd NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 2.034 g of a yellow oil. Column chromatography on 100 g of silica gel (25% benzene-hexanes) provided 0.788 g (48%) of phenol 35 as a yellow oil: IR (neat) 3550, 3077, 2942, 2866, 1618, 1578, 1495, 1426 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.23 (s, 1 H), 6.00 (ddt, J = 17.2, 10.0, 6.2 Hz, 1 H), 5.20 (app dq, J = 17.3, 1.7 Hz, 1 H), 5.12 (app dq, J = 9.9, 1.7 Hz, 1 H), 5.01 (s, 1 H), 3.51 (app dt, J = 6.2, 1.6 Hz, 2 H), 2.67 (t, J = 6.1 Hz, 2 H), 2.58 (t, J = 6.1 Hz, 2 H), 1.71–1.88 (m, 4 H), 1.25–1.39 (m, 3 H), 1.15 (d, 7.2 Hz, 18 H); ¹³C NMR (75 MHz, CDCl₃) $\delta\,153.3,151.9,137.0,136.5,116.3,115.7,112.5,110.8,31.8,29.9,28.6,23.7,22.8,18.3,13.3;$ HRMS-ESI (m/z): [M + Na]⁺ calcd for C₂₂H₃₆O₂Si, 383.2377; found, 383.2380.

- **4.6.2. 5,6-Dimethyl-2-***tert***-butyl-3-**(**triisopropylsiloxy)phenol (28)**—Reaction of siloxy alkyne 10j (0.198 g, 0.778 mmol) with MeLi solution (1.63 M in Et₂O, 0.49 mL, 0.80 mmol) and ketene **7a** (0.200 g, 0.792 mmol) in 5 mL of THF according to the general procedure and purification by column chromatography on 20 g of silica gel (elution with 2% EtOAchexanes) provided 0.180 g of a yellow oil. Further purification on a column of 20 g silica gel (elution with 25% benzene-hexanes) afforded 0.151 g (55%) of phenol **28** as a pale yellow oil: IR (neat) 3622, 2947, 2868, 1610, 1567, 1484 cm^{-1; 1}H NMR (500 MHz, CDCl₃) δ 6.22 (s, 1 H), 5.13 (s, 1 H), 2.17 (s, 3 H), 2.07 (s 3 H), 1.57 (s, 9 H), 1.37 (sept, J = 7.5 Hz, 3 H) 1.15 (d, J = 7.5 Hz, 18 H); ¹³C NMR (75 MHz, CDCl₃) δ 154.2, 153.8, 134.8, 121.5, 115.6, 114.3, 36.7, 32.5, 20.8, 18.6, 13.9, 11.9; HRMS-ESI (m/z): [M + H]⁺ calcd for C₂₁H₃₈O₂Si, 351.2714; found, 351.2719.
- **4.6.3. 5,6-Dimethyl-2-phenyl-3-(triisopropylsiloxy)phenol (29)**—Reaction of siloxy alkyne 10i (0.200 g, 0.729 mmol) with MeLi solution (1.63 M in Et₂O, 0.46 mL, 0.75 mmol) and ketene **7a** (0.1850 g, 0.733 mmol) in 5 mL of THF according to the general procedure and purification by column chromatography on 15 g of silica gel (elution with 20% benzene-hexanes) afforded 0.080 g (30%) of phenol **29** as a pale yellow oil: IR (neat) 3552, 2942, 2867, 1621, 1570, 1463 cm^{-1; 1}H NMR (300 MHz, CDCl₃) δ 7.42–7.49 (m, 2 H), 7.32–7.39 (m, 3 H), 6.36 (s, 1 H), 4.97 (s, 1 H), 2.26 (s, 3 H), 2.15 (s 3 H), 1.01–1.14 (m, 3 H) 0.92 (d, J = 7.5 Hz, 18 H); ¹³C NMR (75 MHz, CDCl₃) δ 151.5, 151.0, 137.4, 134.0, 131.4, 131.4, 129.2, 129.2, 128.0, 117.4, 115.1, 112.4, 20.6, 18.1, 13.0, 11.7; HRMS-ESI (m/z): [M + H]⁺ calcd for C₂₃H₃₄O₂Si, 371.2401; found, 371.2412.
- **4.6.4. 6-Ethyl-5-methyl-2-[(1***E***)-2-phenylethenyl]-3-(triisopropylsiloxy)phenol (32)**—Reaction of siloxy alkyne **10d** (0.226 g, 0.752 mmol) with MeLi solution (1.50 M in Et₂O, 0.50 mL, 0.75 mmol) and ketene **7c** (0.200 g, 0.750 mmol) in 5 mL of THF according to the general procedure and purification by column chromatography on 15 g of silica gel (gradient elution with 25–38% benzene-hexanes) afforded 0.111 g (37%) of phenol **32** as a

pale yellow oil: IR (neat) 3552, 2942, 2867, 1621, 1570, 1463 cm^{-1; 1}H NMR (500 MHz, CDCl₃) δ 7.50 (d, J = 7.7 Hz, 2 H), 7.37 (t, J = 7.7 Hz, 2 H), 7.31 (d, J = 17.1 Hz, 1 H), 7.25–7.29 (m, 1 H), 7.03 (d, J = 17.1, 1 H), 6.28 (s, 1 H), 5.58 (s, 1 H), 2.64 (q, J = 7.5 Hz, 2 H), 2.26 (s, 3 H), 1.29 (sept, J = 7.6 Hz, 3 H) 1.15 (t, J = 7.6 Hz, 3 H), 1.11 (d, J = 7.4 Hz, 18 H); 13 C NMR (75 MHz, CDCl₃) δ 152.0, 151.6, 137.5, 136.4, 131.3, 128.6, 127.4, 126.1, 122.7, 121.5, 113.3, 112.5, 19.5, 19.4, 18.0, 13.7, 12.9; HRMS-EI (m/z): M⁺ calcd for C₂₆H₃₈O₂Si, 410.2636; found, 410.2646.

4.6.5. 5-(tert-Butyldimethylsiloxy)-3,4-dimethyl-2-(triisopropylsilyl)phenol (37a) or 5-(tert-butyldimethylsiloxy)-2,3-dimethyl-4-(triisopropylsilyl)phenol (37b) and 2-(tert-butyldimethylsilyl)-5,6-dimethyl-3-(triisopropylsiloxy)phenol (38)— Reaction of siloxy alkyne 10k (0.250 g, 0.800 mmol) with MeLi solution (1.63 M in Et₂O, 0.50 mL, 0.82 mmol) and ketene **7a** (0.205 g, 0.812 mmol) in 5 mL of THF according to the general procedure provided 0.501 g of orange oil. NMR analysis of this material indicated the presence of two aromatic products 37 and 38 in a ratio of 66:34 and an estimated combined yield of 40-60%. Pure samples of each compound could not be obtained without significant losses due to the presence of impurities with similar chromatographic properties and the fact that both compounds underwent partial decomposition upon attempted purification by chromatography under a variety of conditions. A pure sample of 38 was obtained by the following procedure. Column chromatography on 20 g of silica gel deactivated with acetone and triethylamine (elution with 5% EtOAc-1% Et₃N-hexanes) provided 0.120 g of a yellow oil which was applied to the top of a column of 5 g of acetone-deactivated silica gel and eluted with 0-1% EtOAc-hexanes to yield 0.047 g (14%) of phenol 38 as a white powder, mp 92-95 °C: IR (CH₂Cl₂) 3603, 3053, 2948, 2948, 2868, 1601, 1469 cm-1; 1H NMR (500 MHz, CDCl₃) δ 6.25 (s, 1 H), 4.96 (s, 1 H), 2.21 (s, 3 H), 2.06 (s, 3 H), 1.42 (sept, J = 7.6 Hz, 3 H), 1.15 (d, J = 7.6 Hz, 18 H), 0.95 (s, 9 H), 0.40 (s, 6 H); 13 C NMR (75 MHz, CDCl₃) δ 160.3, 160.1, 139.5, 113.7, 112.6, 108.5, 27.5, 20.9, 18.8, 18.6, 14.0, 11.5, -0.9; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{44}O_2Si_2$, 409.2953; found, 409.2957. A pure sample of **37** could not be obtained, but a sample of sufficient purity for identification of NMR characteristics was obtained by the following procedure. The crude product of another run of the benzannulation was first partially purified by column chromatography on 20 g of silica gel deactivated with acetone and triethylamine (elution with 5% EtOAc-1% Et₃N-hexanes) to afford 0.133 g of a red oil. This material was dissolved in 10 mL of Et₂O, washed with five 5-mL portions of satd aqueous NH₄Cl solution, dried over MgSO₄, filtered, and concentrated to afford 0.069 g of a sample of the major benzannulation product assigned as either 37a or 37b (ca. 80% purity) as a yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 6.20 (s, 1 H), 4.87–5.00 (br s, 1 H), 2.31 (s, 3 H), 2.08 (s, 3 H), 1.66 (sept, J = 7.5 Hz, 3 H), 1.09 (d, J = 7.5 Hz), 1.00 (s, 9 H), 0.27 (s, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 160.1, 154.8, 146.8, 117.7, 115.7, 104.3, 27.6, 23.1, 20.4, 19.3, 14.5, 12.1, -2.7.

4.6.6. 4,5-Dimethyl-3-*tert***-butyldimethylsiloxy-1-triisopropylsiloxy-benzene (39)** —A 5-mm NMR tube was charged with a solution of phenol **38** (0.026 g, 0.064 mmol) in 0.70 mL of CDCl₃. The reaction mixture was heated at reflux for 3.5 h then allowed to cool and concentrated to yield 0.025 g (96%) of **39** as a pale yellow oil: IR (neat) 2945, 2866, 1603, 1473, 1333 cm^{-1; 1}H NMR (CDCl₃, 500 MHz) δ 6.35 (d, J = 2.4, 1 H), 6.22 (d, J = 2.4, 1 H), 2.18 (s, 3 H), 2.04 (s, 3 H), 1.22 (m, 3 H), 1.10 (d, J = 7.3, 18 H), 1.01 (s, 9 H), 0.19 (s, 6 H); ¹³C NMR δ 154.6, 154.3, 139.0, 120.5, 115.3, 108.9, 26.5, 21.2, 19.0, 18.7, 13.4, 12.6, -3.6; HRMS-ESI (m/z): [M + H]⁺ calcd for C₂₃H₄₄O₂Si₂, 409.2953; found, 409.2959.

4.7.1. 2-Butyl-5,6-dimethylresorcinol (40)—A 10-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of phenol **26** (0.200 g, 0.570 mmol) in 2 mL of THF and stirred at 0 °C while TBAF solution (1.0

M in THF, 0.85 mL, 0.85 mmol) was added. The reaction mixture was allowed to slowly warm to rt over 2.5 h, and then partitioned between 5 mL Et₂O and 5 mL water. The aqueous phase was extracted with 5 mL of Et₂O, and the combined organic phases were washed with 5 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to yield 0.303 g of an orange-brown oil. Column chromatography on 15 g of silica gel (elution with 10% EtOAchexanes) afforded 0.086 g (77%) of the resorcinol **40** as a white powder, mp 126–129 °C: IR (neat) 3426, 3054, 2987, 1631, 1422 cm^{-1; 1}H NMR (300 MHz, CDCl₃) δ 6.25 (s, 1 H), 4.67 (s, 1 H), 4.43 (s, 1 H), 2.59 (t, J = 7.6 Hz, 2 H), 2.19 (s, 3 H), 2.08 (s, 3 H), 1.33–1.57 (m, 4 H), 0.93 (t, J = 7.2 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 152.6, 151.8, 135.5, 114.2, 112.5, 109.3, 31.8, 23.5, 23.1, 20.3, 14.3, 11.6; HRMS-ESI (m/z): [M + H]⁺ calcd for C₁₂H₁₈O₂, 195.1385; found, 195.1386.

4.7.2. 3-Butyl-4-hydroxy-5,6-dimethyl-ortho-quinone (41)—A 100-mL, two-necked, round-bottomed flask equipped with a rubber septum and 50-mL addition funnel fitted with an argon inlet adapter was charged with a solution of phenol 26 (0.187 g, 0.533 mmol) in 30 mL of acetone and stirred at rt while a solution of Na₂HPO₄ (0.56 g, 3.9 mmol) and potassium nitrosodisulfonate (0.575 g, 2.1 mmol) in 20 mL of water was added dropwise over 3 min. The resulting solution was stirred at rt for 24 h and then extracted with three 30-mL portions of EtOAc. The combined organic phases were dried over MgSO₄, filtered, and concentrated to afford 0.163 g of an orange oil. This material was diluted with hexanes and concentrated onto 0.450 g of silica gel which was transferred to the top of a column of 15 g silica gel. Elution with 0-10% EtOAc-hexanes provided 0.146 of an orange oil. Further concentration (0.2-0.3 torr, rt, 1 h) followed by column chromatography on 10 g of silica gel (elution with 5% EtOAchexanes) yielded 0.073 g (66%) of quinone 41 as fluorescent orange needles, mp 63–68 °C: IR (KBr) 3392, 2956, 2928, 2859, 1650, 1633, 1620, 1365; ¹H NMR (300 MHz, CDCl₃) δ 6.94 (s, 1 H), 2.39-2.46 (m, 2 H), 2.04 (t, J = 1.1 Hz, 3 H), 2.03 (t, J = 1.1 Hz, 3 H), 1.26-1.49(m, 4 H), 0.90 (t, J = 7.1 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 187.6, 184.0, 150.8, 143.8, 136.3, 121.8, 30.7, 23.01, 22.95, 14.1, 13.1, 11.8; HRMS-ESI (m/z): $[M + H]^+$ calcd for C₁₂H₁₆O₃, 209.1172; found, 209.1171.

4.7.3. 5-Triisopropylsiloxy-1,2,3,4,7,8,9,10-octahydrobenzo[d]naphtho[1,2-b] furan (43)—A 10-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with a solution of phenol 34 (0.125 g, 0.311 mmol) in 2 mL of CH₂Cl₂ and VO(acac)₂ (0.006 g, 0.02 mmol). The mixture was stirred for 5 min, and then anhydrous TBHP solution (4.0 M in toluene, 0.100 mL, 0.400 mmol) was added. The rubber septum was replaced with a cold finger reflux condenser and the mixture was heated at reflux for 4.5 h. Additional VO(acac)₂ (0.006 g, 0.02 mmol) and TBHP solution (4.0 M in toluene, 0.100 mL, 0.400 mmol) were added, and heating was continued for 2 h. TFA (0.060 mL, 92 mg, 0.81 mmol) was next added and the reaction mixture was heated at reflux for an additional 21 h and then allowed to cool to rt. Concentration afforded 0.260 g of a viscous blue-green oil which was diluted with CH₂Cl₂ and concentrated onto 0.600 g of silica gel which was transferred to the top of a column of 20 g of silica gel and eluted with 5% benzene-hexanes to provide 0.068 g (55%) of **43** as a yellow oil: IR (neat) 2940, 1618, 1592, 1507, 1463, 1448 cm⁻¹ ¹H NMR (300 MHz, CDCl₃) δ 6.30 (s, 1 H), 2.80–2.87 (m, 4 H), 2.74–2.78 (m, 2 H), 2.68–2.72 (m, 2 H), 1.77–1.92 (m, 8 H), 1.34 (sept, J = 7.8 Hz, 3 H), 1.14 (d, J = 7.5 Hz, 18 H); ¹³C NMR (75) MHz, CDCl₃) δ 154.9, 151.9, 148.1, 132.8, 118.2, 114.1, 113.2, 112.2, 30.2, 24.2 (2 C), 23.8, 23.54, 23.48, 23.2, 23.1, 18.9, 14.0; HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{25}H_{38}O_2Si$, 399.2714; found, 399.2716.

4.8. Allylation of phenolic benzannulation products

4.8.1. General procedure: 2-propenyl 2-(2-Propenyl)-3-triisopropylsiloxy-5,6,7,8-tetrahydronaphthyl ether (45)—A 10-mL round-bottomed

flask equipped with a rubber septum and argon inlet needle was charged with K₂CO₃ (0.100 g, 0.723 mmol) and NaI (0.021 g, 0.14 mmol) and flame dried under vacuum. The flask was back-filled with argon, allowed to cool to rt, and a solution of naphthol 35 (0.083 g, 0.23 mol) in 2 mL of acetone was added. Allyl bromide (0.100 mL, 0.140 g, 1.16 mmol) was added, the septum was replaced with a cold finger condenser, and the reaction mixture was heated at reflux for 18 h. Additional allyl bromide (0.100 mL, 0.140 g, 1.16 mmol) was then added, and heating was continued for an additional 18 h. The resulting mixture was allowed to cool to rt and partitioned between 5 mL of Et₂O and 5 mL of water. The aqueous phase was extracted with two 5-mL portions of Et₂O, and the combined organic phases were dried over MgSO₄, filtered, and concentrated to yield 0.171 g of a yellow oil which was diluted with hexanes and concentrated onto 0.300 g of silica gel which was transferred to the top of a column of 10 g of silica gel. Elution with 5–10% benzene-hexanes furnished 0.068 g (74%) of allyl ether 45 as a yellow oil: IR (neat) 3078, 2942, 2867, 1637, 1605, 1573, 1477, 1425 cm^{-1; 1}H NMR (300 MHz, CDCl₃) δ 6.35 (s, 1 H), 6.11 (ddt, J = 17.1, 10.5, 5.3, 1 H) 6.00 (ddt, J = 17.1, 10.0, 6.0, 1 H), 5.43 (app dq, J = 17.2, 1.7 Hz, 1 H), 5.24 (app dq, J = 10.5, 1.5 Hz, 1 H), 4.99 (app dq, J = 17.1, 1.8 Hz, 1 H), 4.94 (app dq, J = 10.1, 1.7 Hz, 1 H), 4.38 (dt, J = 5.3, 1.6 Hz, 2 H), 3.41 (dt, J = 6.0, 1.6 Hz, 2 H), 2.64-2.71 (m, 4 H), 1.72-1.78 (m, 4 H), 1.24-1.36 (m, 3 H), 1.11 $(d, J = 7.1 \text{ Hz}, 18 \text{ H}); ^{13}\text{C NMR} (75 \text{ MHz}, \text{CDCl}_3) \delta 156.3, 152.6, 137.9, 136.4, 134.6, 130.3,$ 123.1, 121.1, 116.8, 114.4, 73.4, 29.8, 29.2, 23.7, 23.4, 23.3, 18.4, 13.3; HRMS-ESI (m/z): [M +H]⁺ calcd for C₂₅H₄₀O₂Si, 401.2870; found, 401.2861.

4.8.2. 2-Propenyl 2-(3-butenyl)-6-ethyl-5-methyl-3-triisopropylsiloxy-phenyl ether (44)—Reaction of phenol **31** (0.083 g, 0.23 mol) with K₂CO₃ (0.100 g, 0.723 mmol), NaI (0.021 g, 0.14 mmol), and allyl bromide (0.200 mL total, 0.280 g, 2.32 mmol) in 2 mL of acetone according to the general procedure and purification by column chromatography on 10 g of silica gel (elution with 0–10% benzene-hexanes) provided 0.060 g (65%) of allyl ether **44** as a yellow oil: IR (neat) 3077, 2945, 2867, 1640, 1603, 1569, 1479 cm^{-1; 1}H NMR (300 MHz, CDCl₃) δ 6.41 (s, 1 H), 6.11 (ddt, J = 17.2, 10.4, 5.2, 1 H) 5.91 (ddt, J = 17.1, 10.2, 6.6, 1 H), 5.46 (app dq, J = 17.1, 1.7 Hz, 1 H), 5.26 (app dq, J = 10.4, 1.5 Hz, 1 H), 5.04 (app dq, J = 17.1, 1.7 Hz, 1 H), 4.96 (dm, J = 10.1 Hz, 1 H), 4.30 (dt, J = 5.2, 1.6 Hz, 2 H), 2.63–2.71 (m, 2 H), 2.58 (q, J = 7.5, 2 H), 2.25–2.34 (m, 2 H), 2.23 (s, 3 H), 1.22–1.36 (m, 3 H), 1.08–1.14 (m, 21 H); ¹³C NMR (75 MHz, CDCl₃) δ 156.6, 152.7, 139.4, 134.8, 134.6, 128.5, 123.3, 116.7, 116.4, 114.3, 75.3, 34.4, 24.9, 20.1, 19.6, 18.4, 15.0, 13.4; HRMS-ESI (m/z): [M + H]⁺ calcd for C₂₅H₄₂O₂Si, 403.3027; found, 403.3017.

4.9. Ring closing metathesis

4.9.1. General procedure: 6-triisopropylsiloxy-2,5,8,9,10,11-hexahydronaphtho [1,2-b]oxepine (47)—A 50-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with the ruthenium metathesis catalyst **48** (0.006 g, 0.007 mmol), 20 mL of CH₂Cl₂, and a solution of allyl ether **45** (0.056 g, 0.14 mmol) in 10 mL of CH₂Cl₂. The septum was replaced with a cold finger condenser fitted with an argon inlet and the reaction mixture was heated at reflux for 1 h and then allowed to cool to rt and concentrated to yield 0.080 g of a brown oil. Column chromatography on 5 g of silica gel (elution with 1% EtOAc-hexanes) afforded 0.050 g (96%) of **47** as a yellow oil: IR (neat) 2944, 2867, 1609, 1572, 1481 cm^{-1; 1}H NMR (300 MHz, CDCl₃) δ 6.34 (s, 1 H), 5.77–5.88 (m, 1 H), 5.40 (dm, J = 11.3, 1 H), 4.52 (app quint, J = 2.4, 2 H), 3.51 (dd, J = 5.3, 2.0 Hz, 2 H), 2.62–2.69 (m, 4 H), 1.70–1.80 (m, 4 H), 1.21–1.34 (m, 3 H), 1.11 (d, J = 7.0 Hz, 18 H), ¹³C NMR (75 MHz, CDCl₃) δ 157.3, 150.4, 136.2, 127.7, 126.6, 124.5, 122.4, 114.9, 69.9, 29.8, 23.4, 23.3, 23.2, 23.1, 18.3, 13.3; HRMS-ESI (m/z): [M + H]⁺ calcd for C₂₃H₃₆O₂Si, 373.2557; found, 373.2567.

4.9.2. 10-Ethyl-9-methyl-3-triisopropylsiloxy-5,6-dihydro-2H-benzo[*b***]oxocine (46)**—Reaction of allyl ether **44** (0.044 g, 0.11 mmol) with ruthenium catalyst **48** (0.005 g, 0.006 mmol) in 25 mL of CH_2Cl_2 according to the general procedure and purification by column chromatography on 5 g of silica gel (elution with 1% EtOAc-hexanes) afforded 0.039 g (95%) of **46** as a yellow oil: IR (neat) 2944, 2867, 1603, 1569, 1465 cm^{-1; 1}H NMR (300 MHz, $CDCl_3$) δ 6.41 (s, 1 H), 5.81 (dtt, J = 11.4, 6.7, 1.5 Hz, 1 H), 5.40 (dtt, J = 11.3, 4.5, 1.2 Hz, 1 H), 4.68 (dd, J = 4.6, 1.3, 2 H), 2.97 (d, J = 6.3 Hz, 1 H), 2.94 (d, J = 4.8 Hz, 1 H), 2.60–2.69 (m, 2 H), 2.59 (q, J = 7.5 Hz, 2 H), 2.23 (s, 3 H), 1.21–1.35 (m, 3 H), 1.11 (d, J = 7.0 Hz, 18 H), 1.12 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 152.0, 134.7, 133.5, 128.2, 125.3, 122.4, 116.0, 71.9, 28.0, 25.7, 19.9, 19.6, 18.4, 14.9, 13.3; HRMS-ESI (m/z): [M + H]⁺ calcd for $C_{23}H_{38}O_2Si$, 375.2714; found, 375.2713.

Acknowledgements

We thank the National Institutes of Health (GM 28273), Merck Research Laboratories, and Boehringer Ingelheim Pharmaceuticals for generous financial support. Y. Z. was supported by a Po Ting Ip Postdoctoral Fellowship and W. F. A. was supported in part by a fellowship from the Kenneth M. Gordon Fund.

References and notes

- Preminary communication: Austin WF, Zhang Y, Danheiser RL. Org Lett 2005;7:3905. [PubMed: 16119928]
- Reviewed in (a)DanheiserRLDudleyGBAustinWFDanheiserRLScience of SynthesisThiemeStuttgart200623493568(b)TidwellTTKetenes2John Wiley and SonsHoboken, NJ2006
- (a) Danheiser RL, Martinez-Davila C, Sard H. Tetrahedron 1981;37:3943.
 (b) Danheiser RL, Gee SK, Sard H. J Am Chem Soc 1982;104:7670.
 (c) Danheiser RL, Gee SK. J Org Chem 1984;49:1672.
 (d) Danheiser RL, Brisbois RG, Kowalczyk JJ, Miller RF. J Am Chem Soc 1990;112:3093.
- For applications in the total synthesis of natural products, see Dudley GB, Takaki KS, Cha DD, Danheiser RL. Org Lett 2000;2:3407. [PubMed: 11029223] and references cited therein.
- For reviews of the chemistry of silylketenes, see: (a)GeorgeDMDanheiserRLDanheiserRLScience of SynthesisThiemeStuttgart, Germany2006235399(b)PonsJ-MKocienskiPJFlemingIScience of SynthesisThiemeStuttgart, Germany20014657668
- (a) Danheiser RL, Sard H. J Org Chem 1980;45:4810.
 (b) Loebach JL, Bennett DM, Danheiser RL. J Org Chem 1998;63:8380.
 (c) Bennett DM, Okamoto I, Danheiser RL. Org Lett 1999;1:641. [PubMed: 10823193]
- 7. (a) Loebach JL, Bennett DM, Danheiser RL. J Am Chem Soc 1998;120:9690. (b) Dalton AM, Zhang Y, Davie CP, Danheiser RL. Org Lett 2002;4:2465. [PubMed: 12123352] (c) Rigby JH, Wang Z. Org Lett 2003;5:263. [PubMed: 12556167] (d) Davie CP, Danheiser RL. Angew Chem, Int Ed 2005;44:5867. (e) Moser WH, Feltes LA, Sun L, Giese MW, Farrell RW. J Org Chem 2006;71:6542. [PubMed: 16901142]
- For related reactions involving silylated bisketenes, see: (a) Colomvakos JD, Egle I, Ma J, Pole DL, Tidwell TT, Warkentin J. J Org Chem 1996;61:9522. (b) Huang W, Tidwell TT. Synthesis 2000:457.
 (c) Allen AD, Huang WW, Moore PA, Far AR, Tidwell TT. J Org Chem 2000;65:5676. [PubMed: 10970310]
- (a) Danheiser RL, Miller RF, Brisbois RG, Park SZ. J Org Chem 1990;55:1959. Danheiser, RL.; Miller, RF.; Brisbois, RG. Organic Syntheses. Collect Vol IX. Wiley; New York: 1998. p. 197
- 10. (a) Maas G, Brückmann R. J Org Chem 1985;50:2801. (b) Brückmann R, Schneider K, Maas G. Tetrahedron 1989;45:5517.
- 11. For reviews of the chemistry of ynolates, see: (a) Shindo M. Tetrahedron 2007;63:10. (b) Shindo M. Synthesis 2003:2275. (c) Shindo M. Chem Soc Rev 1998;27:367.
- 12. Kowalski CJ, Lal GS, Haque MS. J Am Chem Soc 7127;1986:108.
- 13. Stork G, Hudrlik PF. J Am Chem Soc 1968;90:4464.
- 14. (a) Julia M, Saint-Jalmes VP, Verpeaux JN. Synlett 1993:233. (b) Julia M, Saint-Jalmes VP, Plé K, Verpeaux JN, Hollingworth G. Bull Soc Chim Fr 1996;133:15.

15. For a discussion of the 6π electrocyclization of 3-oxido-1,3,5-hexatrienes, see: Magnus P. Nouv J Chem 1978;2:555.

- 16. For prior examples of 6π electrocyclization reactions involving enolate derivatives, see: (a) White JD, Skeean RW. J Am Chem Soc 1978;100:6296. (b) White JD, Skeean RW, Trammell GL. J Org Chem 1985;50:1939. (c) Magomedov NA, Ruggiero PL, Tang Y. J Am Chem Soc 2004;126:1624. [PubMed: 14871080] (d) Magomedov NA, Ruggiero PL, Tang Y. Org Lett 2004;6:3373. [PubMed: 15355055] and references cited therein.
- 17. For a recent theoretical study and leading references, see: Takahashi M, Kira M. J Am Chem Soc 1999;121:8597.
- (a) Moser WH, Sun L, Huffman JC. Org Lett 2001;3:3389. [PubMed: 11594841] (b) Fogel L, Hsung RP, Wulff WD, Sommer RD, Rheingold AL. J Am Chem Soc 2001;123:5580. [PubMed: 11389643] (c) Chamberlin S, Wulff WD. J Org Chem 1994;59:3047.
- Blanco SE, Almandoz MC, Ferretti FH. Spectrochim Acta, Part A 2005;61:93.and references cited therein
- 20. Yu W, Jin Z. Tetrahedron Lett 2001;42:369.
- 21. The metalation of 1-phenyl-4-penten-1-yne with MeLi has previously been reported: Klein J, Brenner S, Medlik A. Isr J Chem 1971;9:177.
- 22. Separation of these phenols from byproducts was not possible without significant losses, precluding an accurate determination of yield.
- 23. A related thermal 1,3 carbon to oxygen shift in a 2-t-butyldimethylsilyl-substituted phenol has recently been reported: Eastham SA, Ingham SP, Hallett MR, Herbert J, Quayle P, Raftery J. Tetrahedron Lett 2006;47:2299.
- 24. Thermal 1,3-rearrangement of 2-trimethylsilylphenol has previously been described: Cooper GD. J Am Chem Soc 1961;26:925.
- 25. For a review of palladium-catalyzed cyclizations of this type, see: Zeni G, Larock RC. Chem Rev 2004;104:2285. [PubMed: 15137792]
- 26. These conditions have been employed by Hegedus for the cyclization of 2-allylanilines to indoles. See: Hegedus LS, Allen GF, Bozell JJ, Waterman EL. J Am Chem Soc 1978;100:5800.
- 27. Lattanzi A, Senatore A, Massa A, Scettri A. J Org Chem 2003;68:3691. [PubMed: 12713380]
- 28. For reviews of the application of ring closing metathesis to the preparation of heterocycles, see: (a) Chattopadhyay SK, Karmakar S, Biswas T, Majumdar KC, Rahaman H, Roy B. Tetrahedron 2007;63:3919. (b) Deiters A, Martin SF. Chem Rev 2004;104:2199. [PubMed: 15137789]
- 29. Hill JG, Rossiter BE, Sharpless KB. J Org Chem 1983;48:3607.
- 30. (a) Watson SC, Eastham JF. J Organomet Chem 1967;9:165. (b) Ellison RA, Griffin R, Kotsonis FN. J Organomet Chem 1972;36:209.
- 31. Danheiser RL, Helgason AL. J Am Chem Soc 1994;116:9471.
- 32. Zhang L, Kozmin SA. J Am Chem Soc 2004;126:10204. [PubMed: 15315407]
- 33. Sweis RF, Schramm MP, Kozmin SA. J Am Chem Soc 2004;126:7442. [PubMed: 15198582]
- 34. Sun J, Kozmin SA. Angew Chem Int Ed 2006;45:4991.
- 35. LiHMDS solution was prepared by the reaction of HMDS (2.8 mL, 2.1 g, 13 mmol) with 5.0 mL of BuLi solution (2.49 M in hexanes, 13 mmol) in 6.4 mL of THF.
- 36. Akai S, Kitagaki S, Naka T, Yamamoto K, Tsuzuki Y, Matsumoto K, Kita Y. J Chem Soc, Perkin Trans 1 1996:1705.

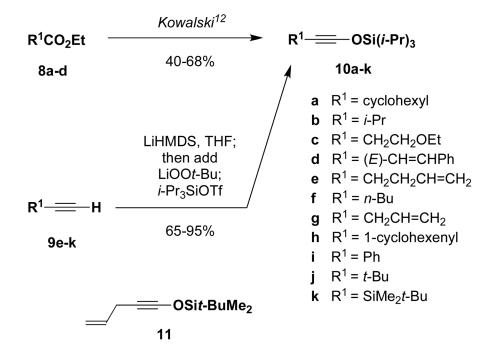
Figure 1. NOE studies on benzannulation product **31**.

Scheme 1.Benzannulation strategy based on the reaction of lithium ynolates with TAS-vinylketenes.

$$\begin{array}{lll} \textbf{a} & R^2 = CH_3, \ R^3 = CH_3 & \text{hv (300 nn} \\ \textbf{b} & R^2, R^3 = -(CH_2)_4 - & \text{benzene} \\ \textbf{c} & R^2 = CH_3, \ R^3 = Et & \text{rt, 4 h} \\ \textbf{d} & R^2 = CH_3, \ R^3 = C_6H_{11} & \end{array}$$

$$R^3$$
 Si(i -Pr)₃

Scheme 2. Preparation of TAS-vinylketenes.



Scheme 3. Preparation of siloxy alkynes.

Scheme 4. Proposed benzannulation reaction pathway and potential side reactions.

Scheme 5. Crossover experiment.

Scheme 6. Mechanism of silyl shift in benzannulation.

OR¹ OSi(
$$i$$
-Pr)₃ t -BuMe₂Si HO CH₃ CH_3 CH_3

Scheme 7. Results of benzannulation of TAS-vinylketene 7e with the ynolate derived from 10k.

Scheme 8. Desilylation and oxidation of benzannulation product 26.

Scheme 9. Palladium-catalyzed cyclization of benzannulation product **35**.

Scheme 10. Synthesis of benzofuran from benzannulation product 34.

Scheme 11. Synthesis of oxygen heterocycles via ring closing metathesis.

Austin et al.

Table 1

Benzannulation via reaction of TAS-vinylketenes with lithium ynolates

	yield (%) ^a	37	67–71	43	44 48	44-46
	product	Ph HO CH ₃	Cy Cy HO	OSi(/-Pr/ ₃	OSi(i-Pr) ₃ HO	EtO OSI(/-Pr) ₃ HO CH ₃
	ketene	7c	42	d7	J	74
	alkyne	10d	10a	10h	Ξ	10c
	entry	r	∞	6	01	=
	yield (%) ^a	62	65	55	30	46
OSI((-Pr) ₃ R ¹ HO R ³	Product	OSI(/-Pr) ₃ HO CH ₃	i-Pr HO CH ₃	f-Bu OSi(i-Pr) ₃	\ /	Eto OSi(i-Pr) ₃
t equiv MeLi, THF rt 0.5-4 h then add OCC SI(t-Pn)s 1.0 equiv rt, 30-60 min R3 7a-d	ketene	7a	7a	7a	7a	7c
	Alkyne	10f	10b	10j	10i	10c
R1 OSIR ₃	entry	-	6	m	4	8

Page 25

Austin et al.

	yield $(\%)^a$	
	product	see text
	ketene	7a
	alkyne	10k
	entry	12
	yield $(\%)^a$	68–70
→ R ¹ OSI((-Pr) ₃	Product	OSi(i-Pr) ₃
1 equiv MeLi, THF r 0.5-4 h then add OC Si(i-Pr) ₃ 1.0 equiv rt, 30-60 min R³ 7a-d	ketene	22
1 equiv THF rt then add 1.0 equiv rt, 30-60 min	Alkyne	10e
OSiR ₃	entry	ς ·

 $\boldsymbol{a}_{\text{L}}$ Isolated yield of products purified by column chromatography.

Page 26