PART I. EXTENDING ALLENYL AZIDE CYCLOADDITION CHEMISTRY: PHOTOCHEMISTRY AND CU(I) MEDIATION. PART II. EFFORTS TOWARD THE TOTAL SYNTHESIS OF (-)-KINAMYCIN F. PART III. EFFECT OF STRENGTH AND SYMMETRY OF HYDROGEN BONDS ON QUINONE REDUCTION POTENTIAL.
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ABSTRACT

Photochemical irradiation of 2-(3-alkenyl)allenylphenyl azides in the presence of excess CuI furnished functionalized 2,3-cyclopentenyldiones in good yield with only trace amounts of C-N bonded regioisomers. These results represent a significant departure from the modest-to-nonexistent regioselectivity observed upon thermolysis of these same substrates. The scope and limitation of this methodology is discussed. Mechanistic insight was aided by a collaborative effort with DFT computational models. These studies suggest that the allenyl azide cyclization cascade proceeds through a highly reactive indolidene intermediate. A synthetic effort toward the synthesis of the fischerindole class of natural products utilizing this methodology is also discussed.

A total synthesis effort toward the diazoparaquinone natural product (-)-kinamycin F is reported. A strategy utilizing a Hauser annulation to assemble the core tetracycle is employed.

A series of 11 simple naphthoquinone derivatives featuring H-bond donor amides at one or both peri positions were prepared and some salient physical properties were measured. A correlation between both IR frequency and NMR peak position, as indicators of internal H-bond strength, and the quinone single electron reduction potential was observed.
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1.1 Introduction.

The foundation of the allenyl azide cycloaddition/cyclization cascade described in this chapter and Chapter 2 is rooted in 1,3-diradical cyclization chemistry. Trimethylenemethane (TMM) 1,3-diyls have been exploited via trapping with alkenes to yield a variety of polycyclic frameworks. Intramolecular variants of this reaction have shown promise for the assembly of congested carbon skeletons. A relatively underexplored version of TMM diyl is the azatrimethylenemethane (ATMM) diyl, wherein one methylene unit is replaced by a nitrogen atom. An obvious use of ATMMs is to provide nitrogen-containing polycyclic heterocycles when combined with an appropriate trapping reagent. ATMM diyl chemistry recently has enjoyed a renaissance as a consequence of developments in allenyl azide chemistry. Both experimental and computational probing of the cascade reaction sequence that emerges from this combination has led to a thorough mechanistic understanding. As part of these studies, an isoelectronic form of a benzannelated ATMM species that doesn’t involve diradicals was identified. This species, an indolidene, has its own rich chemistry that leads to 2,3-cyclopentenannelated indole products.
1.2 1,3-Diradical Cyclization Chemistry

1.2.1 Trimethylenemethane Diyl Fundamentals.

The inspiration for the allenyl azide cyclization cascade comes from 1,3-diradical cyclization chemistry. The azatrimethylenemethane diyl (ATMM, 1-3) is related to the “parent” 1,3-diy1, trimethylenemethane (1-1) (Figure 1).\(^1\) Whereas the TMM species has long been studied, the synthetic potential of the ATMM species has been, until our recent efforts, largely ignored. Appropriate trapping/reacting of an ATMM diyl intermediate conceivably could lead to simultaneous C-C and C-N bond formation. Trapping reactive intermediates is a synthetic strategy used to make otherwise difficult-to-construct architectures. Building functionality into molecules that can easily be transformed into these reactive diyl intermediates and thus promote some desired bond forming reaction(s) underlies the work described herein.

![Figure 1: Trimethylenemethane (TMM) and azatrimethylenemethane (ATMM).](image)

TMM diyl species have been generated reliably through the loss of N\(_2\) gas from an appropriately substituted diazene. For example, upon heating or photochemical irradiation, the loss of N\(_2\) from 1-5 affords a TMM species, which in the absence of a trap, or “diylophi1e”, closes to give mostly methylenecyclopropane (1-6) (Figure 2).\(^2\)
1.2.2 Trimethylenemethane Trapping.

Little and coworkers have shown that thermolysis of dimethyl diazene 1-8 at 70-75 °C in the presence of cyclopentenone gave a 90-98% yield of adducts 1-9-1-11 (Figure 3). Unfortunately, this process proceeds with virtually no stereoselectivity or regioselectivity.

Figure 3: Little’s intermolecular diyl trapping via TMM.

An intramolecular example of TMM trapping was also demonstrated by Little (Figure 4). As opposed to the results in the intermolecular example, the intramolecular case shows remarkable improvement in regioselectivity and stereoselectivity. This methodology offered a new approach to polycyclopentenyl architectures, and has been exploited in many natural product syntheses.
TMM cyclization through adjacent unsaturation (olefin or carbonyl) also was demonstrated by Little in 1985 (Figure 5). Heating diazine 1-15 produced diene 1-17 (X = CH$_2$) or furan 1-16 (X = O) (from double-bond isomerization/aromatization) in good yield. This example showed not only that diylophiles directly linked to a 1,3-diyl (via a C-C bond) could participate in trapping/cyclization, but that heteroatoms were tolerated in this cyclization as well.
1.3 Allenyl Azide Cycloaddition Overview.

Many examples of organic azides cycloadding to allenes have been documented. The utility of an intermolecular version of this reaction is less than ideal due to the multiple regioisomers that typically are obtained (Figure 6). Triazolines of the type 1-21 and 1-23 are usually the major product of these cycloadditions, especially as the number of substituents on the reacting allene increases (i.e. $R_2, R_3 \neq H$ in 1-19). These triazolines are not useful for ATMM diyl generation. These observations indicate that the steric interaction between the $R_1$ group of the azide and the $R$ groups of the non-participating double-bond of the allene cannot be ignored.

![Figure 6: Possible regioisomers for intermolecular azide addition to an allene.](image)

Bleiholder and Shechter demonstrated this trend in the addition of several aryl azides 1-24 to tetramethylallene (1-25) to give triazolines 1-26 in poor to good yields (Figure 7). None of the other possible regioisomer (or degradation products thereof) was observed. When they subjected unsubstituted allene (1-27) to similar conditions, several products were obtained in very low yield which corresponded to both regioisomeric cycloadditions (1-28 and 1-29) as well as a degradation product which could not be traced conclusively to either parent cycloadduct (Figure 8).
1.3.1 Contributions from Quast.

The area of ATMM chemistry was thoroughly investigated by Helmut Quast over several decades.\(^1\) One of his major contributions was to provide persuasive evidence for the existence of the ATMM diyl by N\(_2\) loss from 5-methylene triazolines. Upon thermolysis or irradiation of triazoline 1-30, cyclopropaneimine 1-33 is formed quantitatively with excellent regioselectivity from ATMM diyls 1-31/1-32 (Figure 9).\(^{1c}\)

Quast proposed that the product of N\(_2\) extrusion originates on a least-motion path (Figure 10). Breaking the N-N bond of 1-30 gives diazenylazaallyl diradical 1-34, which, upon loss of N\(_2\), gives orthogonal diradical 1-35. After bond rotation to the bis-orthogonal ATMM diradical 1-36, diyl closure occurs to give the observed product 1-33.
The cyclization regioselectivity of the diradical intermediate(s) apparently is determined by product stability. No trace of methylene aziridine 1-37 was observed.

Figure 9: Quast’s triazoline conversion to cyclopropylimine via ATMM.

Figure 10: Mechanistic pathway to 1-33 via ATMM proposed by Quast.

1.3.2 Intramolecular Allenyl Azide Cycloaddition.

In the allene/azide cycloaddition, regiochemistry can be controlled via an intramolecular process. With an appropriately sized tether linking allene to azide, the regiochemistry shown in Figure 11 can be accessed. Triazoline regioisomer 1-39 is perfectly poised to extrude N$_2$ and deliver an ATMM diyl.
Mukai and coworkers recently reported an intramolecular allenyl azide cycloaddition, demonstrating this principle (Figure 12).\textsuperscript{7} The [3+2] cycloaddition of \textbf{1-40} does cleanly proceed to form a single triazoline regioisomer \textbf{1-41}. Subsequent alkene migration gives the very stable triazole \textbf{1-42}, effectively shutting down any possible loss of N\textsubscript{2} and thus accessing ATMM diyl chemistry. Although irrelevant to Mukai’s goals, this example effectively illustrated that an ATMM precursor triazoline could be prepared from simple linear substrates.

We postulated that terminal disubstitution of the allene, as indicated in \textbf{1-43}, would halt this isomerization/aromatization (Figure 13). Additionally, with a system such as allene \textbf{1-43}, diyl closure of putative ATMM intermediate \textbf{1-45} to a three-membered ring (i.e., \textbf{1-48-1-50}) should be energetically prohibitive,\textsuperscript{8} allowing for alternative reaction pathways to be expressed. With these two hurdles overcome (proper
regioselectivity of allene-azide cycloaddition and prevention of triazole formation), the allenylation azide/ATMM cascade cyclization should be achievable.

1.4 Recent Results from the Feldman Lab.

1.4.1 5-Azidoallene Substrates.

The first foray into this methodology was explored in the Feldman laboratory by Dr. Malliga R. Iyer using a series of 1-aryl- and 1-vinyl-substituted 5-azidoallenes 1-51 and 1-55, respectively.\(^{9,10}\) This breakthrough in allenylation azide/ATMM chemistry utilizes a built-in diylophile (arene or alkene), which can close to give polycyclic pyrrolidines (Figure 14). The expected pyrrolidines 1-53 and 1-57 were not directly isolable; however, upon trapping with TMSCN, adducts 1-54 and 1-58 were the only products from these reactions (yields shown in Table 1). This series of examples demonstrated that allenylation azide cycloaddition chemistry can be used to assemble polycyclic heterocyclic frameworks from easy-to-construct starting materials.
1.4.2 2-(Allenyl)phenyl Azide Substrates.

After initial exploration with the alkenyl azides bearing a saturated alkyl tether, a new series of substrates were envisioned, which featured an aryl unit connecting the two...
functional groups (i.e., 1-59). It was thought that this new framework could lead to 2,3-cyclopentannelated indoles (i.e., 1-61) in the same manner as the alkyl substrates led to polycyclic pyrrolidines (Figure 15). When this extension was explored in 2006, the observed regiochemistry of diyl collapse was quite distinct from the simple, saturated-tether 5-azidoallene substrates.

A series of allenes 1-59 were subjected to thermolysis conditions, providing an almost unbiased mixture of 2-3- and 1,2-cyclopentannelated indole polycycles (1-61 and 1-62, respectively, Figure 16). N-Cyclized indoles 1-62 were typically isolated as the pyrrole isomer 1-63 after purification on SiO₂. A survey of the substitutions, yields and ratio of products for these reactions are reported in Table 2.

Figure 15: Anticipated extension of allenyl azide towards 2,3-cyclopentannelated indoles.

Figure 16: Thermolysis of 2-allenyl(phenyl) azides.
In most examples examined, a nearly 1:1 mixture of C-C and C-N cyclized products was observed. From an exploration of substituent effects, it was clear that neither steric bulk nor electronic influence at the R₁ and R₂ positions influenced product ratios (entries a-d, Table 2). Altering the size of R did seem to have some affect on the product ratio; as the size of R increased, the bias toward C-cyclized product 1-61 increases. Although entries e and f also provided a nearly equal mixture of products, they did show that this methodology could be extended to the synthesis of tetracyclic indoles.

### 1.5 Mechanistic Insights.

A rationale for the observed difference in product regiochemistry between allenes 1-55 and 1-59 was initially a matter of some speculation. In order for this methodology to be implemented for target directed synthesis of 2,3-cyclopentannulated indoles (i.e., 1-61), a better understanding of the inherent reactivity of the allenyl azide cyclization...
cascade was essential. Soon after reporting these initial results, the Feldman laboratory began a collaborative computational effort to aid in this task.

1.5.1 Initial Assumptions.

The initial design for the allenyl azide cycloaddition was inspired from the TMM and ATMM literature and the first examples that were explored gave products expected from invoking these intermediates. After the 2-(allenyl)phenyl azide substrates provided unexpected C(2)-N(1) annelated indoles in roughly equal amounts to the expected C(2)-C(3) annelated indoles, a divergence in mechanistic pathways between the two series could not be ignored.

1.5.2 Computational Studies.

Shortly after these initial reports from the Feldman laboratory, a computational chemist, Dr. Carlos Silva López (Universidade de Vigo) became a collaborator in the investigation of the mechanism of the allenyl azide cycloaddition cyclization. Initial computational explorations of the model saturated-tether substrate 1-64 via Density Functional Theory (DFT) calculations led to a clearer understanding of the reaction pathway (Figure 17). The rate-determining step is the initial [3+2] cycloaddition to give triazoline 1-65, which, upon loss of N₂, gives isomeric diyls 1-66 and 1-67. These two diyls should be in rapid equilibrium under the experimental conditions. Diyl 1-66 faces a
much higher energetic barrier to cyclization than does 1-67, and so 1-68 is formed instead of bicycle 1-69 (not observed experimentally).

![Diagram](image)

Figure 17: Mechanistic profile for reaction cascade of allene 1-64 via DFT calculation.

When calculations were performed on the unsaturated-tether allenyl azide 1-59 (R, R₁, R₂ = H) a dramatic change in reaction intermediates was found (Figure 18). An alternative reactive species was found in the indolidene or “closed shell” species 1-71 and 1-72, which arose from a concerted loss of N₂ from triazoline 1-70. These two regioisomeric indolidene species are highly unlikely to interconvert under the experimental conditions. In this case, the key bond forming step is not a diyl closure, but a 12π electron electrocyclization to give the annelated five-membered ring. The rotation of the C-C bond indicated in 1-70a dictates the regioisomer of indolidene formed and, ultimately, the regiochemistry of the cyclization cascade product(s) (Figure 19). The concerted loss of N₂ from 1-70 is a formal [10π + 2π] thermal, suprafacial pericyclic retrocycloaddition, which is formally forbidden by the Woodward-Hoffman rules.¹³ Thus a more thorough examination of this mechanistic detail is necessary.
The key to understanding this “forbidden” process was to recognize the relationship of the two $\pi$ systems involved (the indole and the $N_2$). Results obtained from the computational techniques ACID$^{14}$ (Anisotropy of the Current Induced Density) and NICS$^{15}$ (Nucleus Independent Chemical Shift) shed light on this dilemma. These techniques provide estimations of electron density in off-atom regions of space, such as the regions between the cleaving atoms in the transition state for $N_2$ loss in 1-70a. Calculations on indolidine 1-70 indicate that there is almost no electron density occupying the breaking C-N and N-N bond regions in the concerted $N_2$ extrusion.
Effectively, there is no electron flow, or electronic communication, between the two \( \pi \) systems, unlike the similar case of the hetero-Diels-Alder cycloreversion (butadiene and \( \text{N}_2 \)), where there is significant electron delocalization at the cleavage points. This subtle caveat of electronics effectively removes this example from the realm of the Woodward-Hoffman rules.

The argument for a concerted, as opposed to a stepwise, loss of \( \text{N}_2 \) also was supported by CASSAF (Complete Active Space Self-Consistent Field) calculations. For triazoline 1-75 the conversion to a diazo diradical 1-77 was found to have an activation barrier of 25.0 kcal/mol, compared to the direct conversion of 1-75 to 1-76 which required 17.4 kcal/mol (Figure 20).

![Figure 20: Activation barriers for step-wise versus concerted \( \text{N}_2 \) loss.](image)

### 1.5.3 Regioselectivity Differences.

The key to understanding the different cyclization regiochemistry of the saturated-tether and phenyl-tether substrates lies in the energetics of equilibration between regioisomeric diyls or alkenes, respectively. These calculated data are shown in Figure 21. In the case of the 5-azidoallenes, isomeric diyls 1-66 and 1-67 are in rapid equilibrium under the experimental conditions. The much lower barrier for C-C bond
formation over C-N formation dictates the product distribution (favoring the former). In the 2-(allenyl)phenyl azide case, the two isomeric reactive indolidines 1-71 and 1-72 do not interconvert under the experimental conditions ($\Delta G^\ddagger = 24.2$ kcal/mol). Once formed, their ratio will dictate the product ratio. Based on the results in Table 2, only subtle differences in product ratio can be achieved by substitution changes at the allenic R position on 1-59. Thus Curtin-Hammet-type kinetics operate in the former case, but not in the latter one.

![Figure 21: Energetic profiles explaining product distributions of allenyl azide cascades.](image)

Since the ratio of indolidenes 1-71 and 1-72 dictates the ratio of cyclized indole products formed, a better understanding of the formation of these indolidenes is necessary. The key in understanding indolidene formation lies in the rotation of the vinyl and R$_2$ groups shown in Figure 22. As N$_2$ is extruded from 1-70b and the exocyclic double-bond is forming the vinyl and R$_2$ groups must rotate either clockwise or counterclockwise; the result of this rotation dictates the regiochemistry of the indolidene. If the two groups in 1-70b rotate clockwise, indolidene 1-72a is formed, if they rotate counterclockwise, indolidene 1-71a is formed. The more severe steric interaction with the R$_1$
group experienced by either the vinyl or \( R_2 \) group should be avoided. Computational results support this premise. As the size of \( R_2 \) increases, \( R_1/R_2 \) steric interaction becomes a major energetic factor and indolidene \( 1-71a \) formation dominates. The calculated ratio of \( 1-71a:1-72a \) when \( R_1 = H, R_2 = \text{t-Bu} \) at 110 °C is 2.8:1, which matches remarkably well with the observed value of 2.7:1 (Table 2, entry \( i \)).

![Figure 22: Rotation of C-C bond dictates indolidene regiochemistry.](image)

### 1.6 Indolidene Chemistry.

The inclusion of indolenines in the reaction cascade focused a new interest on these reactive intermediates. The use of indolenines in organic synthesis is scarce. No other examples of electrocyclizations involving this intermediate have been reported to date. The most notable and common use of this reactive species is found in synthetic efforts directed toward the vinblastine series of alkaloids.\(^{16}\)

In 1966, Büchi and Manning postulated the intermediacy of an indolidene in their transformation of ibogaine (\( 1-78 \)) to the hindered nitrile \( 1-81 \), a precursor to the natural product voacangine (Figure \( 23 \)).\(^{17}\) Upon loss of HCl, chloroindolenine \( 1-79 \) gave indolidene \( 1-80 \) which was trapped by \( \text{CN}^- \) to reform the substituted indole \( 1-60 \). In this
case, the inherent stereochemical bias of the fused bicyclic ring system makes this reaction stereoselective.

![Chemical structures](image)

Figure 23: Büchi’s use of an indolidene via chloroindolenine.

Two years later, Kutney and coworkers invoked an indolidene intermediate 1-83 in their studies of the dimeric vinca alkaloids (Figure 24). Again, a chloroindolenine 1-82 was used to initiate indolidene formation. Indolidene 1-83 was electrophilic enough to react with the 15 position of vindoline (1-84, structure abbreviated for clarity), giving dimeric alkaloid 1-85.
In an unusual example of indolidene reactivity, Wentrup and Gross transformed 2-carboxy-substituted indoles 1-86 into the formal [3+3] cyclization dimer 1-88 (90%, R = Me) via indolidene-ketene 1-87 (Figure 25). This example demonstrates the high reactivity of indolidenes and how extending its π system can result in complex transformations.

Figure 24: Kutney’s indole dimerization via an indolidene.

Figure 25: Wentrup’s indolidene-ketene [3+3] dimerization.
1.7 Synthetic Utility.

The foundations for the methodology development described herein have been explored in both the 5-azidoallene and 2-(allenyl)phenyl azide series. Using experimental results in conjunction with a thorough computational effort, the mechanistic intricacies of these allenyl azide cyclization cascades were unveiled. Although the lack of regioselectivity in the 2-(allenyl)phenyl azide case presented a severe limitation to possible target-directed synthesis efforts, this new methodology seemed poised to offer more utility than first communicated. As with any new methodology, there are seemingly endless possibilities for improvement and discovery. Finding a reliable and practical method to control regioselectivity could dramatically enhance the synthesis prospects in the 2-(allenyl)phenyl azide case. Additionally, further substitution patterns (both on the appended olefin and allene) clearly should be explored to fully probe the scope and limitations of this methodology. Finally, with some insight, a target directed total synthesis could be implemented.

1.8 References.


Chapter 2

Expanding Allenyl Azide Cycloaddition Chemistry: Photochemistry and Cu(I) Mediation. Efforts Toward the Synthesis of the Fischerindole Family of Natural Products.

2.1 Introduction.

Several extensions of the allenyl azide cyclization cascade were pursued after the initial contributions from the Feldman laboratory. A variation of the 2-(allenyl)phenyl series was investigated wherein cyclization into an aromatic ring was attempted. An effort toward the synthesis of the fischerindole family of alkaloids was undertaken. During these studies, photochemical initiation of the allenyl azide cycloaddition cascade was explored. Conditions were found where inclusion of Cu(I) caused the reaction products to favor C-C cyclization over C-N cyclization, a significant departure from the previous results where unbiased mixtures of regioisomers were obtained. The scope and limitations of this new method were investigated. A thorough computational study was employed to better understand the role copper plays in the mechanism of the cascade reaction sequence.

2.2 3-Aryl Substituted Allenyl Azides.

A series of allenyl azides with a 3-aryl substituent (2-2) were envisioned as a straightforward extension of the work described in Chapter 1 (Figure 26). Since the 5-azidoallene substrates were observed to cyclize into an aromatic ring, it was postulated
that the same cyclization would proceed with the 2-(allenylphenyl) substrates 2-2 to give benzannelated adducts 2-3 and 2-4.

2.3 Synthesis of 3-arylallenyl azides.

The synthesis of 3-arylallenyl azides was planned to follow the well-established Pd-mediated cross-coupling reaction of propargyl acetate 2-5 and commercially available aryl zincates 2-6 (Figure 27). However, all attempts to directly synthesize allenes 2-7 via this methodology failed. Allene formation was suspected based on TLC observations of

Figure 26: Extension of 3-vinyl to 3-aryl substituted allenyl azide cyclization cascade.

Figure 27: Thermolysis of 3-Aryl-substituted allenyl azides.
the crude reaction mixtures soon after all reagents were added, but only complex product mixtures were observed. A one-pot transformation, wherein the crude reaction mixture was heated at reflux after addition of the zincate and Pd catalyst to the propargyl acetate, was carried out. The only product observed from this procedure was the unexpected 2-styryl indole 2-8 in low-to-moderate yield. Varying the electronic nature of the substituent on the aryl ring did not change the course of this transformation, and the benzannelated tetracycles 2-3 and 2-4 were never observed. The formation of a styrene product in these reactions is rationalized by the two pathways shown in Figure 28. Once [3+2] cycloadduct triazoline 2-9 loses N₂, the observed products could arise from either a hydrogen abstraction via ATMM diyl 2-10a (from stepwise loss of N₂) or from a formal [1,7]-hydrogen shift within 2-10b (from concerted loss of N₂).¹¹

Allene 2-7 (R = H) was synthesized by an alternate route, in another attempt to investigate this transformation. Acetylenic Grignard addition to azido aldehyde 2-11, followed by quenching of the resulting alkoxide with Ac₂O, gave acetate 2-12 (Figure 29). A copper-mediated Sₙ2’ displacement of the acetate produced allene 2-7 in good yield. However, all attempts to effect the desired cyclization cascade on the pure allene 2-7 led only to the previously observed 2-styryl indole 2-8a (81% yield in refluxing toluene).

![Figure 28: Postulated intermediates explaining 2-vinyl indole formation.](image-url)
A rationalization for the divergence in reactivity of these aryl-substituted allenes compared to the vinyl-substituted analogues might be based on the loss of aromaticity via electrocyclization in the former series (Figure 30). A DFT computational study was performed to shed light on this hypothesis. The results do indeed suggest that the relative energies (below structures) and activation energies (above arrows) funnel the reaction pathway to the observed indole 2-8 (Figure 31). For this model to hold, the proton shift associated with aromatization of 2-10b or 2-10c must be a higher energy...
process than the retrocylization of 2-10b/2-10c back to indolenes 2-10 or 2-10a, respectively. An activation energy for this tautomerization was not calculated.

2.4 Targets for Synthesis Using Allenyl Azide Cycloaddition Chemistry.

The fischerindole family of natural products (2-13a-e) was chosen as synthesis targets to showcase this methodology (Figure 32). These alkaloids were isolated from the cyanobacteria *H. welwitschii* (2-13a-d) and *F. muscicola* (2-13e) and possess antifungal properties. They all contain a similar 6-5-5-6 tetracyclic indole core featuring a C-ring *gem*-dimethyl unit and a D-ring with contiguous stereogenic centers.

To date, only Baran and coworkers have reported total syntheses of the fischerindoles 2-13a (unnatural enantiomer), 2-13c (unnatural enantiomer), and 2-13d.22

---

**Figure 31**: Cyclization pathways for aryl-substituted allenes.
Baran’s synthesis utilizes an acid-catalyzed (or clay-mediated) ring closure to form the tetracyclic core of the fischerindoles (2-14b → 2-15b), previously observed as an undesired biproduct by Fukuyama\textsuperscript{23} (2-14a → 2-15a, no yield reported) (Figure 33). Assembly of the cyclization precursor is carried out in one step. Deprotonated indole 2-16a and ketone enolate 2-17a are both oxidized to their corresponding radicals 2-16b and 2-17b, respectively. Under carefully optimized conditions, this direct coupling proceeded in 55% yield for substrate 2-14b. Once tetracycle 2-15b is formed, fischerindoles 2-13a, c, and d are made in 2, 4, and 3 steps, respectively, all in a concise, protecting-group-free route.

Figure 32: The fischerindole alkaloids.
Banwell and coworkers recently reported a synthesis of similar, unfunctionalized fischerindole tetracyclic cores in five steps (Figure 34). Starting from \( \text{N-methylindole} \) (2-19) and dibromocyclopropane 2-21, they arrived at both the cis- and trans- substituted cyclohexane 2-14c in four steps. They affected the same ring closure using Fukuyama’s method to give the trans- and cis-fused 5-6 ring systems (2-15c and 2-15d respectively).
We envisioned that the fischerindoles could be constructed using the allenyl azide cycloaddition/cyclization cascade reaction to form the tetracyclic core. A retrosynthesis for a fischerindole model system 2-20a is presented in Figure 35. We hoped to install the isonitrile functional group from the D-ring ketone. The second C-ring methyl would

Figure 34: Fischerindole cores synthesized by Banwell and coworkers.

Figure 35: Fischerindole model system retrosynthesis.
arise from a cyclopentadienyl anion alkylation of 2-20c, which would be the product of our key allenyl azide cycloaddition cascade reaction of 2-21. This allene should be readily available from well preceded palladium cross coupling of acetate 2-5 and the zincate 2-22a, which was expected to be accessible from the corresponding β-haloenone 2-22b. This species would be synthesized from the corresponding 1,3-diketone 2-23. Acetate 2-5 is available in one step from the known aldehyde 2-11.

2.4.1 Initial Fischerindole Synthesis Efforts.

We began our efforts toward a fischerindole model system with the synthesis of the β-iodo enone 2-24 in very good yield from commercially available diketone 2-23 (Figure 36).26 Acetate 2-5 was accessed via a Grignard addition to the known aldehyde 2-11 in moderate yield. With these two fragments in hand, we set out to form the corresponding zincate of iodide 2-24 via Knochel’s in situ method using activated zinc.27 Repeating his experimental procedures with iodide 2-24 never led to any recognizable products (Figure 37). An attempt to generate 2-22a using highly active Rieke® Zinc was also unsuccessful. An alternate assembly of allene 2-21 was envisioned. This procedure would utilize Sonogashira coupling of acetate 2-25 and iodide 2-24 followed by S_N2’ displacement of the acetate in 2-26 to form the desired allene 2-21 (Figure 38).
The enone functionality in 2-26 presented a possible source of cuprate competition between 1,4-addition and \( S_N2' \) acetate displacement. Because of this competition, we decided to bring the D-ring through this step as a protected alcohol and oxidize it to the ketone in a subsequent step. We therefore synthesized a series of
protected alcohols **2-28a-d** and cyanohydrin **2-28e** using standard methods (Figure 39).

Acetate **2-25** was synthesized in the same manner as described for **2-11** and **2-20**.  

Sonogashira coupling of iodide **2-28a** and acetate **2-25** gave the coupled product **2-29a** in 79% yield (Figure 40). Subsequent methyl cuprate addition proceeded to give the expected allene **2-30a** in high yield. TBAF deprotection of silane **2-30a** revealed alcohol **2-31**, which upon treatment with Dess-Martin periodinane, gave the desired ketone **2-21** in moderate yield. Unfortunately, allene **2-21** did not react to give any recognizable products under any conditions (thermolysis, microwave irradiation, or photolysis). These reactions gave either complete decomposition or no reaction at all.

*Figure 39: Synthesis of starting materials for Sonogashira route.*
Despite the disappointing results with allene 2-21, we did demonstrate that we could rapidly assemble allenyl azides with functionalized D-rings (i.e., 2-30a or 2-31). The next logical step was to subject these alternative substrates to cyclization conditions as well. We were pleased to find that subjecting allene 2-30a to refluxing toluene gave a 1:1.6 mixture of indoles 2-32a and 2-33a respectively (as determined by characteristic signals in the $^1$H NMR of crude thermolysate). N-Cyclized isomer 2-33a could not be isolated, but the corresponding elimination product 2-34 (from SiO$_2$ or alumina chromatography) was isolable (Figure 41). The desired indole 2-32a was isolated as a single diastereomer, whose structure was first assigned by $^1$H NMR (e.g., trans stereochemistry as per C-10-11, $J$(H,H) = 10.2 Hz) and later confirmed by single crystal X-ray analysis.
Gaining access to tetracycle 2-32a prompted an investigation of the cyclization conditions with allenes 2-30b-e as well, which were prepared from acetates 2-29b-e. The synthesis of these allenes proceeded analogously to that of 2-30a (Figure 42).

The results from the thermolysis of these allenes are displayed in Table 3. These results demonstrated the tolerance of this cyclization cascade to various functional groups, including the free alcohol in 2-31. In comparison to allene 2-30a, the ratio for the C-C cyclized tetracycle to the C-N cyclized tetracycle was only marginally improved in the case of allene 2-30d (1:1.4, respectively) and 2-31 (1:3:1, respectively). One deviation from the other examples was noted in the case of the cyanohydrin 2-30e, which proceeded with a cyclization ratio of 1:2.5 (2-32:2-33). The structure and
stereochemistry of cyanohydrin \textbf{2-32e} was solved by single crystal X-ray analysis. This example was also unusual in that the C-N bonded substrate \textbf{2-33e} did not suffer OTBS elimination. These results demonstrated that a variety of substrates were amenable to cascade cyclization to form the desired tetracyclic core of the fischerindoles. The stereochemistry of the indoles \textbf{2-32b-d} and \textbf{2-32f} were originally assigned based on characteristic \textit{trans} \textit{J} values for C-10-C-11 proton coupling and later by spectral similarities to the species whose structure were secured by X-ray analysis, \textbf{2-32a} and \textbf{2-32e}.

### Table 3: Thermolysis of allenes \textbf{2-30b-e} and \textbf{2-31}.

<table>
<thead>
<tr>
<th>allene</th>
<th>R</th>
<th>(R_1)</th>
<th>yield \textbf{2-32} (%)</th>
<th>yield \textbf{2-33} (%)</th>
<th>yield \textbf{2-34} (%)</th>
<th>ratio \textbf{2-32:2-33}</th>
<th>(J(10,11)) \textbf{2-32} (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textbf{2-30b}</td>
<td>TIPS</td>
<td>H</td>
<td>--</td>
<td>--</td>
<td>51</td>
<td>\textbf{2-33} only</td>
<td>9.3</td>
</tr>
<tr>
<td>\textbf{2-30c}</td>
<td>Bn</td>
<td>H</td>
<td>24</td>
<td>--</td>
<td>51</td>
<td>1 : 1.8</td>
<td>10.9</td>
</tr>
<tr>
<td>\textbf{2-30d}</td>
<td>SEM</td>
<td>H</td>
<td>39</td>
<td>--</td>
<td>not isolated</td>
<td>1 : 1.4</td>
<td>10.6</td>
</tr>
<tr>
<td>\textbf{2-30e}</td>
<td>TBS</td>
<td>CN</td>
<td>27</td>
<td>48</td>
<td>--</td>
<td>1 : 2.5</td>
<td>n/a</td>
</tr>
<tr>
<td>\textbf{2-31}</td>
<td>H</td>
<td>H</td>
<td>\textit{34} (2-32f)</td>
<td>25</td>
<td>1.3 : 1</td>
<td>10.7</td>
<td></td>
</tr>
</tbody>
</table>

The utility of this transformation was diminished due to the poor regioselectivity of the cyclization, although this observation was not unexpected based on our previous results discussed in \textbf{Chapter 1}. During this initial work, we probed several experimental variables in the hopes of influencing the cyclization ratio to favor the C-C bonded
product 2-32. We discovered that the reaction concentration (14 mM, 20 mM, and 80 mM) had no appreciable effect on cyclization results. We also demonstrated that reaction time had no effect on the cyclization ratio. Once the allene was consumed (as monitored by TLC), the ratio of 2-32:2-33 remained unchanged upon continued heating. To test whether the two cyclized products could interconvert, pure 2-32a could be recovered unchanged from refluxing toluene. Elevating the temperature from 110 °C to 153 °C (refluxing DMF) in the case of allene 2-30a only led to greater preference for the formation of 2-33a over 2-32a (3:1 vs. 1.6:1, in DMF and toluene, respectively). We planned next to explore the photochemical initiation of the allenyl azide cyclization cascade.

2.5 Initial Photochemical Experiments.

With rapid access to allenyl azides 2-30 and 2-31, we sought new approaches to initiate cyclization with the hope of influencing the ratio of products to favor the C-C cyclized isomer 2-32. On the short list of conditions was photochemistry. We first subjected allene 2-30a to irradiation at 254 nm in MeCN. Much to our surprise and delight, the only recognizable product in the crude photolysate was 2-32 (as determined by 1H NMR), which was isolated in 69% yield. This breakthrough greatly improved the prospects for using this methodology in the synthesis of 2,3-cyclopentannelated indoles. We subjected allenes 2-30b-e and 2-31 to the photochemical conditions as well, the results of which are shown in Table 4. With the exception of TIPS ether 2-30b and cyanohydrin 2-30e, the cyclization ratio now favored the desired C-C cyclized tetracycle
2-32 to the extent that no C-N cyclized tetracycle 2-33 was observed in the crude photolysate. The stereochemical assignment of indole 2-32e was based upon single crystal X-ray analysis.

Table 4: Initial photochemical results with allenes 2-30.

<table>
<thead>
<tr>
<th>allene</th>
<th>R</th>
<th>R₁</th>
<th>yield 2-32 (%)</th>
<th>yield 2-33 (%)</th>
<th>yield 2-34 (%)</th>
<th>Ratio 2-32:2-33</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-30a</td>
<td>TBS</td>
<td>H</td>
<td>69</td>
<td>--</td>
<td>--</td>
<td>2-32 only</td>
</tr>
<tr>
<td>2-30b</td>
<td>TIPS</td>
<td>H</td>
<td>60</td>
<td>--</td>
<td>not isolated</td>
<td>3 : 1</td>
</tr>
<tr>
<td>2-30c</td>
<td>Bn</td>
<td>H</td>
<td>48</td>
<td>--</td>
<td>--</td>
<td>2-32 only</td>
</tr>
<tr>
<td>2-30d</td>
<td>SEM</td>
<td>H</td>
<td>60</td>
<td>--</td>
<td>--</td>
<td>2-32 only</td>
</tr>
<tr>
<td>2-30e</td>
<td>TBS</td>
<td>CN</td>
<td>53</td>
<td>not isolated</td>
<td>--</td>
<td>ca. 1 : 1</td>
</tr>
<tr>
<td>2-31</td>
<td>H</td>
<td>H</td>
<td>60 (2-32f)</td>
<td>--</td>
<td>--</td>
<td>2-32 only</td>
</tr>
</tbody>
</table>

The difference between the photochemical results and the thermal results for the allenyl azide cyclization cascade led us to pause from our pursuit of the fischerindoles and thoroughly investigate the scope of this new reactivity. The pressing question was: What causes the difference in regioselectivity upon photochemical vs. thermal initiation?

We chose to reexamine some of the 2-(allenyl)phenyl azides (Chapter 1) to see if the preference for C-C cyclization was detected in all of the allenes in this series.

We first chose to revisit the unfunctionalized cyclohexene-substituted allene 2-35 under the new photochemical conditions (Table 5). Photochemistry with this allene gave the unremarkable regioisomer ratio of 1:1.1 (2-36:2-37), with isolated yields similar to
those obtained in the thermal case. The initial rationalization for this struck difference in regiochemistry between allenes \(2-30\) and \(2-35\) was tied to the major structural difference between the substrates: the allylic oxygen substitution of \(2-30\). It was not clear, however, why the presence/absence of this group should matter so much, so we proceeded to thoroughly examine more substrates and conditions to obtain a better understanding of the scope of the photochemically initiated allenyl azide cyclization cascade.

### Table 5: Thermolysis and photolysis of allene \(2-35\).

![Schema of reaction](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>yield (2-36) (%)</th>
<th>yield (2-37) (%)</th>
<th>ratio (2-36 : 2-37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>110 °C, toluene</td>
<td>36</td>
<td>51</td>
<td>1 : 1.4</td>
</tr>
<tr>
<td>(b)</td>
<td>254 nm, MeCN</td>
<td>32</td>
<td>27</td>
<td>1.1 : 1</td>
</tr>
</tbody>
</table>

### 2.6 Reproducibility of Initial Photochemical Results.

We began a series of investigations to fully explore the photochemically initiated allenyl azide cyclization cascade only to find that our initial results were completely irreproducible. In an effort to fully chart the photochemical reactivity of allenes \(2-30\) and \(2-31\), we repeated the original conditions on several independently prepared batches of allenes. The ratio of \(2-32:2-33\) seemed to vary beyond explanation depending on batch. Rigorous purification of the allenes was attempted, but all spectral data matched that of the previous “remarkable” batches, which produced the exclusive C-C cyclized
tetracycles 2-32 upon irradiation. Many of these batches began to consistently give cyclization ratios of 1:1 (2-32:2-33). We searched for the variable that had produced the miraculous prior results. In an attempt to solve the mystery, we changed many reaction components, including: glassware (specific vessel), glassware cleaning method (acid and base treatment), MeCN source, solvent, reaction time, light bulbs (new and old), wavelength (254, 300 or 350 nm), temperature, brand of septa used, dryness of reaction solution, degassing duration, and identity of the purging gas (N$_2$ or Ar). As we thoroughly investigated our laboratory technique, a slight difference in certain batches of allenes was noticed. The allenes which produced a nearly unbiased ratio of cyclized products were less colored than that previously used. The original batches of these allenes typically had a slight pinkish hue, which was not considered significant at that time. Could the cause of this coloration be a contaminant, which might be the culprit behind the remarkable improvement in regioselectivity? It seemed extremely unlikely that a contaminant would have ended up in several early batches of multiple allenes 2-30 and 2-31 (purified by column chromatography), but by some minor alteration in laboratory procedure was no longer present in the later allene batches. Making this scenario even more improbable was the result with allene 2-31, which differed from allenes 2-30 in that it was subjected to a subsequent reaction (TBAF deprotection) and purified again by column chromatography before being used in the photochemical cyclization step.
2.7 Identifying the Cause of C-C Cyclization Preference.

After exhaustively eliminating all experimental variables, we looked at the common connection between allenes 2-30 and 2-31. These allenes all arose from identical synthesis routes. The allene-forming step was a copper-mediated SN2’ acetate displacement requiring 10 equivalents of CuI, LiBr, and MeMgBr. If the metal residues from these reagents had bled through the column, or formed a complex with the allene, they might not be detected by standard spectroscopic methods. To this end, we examined the effect of additives on the ratio of products from the allenyl azide cyclization cascade (Table 6, yields not optimized). An excess of CuI, LiBr and Mg powder were added to allene 2-30a and the resulting solution was irradiated at 254 nm in MeCN (entry c). Much to our pleasure, the cyclization ratio was dramatically effected, favoring 2-32 over 2-33 (10:1).

This observation led us to probe specifically for which metal or combination of metals were causing the alteration in product ratio. LiBr and Mg alone seemed to have no effect on the cyclization ratio (entries d and e). When catalytic amounts of CuI were added, little change in the product ratio was observed (entry f). However, when 1 equivalent of a Cu(I) source was added, the ratio once again became biased toward C-C cyclized product 2-32 (entries g, h, j). We investigated CuI as the sole additive in increasing amounts (entries k-n) and discovered that a slight molar excess of CuI provided reproducible results similar to those originally observed, and this procedure led to a good isolated yield of 2-32. We identified 1.5 eq. of CuI in MeCN, with an allene concentration of 5 mM, as the optimum conditions for this transformation (entry n).
also tested Rh (entry r), but an approximately 1:1 mixture of 2-32a and 2-33a was observed.

Table 6: Discovery and optimization of additives in photochemical cyclization cascade.

<table>
<thead>
<tr>
<th>entry</th>
<th>hv (nm)</th>
<th>temp. (°C)</th>
<th>conditions</th>
<th>combined yield (%)</th>
<th>ratio 2-32a : 2-33a</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td></td>
<td>110</td>
<td>no additives</td>
<td>80</td>
<td>1 : 1.6</td>
</tr>
<tr>
<td>b</td>
<td>254</td>
<td>no additives</td>
<td>LiBr (1 eq.)</td>
<td>68</td>
<td>1 : 1.1</td>
</tr>
<tr>
<td>c</td>
<td>254</td>
<td>excess CuI, LiBr, Mg powder</td>
<td>33</td>
<td>&gt;10 : 1</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>254</td>
<td>LiBr (1 eq.)</td>
<td>Mg powder</td>
<td>33</td>
<td>1 : 1.2</td>
</tr>
<tr>
<td>e</td>
<td>254</td>
<td>LiBr (1 eq.), CuI (1 eq.)</td>
<td>not isolated</td>
<td>1 : 1.4</td>
<td></td>
</tr>
<tr>
<td>f</td>
<td>254</td>
<td>CuBr•Me2S (1 eq.)</td>
<td>not isolated</td>
<td>2.8 : 1</td>
<td></td>
</tr>
<tr>
<td>g</td>
<td>254</td>
<td>CuBr•Me2S (0.25 eq.)</td>
<td>17</td>
<td>5.4 : 1</td>
<td></td>
</tr>
<tr>
<td>h</td>
<td>254</td>
<td>Cu(OAc)2 (1 eq.)</td>
<td>not isolated</td>
<td>5 : 1</td>
<td></td>
</tr>
<tr>
<td>i</td>
<td>254</td>
<td>CuI (0.5 eq.)</td>
<td>67</td>
<td>4 : 1</td>
<td></td>
</tr>
<tr>
<td>j</td>
<td>254</td>
<td>CuI (0.8 eq.)</td>
<td>72</td>
<td>6 : 1</td>
<td></td>
</tr>
<tr>
<td>k</td>
<td>254</td>
<td>CuI (1.2 eq.)</td>
<td>67</td>
<td>9 : 1</td>
<td></td>
</tr>
<tr>
<td>l</td>
<td>254</td>
<td>CuI (1.5 eq.)</td>
<td>70</td>
<td>10 : 1</td>
<td></td>
</tr>
<tr>
<td>m</td>
<td></td>
<td>110</td>
<td>CuI (1.5 eq.), 5 mM</td>
<td>75</td>
<td>1 : 1.6</td>
</tr>
<tr>
<td>n</td>
<td></td>
<td>110</td>
<td>CuI (1.5 eq.), 35 mM</td>
<td>66</td>
<td>3.5 : 1</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>110</td>
<td>CuI (1.5 eq.), 51 mM</td>
<td>65</td>
<td>5 : 1</td>
</tr>
<tr>
<td>q</td>
<td>254</td>
<td>CuI (1.5 eq.)</td>
<td>48</td>
<td>1 : 1</td>
<td></td>
</tr>
</tbody>
</table>

These reactions were carried out in a sealed tube.

At this juncture, we were faced with two new questions: (1) Is photochemistry required to obtain regioselectivity favoring C-C cyclization using copper?, and (2) Do thermal and photochemical initiation lead to the same products via the same
intermediate(s)? In order to probe these questions, we decided to test the effects of copper on the thermolytic initiation of the allenyl azide cyclization cascade (entries o-q). If we obtain the same results thermally with copper as we did photochemically with copper, perhaps a common intermediate exists in the cyclization pathway of these two transformations. Thermolysis of 2-30a, under identical conditions as our optimized photochemical conditions, was carried out (entry o). The result was nearly identical to that of the thermal case without copper (entry a). To increase the interaction of Cu with the allene, or with putative downstream reactive intermediates, we increased the overall reaction concentration (entries p-q). With an increased reaction concentration, an increase in C-C cyclized indole was observed, which reached a maximum ratio of 5:1 (2-32:2-33) at 51 mM (virtually saturated in CuI). This result indicates that photochemical and thermal initiation both lead to similar (if not identical) reactive intermediates. When copper is present, the reaction pathway of the allenyl azide cyclization cascade is altered to favor C-C cyclization over C-N cyclization regardless of initiation method.

It is very unlikely that CuI (left over from allene formation) bled through the column during purification and co-eluted with allenes 2-30 (which typically elute in hexanes → 2% Et₂O/hexanes). The more likely scenario is that a Cu-allene complex formed in the crude reaction mixture. If an inadequate amount of aqueous NH₄Cl solution was used to extract the excess copper left over from the reaction, it is conceivable that such a complex could survive workup and chromatography. This hypothesis could be tested by subjecting the samples to atomic absorption spectroscopy and measuring the Cu content. However, we did not have access to this instrumentation at that time.
We revisited the series of cyclohexenol-derived allenes 2-30 and 2-31 with the assumption that we could now gain access to C-C cyclized tetracycles as originally observed. The results of the copper-mediated photochemical conditions, as well as photochemical irradiation without copper, are presented in Table 7. The cyclization results without copper are very similar to those we observed when inconsistencies in early batches were apparent. Typically, these cyclization ratios are nearly 1:1 for the C-C to C-N bonded regioisomers. Our suspicion that photolysis and thermolysis proceed through similar if not identical intermediates was solidified by the similarity in cyclization ratio between the thermolysis and the photolysis (without copper) experiments. The results with copper, however, agree remarkably well with our optimized results with allene 2-30a. Regioisomer ratios favoring C-C cyclized indole 2-32 over C-N cyclized indole 2-33 were as high as 10:1. In addition, these results were reproducible and good yields of 2-32 were obtained for all allenes.

Table 7: Copper-mediated photochemical cyclization of cyclohexenol allenes.

<table>
<thead>
<tr>
<th>entry</th>
<th>allene</th>
<th>R</th>
<th>R_1</th>
<th>hv yield 2-32 (%)</th>
<th>hv yield 2-34 (%)</th>
<th>hv/1.5 eq. CuI yield 2-32 (%)</th>
<th>hv/1.5 eq. CuI yield 2-34 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>2-30a</td>
<td>TBS</td>
<td>H</td>
<td>33</td>
<td>34</td>
<td>62</td>
<td>8</td>
</tr>
<tr>
<td>b</td>
<td>2-30b</td>
<td>TIPS</td>
<td>H</td>
<td>31</td>
<td>45</td>
<td>64</td>
<td>5</td>
</tr>
<tr>
<td>c</td>
<td>2-30d</td>
<td>SEM</td>
<td>H</td>
<td>38</td>
<td>51</td>
<td>60</td>
<td>--</td>
</tr>
<tr>
<td>d</td>
<td>2-30e</td>
<td>TBS</td>
<td>CN</td>
<td>27 (2-33e)</td>
<td>43 (2-33e)</td>
<td>62</td>
<td>7 (2-33e)</td>
</tr>
<tr>
<td>e</td>
<td>2-31</td>
<td>H</td>
<td>H</td>
<td>21 (2-32f)</td>
<td>24</td>
<td>60</td>
<td>not isolated</td>
</tr>
</tbody>
</table>
Since copper was clearly identified as the cause of the regioselectivity preference toward C-C cyclized tetracycles, we sought to fully demonstrate the scope and limitations of the copper-mediated, photochemical initiated allenyl azide cycloaddition cascade.

### 2.8 Demonstrating the Scope and Limitations of CuI Mediation.

We next examined several of the previous allenyl azide substrates under the new copper-mediated photochemical conditions. We probed several substrates with various substitution patterns using our optimized conditions (254 nm, 1.5 eq. CuI, MeCN, 5mM in allene). The results are displayed in Table 8.

Table 8: Copper-mediated photochemical cyclization of allenyl azides.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>ratio 2-39 : 2-40</th>
<th>yield 2-39 (%)</th>
<th>yield 2-40 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>CH₃</td>
<td>-(CH₂)₄-</td>
<td>H</td>
<td>H</td>
<td>2-39 only</td>
<td>54</td>
<td>--</td>
</tr>
<tr>
<td>b</td>
<td>CH₃</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>2-39 only</td>
<td>67</td>
<td>--</td>
</tr>
<tr>
<td>c</td>
<td>CH₂OTBS</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>10 : 1</td>
<td>55</td>
<td>3</td>
</tr>
<tr>
<td>d</td>
<td>t-Bu</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>2-39 only</td>
<td>59</td>
<td>--</td>
</tr>
<tr>
<td>e</td>
<td>CH₃</td>
<td>H</td>
<td>TBS</td>
<td>H</td>
<td>2-39 only</td>
<td>44</td>
<td>--</td>
</tr>
<tr>
<td>f</td>
<td>Ph</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>2-39 only</td>
<td>69</td>
<td>--</td>
</tr>
<tr>
<td>g</td>
<td>CH₃</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>2.2 : 1</td>
<td>53</td>
<td>26</td>
</tr>
</tbody>
</table>

*a* Irradiated at 300 nm.

The thermolysis of allenes 2-38a-d was discussed in Chapter 1. We subjected these same allenes to the optimized copper-mediated photochemical conditions. Following suit with the cyclohexenol substituted allenes 2-30 and 2-31, these allenes
gave excellent regioselectivity favoring C-C cyclized indoles 2-39. Almost no trace of C-N cyclized indole 2-40 was detected in the crude photolysate. We also subjected three new allenes with varying substituents to the copper-mediated photochemical conditions (entries e-g). Remarkably, the sensitive vinylsilane allene 2-38e participated in the cyclization to give allylsilane indole 2-39e in moderate yield. Entry f tested a competition between a phenyl and an alkene cyclization terminator. In contrast to allenes 2-7, where cyclization can occur only through an aryl ring (or participate in the observed formal [1,7]-H shift), this allene can cyclize through an alkene or phenyl ring. As anticipated, the cyclization via the alkene is much more favorable than cyclization into the aromatic ring. Thus, only C-C bonded indole 2-39f was obtained in good yield. Entry g also introduces a unique structural feature to the allenyl azide cyclization cascade with its terminal disubstituted olefin. This disubstitution leads to a quaternary center in 2-39g. Fortunately, this allene did not participate in undesired 6π electrocyclization within the (Z)-diphenylvinyl moiety as previously observed in related compounds. This entry is also unique with respect to its diminished regioselectivity for C-C over C-N cyclization (2.2:1), although the isolated yield of 2-39g is comparable to those of 2-391-f. Another caveat regarding the cyclization of allene 2-38g is that there is no significant improvement in regioselectivity with copper (compare to hv, without copper, 1.9:1). The structural assignment of N-cyclized isomer 2-40g was validated by single crystal X-ray analysis. This example prompted us to extend this methodology to construct other quaternary center-containing polycycles from allenes containing a terminally disubstituted olefin (discussed later in this chapter).
The syntheses of allenes 2-38e-g are shown in Figure 43. TBS acetylene (2-41) was subjected to modified Negishi conditions\textsuperscript{30} to give exclusively the (E)-vinyl iodide 2-42. Sonogashira coupling with acetate 2-25 provided enyne 2-43a, which, when subjected to cuprate addition, gave allene 2-38e. Allene 2-38f was made in a one-pot procedure from acetate 2-12 and isopropenyl zincate (generated in situ from the corresponding Grignard reagent) via palladium-mediated cross-coupling. Bromotriphenylethylene (2-44) was subjected to Sonogashira conditions with TMS acetylene and subsequently deprotected with TBAF to reveal the terminal alkyne 2-45. This alkyne was deprotonated with \textit{n}-BuLi, combined with aldehyde 2-11, and the resulting alkoxide

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{synthesis.png}
\caption{Synthesis of allenes 2-38e-g.}
\end{figure}
was then trapped with Ac₂O to provide propargyl acetate 2-43b in good yield. This acetate was subjected to cuprate addition to provide allene 2-38g in moderate yield.

2.9 Mechanistic Investigations.

Although the scope of the copper-mediated allenyl azide cyclization was thoroughly explored, a central mechanistic question remained unanswered: What role does copper play in the allenyl azide cyclization cascade? To shed some light on this issue, we turned to allene 2-38i (Figure 44).

Figure 44: Silylated allenyl azide reaction pathway.

Previous mechanistic studies⁹ on allene 2-38h had shown that the first step in the allenyl azide cyclization cascade was indeed a [3+2] cycloaddition of the azide with the allene to give unobserved intermediate triazoline 2-46a. This species readily undergoes protodesilylation with adventitious acid to give the isolated aromatic triazole 2-47a. With a similar allene 2-38i in hand, we wanted to investigate its reactivity under photochemical conditions (with and without copper) as well as thermal conditions (with and without
copper). If, under the new conditions, the first step is also a [3+2] cycloaddition of the azide with the allene, we expected to observe 2-47b. The outcome of this study is shown in Table 9.

Table 9: Mechanistic investigation of silylated allenyl azide 2-38i.

<table>
<thead>
<tr>
<th>conditions</th>
<th>yield 2-47b (%)</th>
<th>yield 2-39i (%)</th>
<th>yield 2-40i (%)</th>
<th>yield 2-48 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>110 ºC</td>
<td>53</td>
<td>--</td>
<td>--</td>
<td>23</td>
</tr>
<tr>
<td>110 ºC, 1.5 eq. CuI</td>
<td>40</td>
<td>3</td>
<td>--</td>
<td>6</td>
</tr>
<tr>
<td>254 nm</td>
<td>6</td>
<td>28</td>
<td>35</td>
<td>--</td>
</tr>
<tr>
<td>254 nm, 1.5 eq. CuI</td>
<td>8</td>
<td>48</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

In agreement with our previous observations, the thermolysis of allene 2-38i produced the expected triazole 2-47b along with the unexpected formal acetonitrile adduct 2-48 (structure assigned by single crystal X-ray analysis). A similar product distribution is observed from thermolysis in the presence of copper, with the exception that a trace amount of 2-39i is observed as well. To ensure that copper has the best opportunity for interaction with the allene (or reactive intermediates derived there from), we ran this experiment at a concentration of 51 mM in allene, which is nearly saturated in CuI. Upon photochemical irradiation at 254 nm with no copper present, all products observed can be rationalized by invoking the [3+2] cycloadduct 2-46b, although the
lower temperature of the photochemical reaction (35 – 40 °C) might suffice to minimize protodesilylation, thus allowing for loss of N\textsubscript{2} followed by subsequent C-C or C-N cyclization. A divergence in product distribution is observed when allene \textit{2-38i} is subjected to photochemical irradiation in the presence of copper. The C-C bonded isomer \textit{2-39i} is the major product whereas only minor amounts of triazole \textit{2-47b} are formed. The triazole in this instance may be formed by a competitive non-copper-mediated pathway. Formation of the C-N bonded regioisomer is effectively shut down in the presence of copper. In this case as in all of the others, the shift in product distribution with copper present clearly requires consideration of an alternative reaction course compared to the non-copper case. The synthesis of allene \textit{2-38i} is shown in Figure 45.

![Figure 45: Synthesis of allene 2-38i.](image)

\textbf{2.9.1 Initial Speculation.}

We postulated two mechanisms for the role that copper plays. Using allene \textit{2-35} as an example, these putative mechanisms are presented in Figure 46. Allene \textit{2-35} could undergo the expected [3+2] cycloaddition followed by loss of N\textsubscript{2} to give a mixture of indolidenes \textit{2-52/2-53}. These indolidenes could intercept ligated copper to form \textit{2-52a/2-53}. \textit{2-38j}. \textit{2-38k}. \textit{2-38l}. \textit{2-38m}.
53a, respectively. These copper-bound indolenines might possess different reactivities than that of the unbound analogues. In the case of 2-53a, the copper might effectively block cyclization. Another pathway might involve a copper nitrene 2-49, which upon 6π electrocyclization would form metalocycle 2-50. An alternative Z-alkene-containing metalocycle, which would precede 2-53a, might be disfavored on steric grounds (CH₃ rather than cyclohexenyl) proximal to copper and its ligands. This intermediate could

Figure 46: Possible mechanisms for copper-mediated photochemical cyclization of 2-35.
reductively eliminate to form indolidene 2-52a which should cyclize to give C-C bonded isomer 2-54. This mechanism effectively prevents formation of indolidene 2-53, thus preventing C-N cyclization. The predominant formation of 2-47b and 2-48 in the thermolysis/CuI example makes the former process ([3+2] cycloaddition) the most likely. We communicated our discovery with a computational collaborator, Dr. Carlos Silva López, who began a DFT investigation of the copper-mediated allenyl azide cyclization cascade.

2.9.2 Computational Analysis.

DFT calculations aided our understanding of the reaction pathway of the allenyl azide cascade discussed earlier in this chapter and Chapter 1. To this end, allene 2-55 was investigated (using HCN instead of MeCN as Cu ligand for ease of calculation), and the mechanistic profile is shown in Figure 47. Several coordination numbers for copper were probed. Tricoordinated copper was very bulky (hindering the approach of the reaction termini needed to furnish the final indole product) and yielded unreasonable structures within these calculations. Between single and double coordination, it was found that only a small difference existed in both intermediate structures and relative energies. Since it provides the lowest energy pathway, single HCN complexation was chosen as the coordination environment to carry out the mechanistic study.
Without copper present, indolidenes 2-57 and 2-58 do not equilibrate faster than the corresponding electrocyclic ring closures, and so the ratio of indolidene formed dictates the ratio of cyclized product (see Figure 18, Chapter 1). In the case with copper present, calculations suggest that these energies are perturbed. The activation energy for the cyclization of isomer 2-57 into 2-59 is elevated substantially when copper is present compared to the copper-free case (27 vs 18 kcal/mol, respectively), whereas the barrier for the conversion of 2-58 to 2-60 is essentially unperturbed by the presence of copper. Furthermore, the calculated barrier for the conversion of indolidene 2-57 to indolidene 2-58 is lower than the barrier for electrocyclization of 2-57 to 2-59 (24 vs 27 kcal/mol). These calculated values explain nicely how the presence of copper shifts the product ratio to favor C-C cyclization over C-N cyclization by a modulation in activation energies of the intermediate processes. Because of the raise in activation energy for the electrocyclization of 2-57 to 2-59, equilibration of the indolidenes favors indolidene 2-58, and so the product ratio is ultimately shifted toward the C-C cyclized tricycle 2-60. Thus,
the copper-mediated case corresponds to Curtin-Hammett kinetics, whereas the copper-free case does not.

The limitations of the copper-mediated allenyl azide cyclization should not go unmentioned. We synthesized several allenes which, for various reasons, did not lead to cyclized products upon copper-mediated photochemical cyclization (Figure 48).

When the previously reported allene 2-38j decomposed under photochemical conditions, we speculated that the styryl moiety could be absorbing a photon and diverting the reaction process. Allenes containing an (E)-alkyl substituted olefin 2-38k-m were subjected to photochemical conditions with copper, but in each case only uncharacterized decomposition products resulted. Allene 2-38n, with a trisubstituted olefin, also decomposed under all photochemical conditions attempted (254, 300, 350 nm, and Hg lamp). The syntheses of allenes 2-38k-n are shown in Table 10. Two disubstituted allenes, 2-38o-p, only produced uncharacterized decomposition products.

Figure 48: Allenes that failed to produce cyclized products under copper-mediated photochemical initiation.
under all photochemical copper-mediated conditions examined. The syntheses of these two allenes are shown in Figure 49.

Table 10: Synthesis of allenes 2-38k-n.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>yield 2-43 (%)</th>
<th>yield 2-38 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;OTBS</td>
<td>H</td>
<td>74</td>
<td>72</td>
</tr>
<tr>
<td>b</td>
<td>n-hex</td>
<td>H</td>
<td>26</td>
<td>59</td>
</tr>
<tr>
<td>c</td>
<td>(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;OTBS</td>
<td>H</td>
<td>59</td>
<td>31</td>
</tr>
<tr>
<td>d</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;OTBS</td>
<td>Me</td>
<td>68</td>
<td>75</td>
</tr>
</tbody>
</table>

Figure 49: Synthesis of allenes 2-38o-p.

2.10 Attempted Formation of a Quaternary Center.

Another attempted extension of the allenyl azide cascade was inspired by the results obtained with terminally disubstituted alkenyl allene 2-38g. This example showed that terminal disubstitution of the appended alkene could lead to indole products with quaternary all-carbon centers. The scope of constructing quaternary centers with this
methodology warranted further investigation. Allenes \(2-38q-r\) were synthesized to accomplish this goal (Figure 50).

![Chemical structure](image)

**Figure 50:** Synthesis of allenes \(2-38q-r\).

Sonogashira coupling of iodide \(2-61\) with acetate \(2-25\) gave \(2-62\) in very poor yield. Methyl cuprate addition to acetate \(2-62\) provided allene \(2-38q\) in moderate yield. Bromoiodo alkene \(2-61\) was prepared from reduction of the corresponding ethyl ester \(2-65\), followed by TBS protection of the resulting alcohol. Allene \(2-38r\) arose from methyl cuprate addition to acetate \(2-64\), which in turn came from addition of a lithiated alkyne derived from \(2-63\) to aldehyde \(2-11\). Unfortunately, neither of these allenes led to cyclized products upon irradiation in the presence of copper. No identifiable products were obtained from submitting these allenes to known cyclization conditions (thermolysis, photolysis w/ and w/o copper).
One particular terminally disubstituted alkenyl allene 2-70 underwent undesired electrocyclization (Figure 51). Photochemical isomerization of the known iodide 2-66a produced 2-66b, which, after Sonogashira coupling with TMS acetylene, TMS deprotection and alcohol protection, gave alkyne 2-67 in moderate yield over three steps. Addition of the deprotonated alkyne to azido aldehyde 2-11, followed by trapping of the corresponding alkoxide with Ac₂O, gave acetate 2-68a in good yield. Methyl cuprate addition cleanly provided substituted naphthalene 2-69 in moderate yield. This product likely results from a 6π electrocyclization of the phenyl ring with the allene and connecting alkene (2-70), followed by tautomerization of bicycle 2-71. This example was notably different from the successful cyclization of triphenylalkenyl allene 2-38g. We rationalize this difference as a consequence of the additional phenyl group at the R₁ position (Table 8 designation) in 2-38g, which might prevent access to the appropriate planar conformation of the 1,3,5-triene (as drawn in 2-70) required for electrocyclization. Thus, we speculate the conformational consequences of the greater R//R₁ steric interaction in 2-38g (Me//Ph vs Me//H in 2-70) prevent this undesired electrocyclization and allow for the desired alleny l azide cyclization to occur. Sonogashira coupling of acetate 2-25 with the known iodide 2-72 produced enyne 2-68b in poor yield. When subjected to standard cuprate conditions, no allene formation was detected. In this instance, only a complex mixture of unidentified products was observed.
We attempted to synthesize additional terminally disubstituted alkenyl allenes 2-75a-c, but the cuprate addition to acetates 2-74a-c all failed for unknown reasons (Figure 52). We synthesized these acetates from the addition of the lithiates of known bis-alkynes 2-73a-c to aldehyde 2-11 followed by trapping of the corresponding alkoxide with Ac₂O. It became apparent that there was a very narrow structural window for the formation of a stable, terminally disubstituted alkenyl allene. With further investigation, conditions may be uncovered to allow this process to occur with a broader variety of substrates.
The discovery of the copper-mediated photochemical cyclization of allenyl azides proved to be an interesting deviation from the original, copper-free thermal case. The robustness of this new transformation was demonstrated with a variety of allenes. With the exception of allenes 2-38j-p, all other substrates tested participated in this transformation, usually with exceptional regioselectivity for C-C bond formation over C-N bond formation. With the aid of computational tools, a rationale for the copper-mediated divergence in regioselectivity was unveiled. This addition to allenyl azide methodology features excellent selectivity for the synthesis of C(2)-C(3) cyclopentannelated indoles.

2.11 Progress Toward the Fischerindole Alkaloids.

We set out to continue our studies toward the synthesis of the fischerindole alkaloids with the exploration of the copper-mediated photochemically initiated allenyl azide cyclization cascade completed. Several strategies for exploring a model system for these natural products are presented in Figure 53. One of the challenges in completing a synthesis of the fischerindoles involves the trans fusion of the C-D ring system that exists...
in all but one member of this family of alkaloids. We hoped that the stereochemical information at the C-10 and C-11 positions of 2-32 (produced by the allenyl azide cyclization) could be used to influence the stereochemistry at the 15-position (cf. 2-78).

The first route envisioned was the N-protection and oxidation of alcohol 2-32f (R, R1 = H) to the corresponding ketone. This compound should be deprotonated easily, and the corresponding cyclopentadienyl anion should alkylate on the only non-bridgehead carbon, producing the gem-dimethyl C-ring desired for the fischerindoles. Another approach might include cyclopropanating tetracycle 2-32 to give 2-79. This cyclopropane could be hydrogenated to give the gem-dimethyl C-ring 2-80 or the undesired bridgehead-methylated isomer (not shown). If cyclopropane 2-83 could be made, the resulting hydrogenation could only produce the desired gem-dimethyl C-ring 2-80. We thought that this cyclopropane could arise from exocyclic olefin 2-82, which could come from protodesilylation of 2-81. To accomplish this goal, we would have to synthesize the silylmethyl allene 2-84. One last idea involved synthesizing oxygenated allene 2-85 in the hopes that it would also participate in the allenyl azide cyclization cascade to give enol ether 2-86. Revealing the corresponding ketone should allow for gem-dimethylation of the C-ring using standard titanium mediated conditions.

Unfortunately all attempts to oxidize tetracycle 2-32f (R, R1 = H) failed (PCC, TPAP/NMO, Jones, Swern, Dess-Martin periodinane, TEMPO, and BiPh3CO3), giving either no reaction or decomposition. Perhaps the resulting cyclopentadiene 2-76 was formed, but was too sensitive to be isolated or observed. Attempts to form cyclopropane 2-79 via Simmons-Smith conditions on 2-32 also failed. Typically, these attempts resulted in decomposition of the starting tetracycle.
We next sought to synthesize allene 2-84. Fortunately, the cuprate conditions used extensively in this work were amenable to using TMSCH$_2$MgCl instead of
MeMgBr, and so the synthesis of allene 2-84a was accomplished in excellent yield (Figure 54). Allene 2-84a was subjected to thermolysis, photolysis, and photolysis with copper, the results of which are shown in Table 11.

![Figure 54: Synthesis of allene 2-84a.](image)

<table>
<thead>
<tr>
<th>conditions</th>
<th>ratio 2-88:2-89:2-90</th>
<th>yield 2-88 (%)</th>
<th>yield 2-89 (%)</th>
<th>yield 2-90 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>110 °C toluene</td>
<td>0:1.4:1</td>
<td>--</td>
<td>41</td>
<td>35</td>
</tr>
<tr>
<td>hv, 254 nm MeCN</td>
<td>2:1:4</td>
<td>25^a</td>
<td>11</td>
<td>50</td>
</tr>
<tr>
<td>hv, 254 nm MeCN 1.5 eq. CuI</td>
<td>1.6:1:0</td>
<td>not isolated</td>
<td>not isolated</td>
<td>--</td>
</tr>
</tbody>
</table>

^a NMR yield (not isolated)

The results that were obtained from cyclization of allene 2-84a deviated from other examples previously discussed. Under thermal conditions, none of the C-C isomer 2-88 was observed; only the alkene 2-89 and C-N cyclized indole 2-90 were identified. Surprisingly, indole 2-90 does not eliminate TBSOH upon chromatography (structure
established by single crystal X-ray analysis). Photochemical initiation provides a mixture of both expected cyclized tetracycles 2-88 and 2-90 as well as alkene 2-89. We could not isolate the C-C bonded isomer 2-88, due to its instability towards any methods of chromatographic purification attempted (deactivated SiO$_2$, alumina, cold column, or HPLC). Thus, we can only report an $^1$H NMR yield based upon the crude product mixture. The copper mediated photochemical conditions did prevent C-N isomer 2-90 from forming, but alkene 2-89 was formed to a significant extent. The mixture of these two products (2-88 and 2-89) could not be separated by any means at our disposal. Alkene 2-89 likely arises from a formal [1,7]-TMS shift equivalent to that seen in Figure 28 (H = TMS). The corresponding TMS indole is observed in the crude thermolysate/photolysate, but suffers protodesilation upon SiO$_2$ chromatography.

The disappointing results with allene 2-84a prompted us investigate synthesis of the oxygenated allene 2-85. We attempted to perform an isomerization on acetate 2-29a as well as several other propargyl acetates, but these efforts did not meet with success. We decided to thoroughly investigate the isomerization of acetate 2-12. The isomerization product 2-85a was not observed under various metal-mediated conditions (Ag, Au, and Pt)\textsuperscript{36}. Upon elevating the temperature during these attempted isomerizations, the only product observed was triazole 2-91, resulting from a simple [3+2] cycloaddition (Figure 55).
We attempted to attach a protecting group to the indole nitrogen in our efforts to functionalize tetracycles 2-32. The basic conditions of this transformation led, however, to deprotonation of the cyclopentadiene and subsequent elimination of the adjacent alcohol or protected alcohol to give fulvenes 2-92a-b (Figure 56). We also observed oxygen elimination when trying to remove the silicon protecting groups (TBS, TIPS, or SEM). The F⁻ ion is apparently basic enough to effect this elimination as well, as seen in

Figure 55: Thermally induced [3+2] Cycloaddition of acetate 2-12.

Figure 56: Formation of fulvenes 2-92 from tetracycles 2-32.
the conversion of $2\text{-}32d \rightarrow 2\text{-}92c$. We initially assigned the structures of $2\text{-}92a\text{-}c$ based on lack of any diastereotopic proton signals, as well as from the two new $^{13}\text{C}$ NMR signals in the alkene region. Spectroscopic data for $2\text{-}92a$ and $2\text{-}92c$ share many similarities to that of $2\text{-}92b$ whose structure was confirmed by single crystal X-ray analysis.

We next turned to a series of transformations reported by Alabugin and coworkers in the hopes of making use of these fulvenes (Figure 57). They demonstrated that fulvene $2\text{-}93$ could undergo nucleophilic attack at the 6-position by either alkyl lithiate $2\text{-}96$, $n\text{-}\text{BuLi}$, or hydride (from LiAlH$_4$) to give intermediate cyclopentadienyl species $2\text{-}94$ ($n\text{-}\text{BuLi}$ adduct shown), which can be quenched with either a proton to give species $2\text{-}95a\text{-}c$, or with TMSCl to give allylsilane $2\text{-}95d$. Not surprisingly, the cyclopentadienyl anion always quenched with the electrophile ($\text{H}^+$ or TMS$^+$) at the least substituted position of the five-membered ring. We sought to apply this method to fulvene $2\text{-}92a$ to install the gem-dimethyl moiety of the C-ring. Fortunately, this method worked as expected, using LiAlH$_4$ and MeI under the reported conditions to provide $2\text{-}97$ (Figure 58). Unfortunately, this transformation left the D-ring devoid of functionality for further manipulation. All attempts to use a heteroatom nucleophile (TMSO$^-$ and BnNH$^-$) in the hopes of installing the isonitrile group found in the fischerindoles failed, most likely due to the reversibility of the addition (i.e., the cyclopentadienyl anion ejects RO$^-$ or R$_2$N$^-$). We also were unable to effect this transformation with cyano-fulvene $2\text{-}92b$. Additionally, we attempted a conjugate addition to the extended unsaturated cyanide with methyl cuprate, with the hope of installing the C-ring gem-dimethyl. Unfortunately, no reaction was observed. When an excess amount of cuprate was used,
only decomposition ensued. If these additions could be accomplished, a facile route to a functionalized fischerindole core would result.

During our investigation of functionalizing tetracycles 2-32, we discovered that hydrogenation of benzylated indole 2-32c failed to remove the benzyl group, but did cleanly hydrogenate the tetrasubstituted olefin within the five-membered ring to give a
single diastereomer 2-98c. We also hydrogenated several other indole tetracycles, all of which gave a single diastereomeric product in very good yield (Table 12). The stereochemistry of tetracycle 2-98e was secured by single crystal X-ray analysis. The syn stereochemistry at the 5-6 (C-D) ring fusion does not map into the structures of the fischerindoles (2-13a-d). However, cis-fused fischerindole L (2-13e) might be accessed via this methodology. All attempts to obtain the anti stereochemistry at the C-D ring fusion via other hydrogenation catalysts (Crabtree’s and Wilkinson’s catalyst) resulted in no reaction, even at elevated pressure (500 psi).

Table 12: Hydrogenation of indole tetracycles 2-32.

<table>
<thead>
<tr>
<th>indole tetracycle</th>
<th>R</th>
<th>Rᵢ</th>
<th>yield 2-98 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-32a</td>
<td>TBS</td>
<td>H</td>
<td>100</td>
</tr>
<tr>
<td>2-32c</td>
<td>Bn</td>
<td>H</td>
<td>71</td>
</tr>
<tr>
<td>2-32e</td>
<td>TBS</td>
<td>CN</td>
<td>90</td>
</tr>
<tr>
<td>2-32f</td>
<td>H</td>
<td>H</td>
<td>65</td>
</tr>
</tbody>
</table>

We envisioned the synthesis of a fischerindole L model system 2-99 based on the results obtained from the hydrogenation of indoles 2-32, (Figure 59). We planned to install the gem-dimethyl of the C-ring via an enolate, which could arise from aldehyde 2-100. This aldehyde could come from hydrogenation and oxidation of alcohol 2-101. This tetracycle was predicted to arise from the copper-mediated photocyclization of
allene 2-102, which could stem from palladium coupling of acetate 2-103\textsuperscript{11} and zincate 2-104.

![Diagram of synthetic pathway]

Figure 59: Restrosynthesis of functionalized tetracycle 2-99.

We suspected that a major challenge in this route would likely involve successful generation of alkenyl zincate 2-104 for the Pd\textsuperscript{0} mediated cross coupling. Fortunately, straightforward conditions of lithium-halogen exchange of iodide 2-28a using t-BuLi, followed by transmetalation with ZnCl\textsubscript{2}, generated zincate 2-105 in situ which coupled nicely with acetate 2-103 to provide allene 2-106 in 64\% yield (Figure 60). Copper-mediated cyclization furnished the desired tetracycle 2-107 in 59\% yield as the only product. Since we knew from previous efforts that the D-ring TBS group could not be removed under room-temperature flouride conditions, we subjected indole 2-107 to TBAF at 0 \degree C and were delighted to obtain alcohol 2-108 in good yield.
We then subjected both indoles 2-107 and 2-108 to standard hydrogenation conditions and obtained the expected syn diastereomers in good yield (Figure 61). We also attempted other hydrogenation conditions (Crabtree’s, and Wilkinson’s catalyst) to fashion the anti ring fusion stereochemistry, but no reaction was observed under these conditions.

Although we were unable to obtain the desired anti ring fusion to exploit in fischerindole synthesis (2-13a-d), application of the chemistry detailed in Figure 59 with indole 2-110 makes a very promising start toward completing a model system for fischerinole L (2-13e).
2.12 References.


37  Kovalenko, S. V.; Peabody, S.; Manoharan, M.; Clark, R. J.; Alabugin, I. V. Org. Lett. 2004, 6, 2457.
Chapter 3
Total Syntheses of the Kinamycins.

3.1 Introduction.

The diazoparaquinone family of antibiotics represents the most prevalent class of the few diazo-containing natural products known. Representative members are the kinamycins (3-1a-j), prekinamycin (3-2) and isoprekinamycin (3-3), and the dimeric diazoparaquinone lomaiviticin A (3-4) (Figure 62). Many members of this structural family possess anti-cancer activity in the nanomolar-to-low micromolar range. Their architectural similarities lie in the core 6-6-5-6 ring system as well as a highly oxygenated D-ring. Prekinamycin (3-2) shares this architectural similarity, but has an aromatic D-ring. As a result of the simplified structure of prekinamycin 3-2, several direct total syntheses have been reported.

Biological activity data on several diazoparaquinones recently have been reported. Several members of this family have been investigated for anti-cancer activity. The most potent of these compounds is lomaiviticin A (3-4), which, against a number of cancer cell lines, showed cytotoxicity with IC$_{50}$ values ranging from 0.01 to 98 ng/mL. Of note were the IC$_{50}$ values for HL60 leukemia (0.7 nM), A549 lung (3.5 nM) T47D brain (1.8 nM), HCT15 colon (6.0 nM), and A2780DDP ovarian (4.8 nM). Lomaiviticin A (3-4) is also reported to cleave double-stranded DNA under reducing conditions.
Skibo and coworkers have shown that simple prekinamycin derivatives, such as the di-\textit{O}-methyl ether, display IC$_{50}$ values of 0.4 – 1.3 µg/mL against several cancer cell lines (BxPC-3 pancreas, MCF-7 breast, SF-268 CNS, H460 NSC lung, KM 20L2 colorectal, and DU-145 prostate).$^{41}$

Figure 62: The kinamycins, prekinamycins, and lomaivitinc A.

In 2006, Hasinoff and Dmitrienko reported that both kinamycin A (3-1a) and C (3-1c) had very potent cell growth inhibitory effects on Chinese hamster ovary (CHO) cells and human leukemia K562 cells.$^{39a}$ Specifically, cell cycle analysis showed that kinamycin C (3-1c) induced a rapid apoptotic response in K562 cells. In 2007, these
same authors reported IC$_{50}$ values for 72 h growth inhibition of K562 cells for kinamycin F (3-1f, 0.33 µM), A (3-1a, 0.31 µM), and C (3-1c, 0.37 µM). They also reported that kinamycin F (3-1f) promoted single-strand cleavage of the closed circular plasmid pBR322 DNA at 0.20 mM in the presence of physiologically relevant levels (5 mM) of glutathione (at 37 °C). In a separate experiment, glutathione was shown to reductively activate kinamycin F to produce reactive radical species. Despite these in vitro results, the authors demonstrated that in an in vivo environment, kinamycin F induced single-strand DNA damage in K562 cells independent of glutathione concentration. They also demonstrated that kinamycin F weakly binds to DNA.

Shortly thereafter, Melander and coworkers disclosed that 0.25 mM kinamycin D (3-1d) (which probably gets hydrolyzed to kinamycin F (3-1f) under their assay conditions) also promotes single-strand cleavage of pBR322 supercoiled DNA in the presence of 0.57 mM glutathione at 37 °C. The accumulated biological data does not yet permit definitive refinement of a cellular, a biochemical, or a chemical mechanism-of-action for the diazoparaquinones. Dmitrienko, Skibo, Melander, and Feldman each have described/demonstrated alternate, viable mechanism-of-action proposals for the diazoparaquinones. Currently, the bioreductive activation process by which the kinamycins become DNA-damaging agents is not known. Thus, it remains to be seen what the exact role of the diazo group plays, and whether a single or double electron reduction process produces the active DNA-damaging kinamycin species.
3.2 Kinamycin Syntheses.

In recent years, three total syntheses of the kinamycins 3-1 have been reported by the Porco, Nicolaou and Kumamoto-Ishikawa groups. Each route utilizes very different chemistry to functionalize the highly oxygenated D-ring. Also, these routes differ greatly in the key bond-forming step to assemble the respective tetracycles (Figure 63). Porco and Nicolaou both connect the A-B and D-ring fragments via Pd cross-coupling reactions. Porco closes the C-ring via an intramolecular Friedel-Crafts annulation, whereas Nicolaou closes the C-ring by a benzoin—type reaction. By utilizing a Diels-Alder cycloaddition to append the D-ring (diene) to the A-B-C-ring (dieneophile), Kumamoto-Ishikawa’s key ring forming reaction differs greatly from the other two approaches.

Figure 63: Key disconnections used in the three syntheses of the kinamycins.
3.3 Porco’s Total Synthesis of (-)-Kinamycin C.

In 2006, Porco and Lei reported the total synthesis of (-)-kinamycin C (3-1f). This accomplishment represented the first synthesis for any member of this class of natural products. Their synthesis involved a Stille coupling to join the A-B and D ring fragments. The C-ring was later closed using a Friedel-Crafts-based cyclization. The stereochemical control for the highly oxygenated D-ring stemmed from a directed, asymmetric nucleophilic epoxidation reaction. Installation of the diazo group proceeded via oxidation of the corresponding TBS hydrazone.

The synthesis of the D-ring fragment 3-12 began with the readily available dihydroquinone 3-5 (Figure 64). A selective phenol methylation, followed by reduction of the aldehyde, gave diol 3-6 in very good yield. Oxidation, transketalization, and subsequent TBS protection produced ketal 3-7. A Baylis-Hillman reaction with paraformaldehyde installed the critical alcohol unit of 3-8 required for the subsequent tartrate-mediated asymmetric nucleophilic epoxidation. This epoxidation proceeded in excellent yield with 90% ee to give the desired chiral alcohol 3-9. Hydroxyl directed reduction followed by selective mesylation of the primary alcohol yielded 3-10. Reductive demesylation and subsequent deprotection of the ketal revealed the Stille coupling fragment 3-12 in very good yield.
Synthesis of the arylstannane fragment for the Stille coupling started with readily available quinone 3-13 (Figure 65). MOM protection of the A-ring phenol was followed by reduction of the B-ring quinone to the corresponding dihydroquinone, and a final MOM protection gave bromide 3-15. This bromide was stannylated with bis-(tributyltin) under Pd$^0$ cross-coupling conditions at elevated temperature to give the arylstannane fragment 3-16 for Stille coupling.

Figure 65: Synthesis of the arylstannane fragment 3-16 for Stille coupling.
Completion of the synthesis proceeded via a Stille coupling of the two fragments 3-12 and 3-16 to provide 3-17 (Figure 66). Manipulation of the D-ring began with hydride reduction of the ketone and epoxide-opening with Bu₄NOAc and Ti(Oi-Pr)₄ to generate triol 3-18. Acetylation of the D-ring secondary alcohols followed by removal of the TBS group gave 3-19. Oxidation of this primary alcohol to the carboxylic acid 3-20 proceeded in good yield. A TFAA-mediated Friedel-Crafts reaction closed the C-ring and removed two MOM groups simultaneously to produce tetracyle 3-21. Removal of the remaining MOM group proceeded in refluxing CBr₄, followed by Pd/C-air oxidation of the dihydroquinone gave the B-ring quinone 3-22. Bis-(TBS)hydrazine was condensed with 3-22 and the resulting hydrazone then was oxidized with PhIF₂ to complete the first total synthesis of (-)-kinamycin C (3-1c).
3.4 Kumamoto and Ishikawa’s Total Synthesis of (±)-O-Methyl-Kinamycin C.

A racemic synthesis of a kinamycin C analogue (O-methyl-kinamycin C)\(^\text{46}\) was reported in 2007 by the Kumamoto-Ishikawa group.\(^\text{47}\) They did not report any attempt to demethylate the A-ring to complete the synthesis of kinamycin C. Their synthesis differs...
greatly from the other two approaches discussed in this chapter. The tetracycle was assembled by joining the A-B-C ring fragment enone with a Danishefsky-type diene in a [4+2] cycloaddition. Once the tetracycle was formed, a series of functional group manipulations provided the highly oxygenated D-ring which matched that of kinamycin C. The stereochemistry within the D-ring stemmed from the diastereoselectivity of the [4+2] cycloaddition.

Synthesis of the A-B-C ring fragment began with acetylation of naphthalene-1,5-diol (3-24) to give 3-25 (Figure 67). Oxidative bromination in aqueous AcOH produced 2-bromo-5-O-acetyl juglone (3-26). The acetate was hydrolyzed and the resulting phenol was methylated, yielding 3-27. Reduction of the quinone and subsequent methylation of the phenols gave 3-28. Lithium-halogen exchange with BuLi followed by quenching of the resulting aryl lithiate with DMF produced aldehyde 3-29. Knoevenagel condensation of 3-29 with malonic acid provided enone 3-30 in excellent yield. Hydrogenation of 3-30 under standard conditions followed by an intramolecular Friedel-Crafts acylation of acid 3-31 gave benz[f]indenone 3-32 in good overall yield. Dehydrogenation of 3-32 with IBX produced the desired benz[f]indenone A-B-C ring fragment 3-33.
Installation of the D-ring proceeded via a [4+2] cycloaddition with Danishefsky-type diene 3-34 with enone 3-33 to provide tetracycle 3-35 as a single diastereomer (Figure 68). Treatment of 3-35 with CSA revealed the ketone and eliminated MeOH to give enone 3-36. Air oxidation of 3-36 in the presence of KF provided alcohol 3-37 as a single diastereomer.

Directed dihydroxylation gave the all cis triol 3-38, which upon treatment with TMSOTf/Et3N gave silyl enol ether 3-39 in good yield. Epoxidation of the silyl enol ether produced ketone 3-40 with the incorrect configuration at position 1. Epimerization at this position occurred under storage of crude 3-40 at 4 °C for one month, followed by
storage at rt for 3-4 days to provide the desired stereochemistry in 3-41. Protodesilylation of 3-41, followed by acetylation of the secondary alcohols produced diol 3-42. Diastereoselective reduction of the ketone yielded alcohol 3-43 as a 5:1 mixture in favor of the desired stereochemistry at position 2. Formation of the ketal resolved this diastereomeric mixture and dehydrated the C-D ring juncture, providing 3-44 as a single diastereomer. Completion of the synthesis of (±)-O-methyl-kinamycin C (3-45) was achieved by removal of the ketal, acetylation of the secondary alcohol, condensation of the ketone with tosylhydrazone, and, finally, oxidation with CAN to reveal the quinone and diazo functionality.
Figure 68: Completion of O-methyl-kinamycin C.
3.5 Nicolaou’s Total Synthesis of Kinamycins C, F, and J.

In 2007, Nicolaou and coworkers reported the second enantioselective total synthesis of kinamycin C (3-1c) as well as the first total syntheses of kinamycins F (3-1f) and J (3-1j). Their syntheses are highlighted by the joining of the A-B ring fragment with the D-ring fragment via an Ullmann-type coupling. Closure of the C-ring is achieved via a benzoin-like condensation to complete the tetracyclic core of the kinamycins. Through late stage manipulation, the precursor of kinamycin C was converted to kinamycin F (3-1f) and J (3-1j) in 1 and 2 steps, respectively.

Nicolaou began his synthesis of the A-B ring coupling partner 3-51 with a radical allylation of the available bromoquinone 3-16 to provide quinone 3-53 in good yield (Figure 69). Subsequent A-ring benzyl protection followed by reduction of the quinone and methylation of the corresponding dihydroquinone yielded protected bicycle 3-54. Treatment of 3-54 with tert-butoxide brought the olefin into conjugation with the aromatic system, providing isomer 3-55 in excellent yield. Oxidative cleavage of this alkene with OsO₄/NaIO₄ produced the desired aldehyde 3-51.
Construction of the D-ring began with methyl cuprate addition to the known enone 3-52 followed by Saegusa oxidation of the resulting silyl enol ether to produce adduct 3-56 (Figure 70). Stereoselective dihydroxylation of the olefin occurred in good yield to provide diol 3-57, which was protected as the corresponding acetonide 3-58 in excellent yield. Enolization of the ketone in the presence of TMSCl produced the

Figure 69: Nicolaou’s synthesis of A-B ring fragment 3-49.

Figure 70: Nicolaou’s construction of D-ring fragment 3-55.
corresponding silyl enol ether, which underwent a second Saegusa oxidation to establish enone 3-59 in good yield. The D-ring fragment 3-50 was completed with an α-iodination of 3-59.

Assembly of the tetracyclic core began with an Ullmann-type coupling of the two synthesized fragments 3-50 and 3-51 to provide 3-49 in good yield (Figure 71). A benzoin-type reaction using Rovis’ catalyst (3-60) successfully closed the C-ring to produce alcohol 3-61 in good yield. This alcohol was acetylated, exposed to SmI₂, and then treated with Et₃N to cleave the acetate and migrate the double bond into conjugation with the C-ring ketone. Allylic oxidation of the resulting fluorenone (not shown) with SeO₂ installed the alcohol at the 4 position (author’s numbering) to provide 3-48 as a single enantiomer. Removal of the TBS group followed by acetylation of the secondary alcohols and hydrogenolysis of the A-ring benzyl ether gave phenol 3-62. TBS protection of the A-ring phenol and condensation of the ketone with tosyl hydrazone was followed by oxidation with CAN to reveal the quinone and diazo groups in 3-47. This diazoquinone serves as a common intermediate for all three of the kinamycins synthesized. Treatment of 3-47 with dilute HCl removed the A-ring TBS group to complete the synthesis of (-)-kinamycin C (3-1c). Acetylation of the tertiary alcohol followed by treatment with dilute HCl furnished (-)-kinamycin J in good yield (3-1j). Finally, from intermediate 3-47, global deprotection of the acetate and TBS protecting groups with LiOH finished the synthesis of (-)-kinamycin F (3-1f).
Figure 71: Completion of kinamycin C, J and F.


Chapter 4

Efforts Toward the Total Synthesis of (-)-Kinamycin F.

4.1 Introduction.

(-)-Kinamycin F (3-1f) was chosen as a synthesis target within the kinamycin family because, under physiological conditions, it is likely that the acetates of the other kinamycins hydrolyze to produce kinamycin F before any relevant biological interaction takes place. Unlike the other kinamycins, a synthesis of kinamycin F avoids the task of differentially acylating the D-ring tetraol.

Whereas the kinamycin syntheses reported in Chapter 3 began with very simplified D-ring starting materials, our strategy was to use a more highly functionalized D-ring unit that builds upon a route reported in 2001 by Banwell and McRae (Figure 72). The commercially available (1S-cis)-3-bromo-3,5-cyclohexadiene-1,2-diol (4-1) was protected as the corresponding acetonide 4-2, followed by epoxidation of the more electron rich olefin to give epoxide 4-3. Ring-opening of the epoxide with HO⁻ produced the trans-diol 4-4. Deprotection of the acetonide with acid produced the tetraol 4-5 in very good yield. This species could be selectively tri-silylated with TBSCI and imidazole at elevated temperature to give alcohol 4-6 in good yield. With the exception of the missing methyl at position 5, this cyclohexene contains the correct stereochemistry of that found in the D-ring of the kinamycins 4-7.
4.2 Previous Contributions from the Feldman Lab.

Efforts toward a total synthesis of (-)-kinamycin F (3-1f) began in the Feldman laboratory with contributions from Dr. Angela L. Perkins. These efforts allowed access to the fully functionalized D-ring bromide (Figure 73). Oxidation of Banwell’s alcohol 4-6 with Dess-Martin periodinane produced ketone 4-8. This ketone was treated with MeLi, which successfully gave alcohol 4-9 as a single diastereomer in excellent yield. Protection of the tertiary alcohol was accomplished by treatment with TMSOTf, providing bromide 4-10. Unfortunately, an early route utilizing this intermediate failed to advance toward kinamycin F. The problem stemmed from the lability of the tertiary trimethylsilyl ether functional group.
A continuing effort toward kinamycin F was taken on by Dr. Kyle J. Eastman. Once it was discovered that the TMS protecting group on the tertiary alcohol was incompatible with several later transformations, other groups were examined, and benzyl ethers were chosen in this revised approach to kinamycin F. Deprotection of the three silyl ethers was achieved with TBAF/THF to yield tetraol 4-11 quantitatively (Figure 74). This tetraol was previously reported as a brown oil, but we later found that an alternate purification provided 4-11 as a white solid. We used this solid to verify the structure by single crystal X-ray analysis. A global protection of the alcohols with NaH and BnBr produced tetrabenzyl ether 4-12 in good yield. Functionalizing this substrate was achieved through Li-Br exchange with t-BuLi followed by quenching of the corresponding vinyl lithium with CO$_2$ to produce carboxylic acid 4-13. Disappointingly, this substrate did not lead to further progress towards (-)-kinamycin F. In this case, downstream attempts at a Nazarov-type closure of the C-ring on a pre-formed A-B-ring template did not lead to any productive cyclization.
Further progress on this total synthesis project was made by Ms. Lauren A. Sanford. In this approach to the target tetracycle, a strategy featuring Hauser annulation-type addition of a preformed A-B-ring to a C-D-ring was planned. The construction of the C-D-ring synthon follows. The tetrabenzyl ether 4-12 was subjected to Li-Br exchange, and the resulting cyclohexenyl lithiate cleanly reacted with commercially available Weinreb amide 4-14 to produce enone 4-15 (Figure 75). Through a screening of many vinyl cuprate conditions, transmetalation of tetravinyltin with MeLi followed by addition to CuI proved successful for 1,4 vinyl addition to enone 4-15. This reaction was carried out in the presence of TMSCl to trap the enolate as the corresponding silyl enol ether 4-16 (not isolated). Failure to trap this enolate led to some β-elimination of the axial OBn at position 4. Protodesilation of 4-16 with catalytic CSA in MeOH revealed the ketone 4-17. The terminal olefin was subjected to ozonolysis, which produced the

Figure 74: Eastman’s contribution toward the current (−)-kinamycin F synthesis.
corresponding aldehyde 4-18. Subjecting this ketoaldehyde to a variety of aldol conditions produced only a low yield of the desired C-D-ring cyclopentenone plus a complex mixture of other products.

![Chemical structures and reactions]

Figure 75: Sanford’s contribution toward the current (-)-kinamycin F synthesis.

Synthesis of the A-B-ring fragment began with benzyl protection of commercially available amide 4-20 to yield 4-21. Directed ortho metalation of 4-21 followed by DMF
addition produced aldehyde 4-22. This aldehyde was subjected to lactonization with sodium benzenesulfinylate to provide the sulfone 4-23 in poor yield. All attempts at a Hauser annulation\textsuperscript{52} between 4-23 and 4-19 did not produce the desired tetracycle 4-24. Small amounts of tetracyclic material in which the C4 OBn function suffered elimination appeared to be formed in this transformation.

4.3 Current Progress Toward (-)-Kinamycin F.

The first step toward a completing the kinamycin F synthesis was the optimization of the intramolecular aldol condensation that produced 4-19. A list of optimized conditions is shown in Table 13. The highest yield of 4-19 was obtained by treating 4-18 with pyrrolidine and CSA in the presence of 4Å molecular sieves (entry j). With the cyclopentenone readily available, we began investigation of the Hauser annulation. After the disappointing results with sulfone 4-23, we looked to an alternative A-B-ring fragment. In 2007, Nicolaou and coworkers reported very promising results with a similar Hauser annulation A-B-ring fragment.\textsuperscript{53} Their lactone differed in that the sulfone functionality was replaced with a cyanide group. We used their method to prepare the analogous cyanide-bearing lactone 4-25 (Figure 76).
Table 13: Optimization of intramolecular aldol reaction of 4-18.

<table>
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<tr>
<th>entry</th>
<th>reagent(s)</th>
<th>temp (°C)</th>
<th>solvent</th>
<th>time</th>
<th>result</th>
</tr>
</thead>
<tbody>
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<td>a</td>
<td>piperidine•AcOH (1)</td>
<td>60-70</td>
<td>MeOH</td>
<td>12 h</td>
<td>17% 4-19 + 14% 4-19a</td>
</tr>
<tr>
<td>b</td>
<td>piperidine•AcOH (1), 4 Å M.S.</td>
<td>60-70</td>
<td>tol.</td>
<td>24 h</td>
<td>7% 4-19 + 53% 4-18</td>
</tr>
<tr>
<td>c</td>
<td>piperidine•TFA (1)</td>
<td>60-70</td>
<td>tol.</td>
<td>24 h</td>
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<tr>
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<td>rt</td>
<td>MeOH</td>
<td>12 h</td>
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</tr>
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<td>tol.</td>
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</tr>
<tr>
<td>g</td>
<td>piperidine•AcOH (2)</td>
<td>60-70</td>
<td>tol.</td>
<td>24 h</td>
<td>16% 4-19 + 67% 4-18</td>
</tr>
<tr>
<td>h</td>
<td>HCl/dioxane (2)</td>
<td>rt</td>
<td>tol.</td>
<td>15 min</td>
<td>45% 4-19a</td>
</tr>
<tr>
<td>i</td>
<td>pyrrolidine (12), CSA (10), 4 Å M.S.</td>
<td>rt</td>
<td>tol./ MeOH</td>
<td>10 min</td>
<td>51% 4-19</td>
</tr>
<tr>
<td>j</td>
<td>pyrrolidine (3), CSA (1.5), 4 Å M.S.</td>
<td>rt</td>
<td>C6H6</td>
<td>2 h</td>
<td>70% 4-19</td>
</tr>
</tbody>
</table>

entries a-g performed by Ms. Lauren A. Sanford

Figure 76: Synthesis of cyano-lactone 4-25.
We were delighted to observe that Nicolaou’s Hauser conditions to joined 4-25 and 4-19 to give tetracycle 4-24 in 90% yield (Figure 77). Applying these same conditions with the sulfone 4-23 did not produce any of the desired product (Figure 75). Three major tasks lay ahead for the completion of (-)-kinamycin F: (1) Oxidation of the C-D ring juncture. (2) Removal of all of the benzyl protecting groups. and (3) Installation of the diazo function. Attempts to remove the benzyl ethers of 4-24 under standard conditions (H₂, Pd/C) only produced a complex mixture. A variety of

![Chemical diagram](image_url)

Figure 77: Completion of the kinamycin tetracycle and subsequent oxidation.
conditions were screened for the oxidation of 4-24 in the hopes of introducing the quinone and the C-D-ring unsaturation simultaneously. Manganese dioxide proved to be the only oxidant that cleanly yielded a single, isolable product. Upon exposure to 20 equiv. of MnO₂, 4-24 produced dihydroquinone 4-27 in 55% yield. We rationalize the mechanistic course of this transformation by suggesting initial oxidation of the B-ring dihydroquinone to 4-24 to quinone 4-26a. This process likely decreases the pKa of the proton at position 11b. Tautomerization of 4-26a to 4-26b followed by a subsequent tautomerization of the remaining bridgehead proton would lead to the observed oxidized product 4-27. Note that enolization of the cyclopentenone towards C4a never occurs, and so the C4 OBn group survives.

At this stage, we attempted to remove the benzyl ethers. However, under standard hydrogenolysis conditions we were not able to remove all of the benzyl ethers. Instead, we consistently obtained a product which appeared to be “NMR silent”, 4-28. This result was not altogether unexpected from prior studies of the similarly substituted, NMR silent kinobscurinone (4-28a) (Figure 78). Spectral data on this compound were obtained by derivatization as its per-acetate 4-28c. Upon acylation of 4-28, a new compound was obtained, 4-28b, which contained three acetates and thirteen aromatic protons, indicating that two benzyl ethers remained. We assigned the structure as 4-28b based on HMBC/HMGC/NOESY correlations. The tertiary benzyl ether may be left intact due to steric congestion, preventing coordination with the hydrogenation catalyst.
Other hydrogenolysis conditions were explored on substrate 4-27. However, no conditions examined ever produced the desired fully deprotected tetracycle (Table 14). High pressure hydrogenolysis (up to 2000 psi) also failed to remove all the benzyl ethers. Alternative hydrogenation catalysts were employed (Pd black, Raney Ni, PtO₂, and Pd(OH)₂/C), none of which produced the desired fully deprotected tetracycle. Solvent seemed to have no effect on these hydrogenolyses. Transfer hydrogenolysis with formic acid solution failed to remove any of the benzyl ethers of 4-27. We also tried removal of the benzyl ethers with BCl₃, and BBr₃, but only decomposition ensued. Treatment of 4-27 with excess DDQ resulted in no reaction.

Figure 78: Acylation of NMR silent compound 4-28 and kinobscurinone (4-28a).
We therefore looked at alternate protecting groups for the alcohols as the failure of the benzyl ether route became apparent. Revisiting the tetraol 4-11, we sought to append protecting groups that are known to be easier to remove than benzyl ethers, but could also withstand the conditions employed in the late stage conversions already developed. We synthesized the tetra-PMB ether 4-29 and tetra-naphthyl ether 4-30 using similar conditions as with the synthesis of the tetra-benzyl analogue 4-12 (Figure 79).

While PMB-protected bromide did not provide the desired enone 4-31 under the previously reported conditions, the NAP-protected bromide did yield the desired enone 4-32 in moderate yield (unoptimized). At this stage, we decided to attempt removal of the NAP groups using non-hydrogenolytic conditions. Exposure of 4-32 to DDQ yielded the

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>solvent</th>
<th>time</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Pd/C 10%, 1 ATM H₂</td>
<td>THF</td>
<td>20 h</td>
<td>64% 4-28</td>
</tr>
<tr>
<td>b</td>
<td>Pd/C 10%, 1 ATM H₂</td>
<td>Et₂O/MeOH</td>
<td>16 h</td>
<td>55% 4-28</td>
</tr>
<tr>
<td>c</td>
<td>BCl₃ (15 equiv.), -78 °C</td>
<td>CH₂Cl₂</td>
<td>5 min</td>
<td>decomp.</td>
</tr>
<tr>
<td>d</td>
<td>BBr₃ (20 equiv.), -78 °C</td>
<td>CH₂Cl₂</td>
<td>5 min</td>
<td>decomp.</td>
</tr>
<tr>
<td>e</td>
<td>Raney Ni, 1 ATM H₂</td>
<td>EtOH</td>
<td>16 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>f</td>
<td>PtO₂, 1 ATM H₂</td>
<td>MeOH/THF</td>
<td>24 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>g</td>
<td>Pd black 1100 psi H₂</td>
<td>MeOH/THF</td>
<td>100 h</td>
<td>55% 4-28</td>
</tr>
<tr>
<td>h</td>
<td>Pd/C 10%, 2000 psi H₂</td>
<td>THF</td>
<td>24 h</td>
<td>35% 4-28</td>
</tr>
<tr>
<td>i</td>
<td>Pd/C 10%, 500 psi H₂, 45 °C</td>
<td>MeOH/THF</td>
<td>48 h</td>
<td>40% 4-28</td>
</tr>
<tr>
<td>j</td>
<td>Pd black, HCO₂H</td>
<td>MeOH</td>
<td>24 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>k</td>
<td>DDQ (30 equiv.)</td>
<td>CH₂Cl₂/H₂O</td>
<td>4 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>l</td>
<td>Pd(OH)₂, 1 ATM H₂</td>
<td>MeOH</td>
<td>24 h</td>
<td>no reaction</td>
</tr>
</tbody>
</table>
deprotection by-product 2-naphthaldehyde (4-33) in 87% yield (unoptimized), indicating that removal of all four NAP groups is attainable under these conditions. We were unable to isolate the deprotected tetraol. Thus, the NAP protecting group may prove useful in the kinamycin F synthesis efforts.

We chose to revisit the protection of the tertiary alcohol 4-9 during our investigation of alternate protecting groups for the D-ring. Previous results had indicated that protection of this alcohol was very difficult, and only TMSOTf had successfully been employed in this endeavor to synthesize 4-10. In a two step sequence, ketone 4-8 was subjected to MeLi and the crude tertiary alcohol was protected as the NAP ether in 62% over two steps (Figure 80). The success of this transformation has a noteworthy impact on the length of the kinamycin F route. With the ability to protect the tertiary alcohol

Figure 79: Synthesis of PMB and NAP protected D-ring vinyl bromides.
without resorting to a global deprotection/reprotection sequence (i.e., \(4-9 \rightarrow 4-12\), Figure 74), we effectively have one less step to get to the Hauser annulation reaction. In a one-time attempt, Li-Br exchange on \(4-34\) produced the desired enone \(4-35\) in very poor yield. At this juncture, we again wanted to demonstrate that we could remove the NAP protecting group. Treatment of \(4-35\) with DDQ produced the tertiary alcohol in very good yield. We anticipate that removal of the TBS protecting groups can be achieved under mildly acidic conditions, as demonstrated by a similar late stage conversion in Nicolaou’s total synthesis of kinamycins C, F, and J (Chapter 3).

Completion of the C-D-ring cyclopentenone should proceed using the previously optimized conditions for the tetra-benzyl protected D-ring. The A-ring phenol can be protected with a variety functional groups tolerant to the Hauser annulation and the NAP group is suggested by the results above. Joining these two fragments should proceed under the optimized conditions used to construct \(4-24\). Overall, our synthesis of

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**Figure 80**: Successful protection and deprotection of the tertiary alcohol.
kinamycin F (3-1f) promises to be shorter than the previously reported routes (Porco - 26 linear steps to kinamycin C (3-1c), and Nicolaou - 18 linear steps to kinamycin F (3-1f)). With the current progress at hand, we envision a ten-step sequence leading to the tetracyclic core, followed by oxidation, deprotection(s) and diazo formation to give the desired natural product in 13-14 steps. The highlight of this route is the convergent assembly of the tetracycle in one step via a Hauser annulation. Additionally, by using the stereochemistry inherent in diol 4-1, we were able to use substrate control to rapidly provide the fully functionalized D-ring appropriate for the total synthesis of (-)-kinamycin F (3-1f).

4.4 References.


5.1 Introduction.

Plants, green algae, and cyanobacteria are responsible for converting light energy into chemical energy through the process of photosynthesis. All non-photosynthetic organisms depend on the fixed carbon and oxygen produced by this process for their existence. Photosynthesis converts solar energy into chemical energy by way of two protein complexes called photosynthetic reaction centers: photosystem I (PS I) and photosystem II (PS II). The absorption of a photon causes an electron to occupy the singlet excited state and then become translocated across a membrane by a chain of cofactors. The terminal electron acceptor in PS I is a protein-bound Fe₄S₄ cluster, which donates an electron to the soluble protein ferredoxin, a carrier protein. The end result is the reduction of NADP⁺ to NADPH. Photosynthetic reaction centers utilize several transmembrane spanning proteins and various cofactors, such as quinones which function as single electron acceptors. Phylloquinone (5-1, A₁) (Figure 81) is a cofactor found in

Figure 81: Phylloquinone (5-1),
the chain of one-electron acceptors in PS I. It accepts an electron from the primary donor, a chlorophyll monomer. The reduced phylloquinone then donates the electron to F$_x$, a Fe$_4$S$_4$ cluster. The reduction potential of phylloquinone (5-1) in PS I is estimated to be between -700 and -820 mV vs. SHE,$^{56}$ making it one of the most reducing in all of nature. The single electron reduction potential for phylloquinone in DMF is estimated to be 310 mV more oxidizing,$^{57}$ indicating an important role of the protein environment in conferring the strong reduction capacity to the quinone. Thus far, the basis of this difference in reduction potential is not known.

One potential factor is the single hydrogen bond to the oxygen ortho to the phytanyl tail of phylloquinone to the NH of leucine A722 (Figure 82).$^{58}$ Differentially, the quinone acceptor in PS II, plastoquinone-9 (5-2), as well as the quinone in bacterial reaction center (bRC), ubiquinone (5-3, QA) are bound to the protein via two hydrogen bonds, one to each quinone carbonyl (Figure 83). The quinone environment of bRC is

![Figure 82: Phylloquinone (5-1) in the protein environment of PS I.](image)
depicted in Figure 84. The quinones in PS II and BRC function with reduction potentials around 0 mV. The extreme difference in reduction potential between quinone 5-1 and 5-2 or 5-3 as they function in their respective photosynthetic reaction centers is not understood.

![Figure 83: Plastoquinone-9 (5-2) and ubiquinone (5-3).](image)

To investigate the relationship between hydrogen bond strength and quinone reduction potential, as well as to probe the differences in asymmetric (e.g., PS I) vs. symmetric (e.g., PS II, BRC) hydrogen bonding in quinones, 5-substituted-2,3-dimethyl naphthoquinones 5-4 and 5,8-disubstituted-2,3-dimethyl naphthoquinones 5-5 were
envisioned as models (Figure 85). The influence of hydrogen bonding to quinone cofactors has drawn much attention by way of theoretical studies, however, experimental measurement of a symmetrically vs. asymmetrically hydrogen bonded system has yet been thoroughly investigated. Altering the strength(s) of the internal hydrogen-bond would depend on the electron withdrawing/donating property of the R group.

\[ R \cdot H \quad \text{O} \]
\[ \text{5-4} \]
\[ R \cdot H \quad \text{O} \]
\[ \text{5-5} \]

Figure 85: Envisioned asymmetric (5-4) and symmetric (5-5) hydrogen-bonded quinones.

5.2 Recruitment of a Foreign Quinone in the \( A_1 \) Site of Photosystem I.

The \textit{menB} mutant of cyanobacteria \textit{Synechocystis} sp. PCC 6803 cannot synthesize native quinone 5-1 and the organism recruits quinone 5-2 from PS II into the \( A_1 \) site of PS I. The \textit{menB rubA} double mutant in \textit{Synechococcus} sp. 7002 also contains quinone 5-2 (weakly bound) in place of quinone 5-1 and is devoid of all Fe-S clusters, thereby preventing forward electron transfer from the quinone, but also allowing greater accessibility to the quinone binding site. These mutants are ideal for studying electron transfer kinetics with foreign quinones in the \( A_1 \) site due to ease of displacement of quinone 5-2. Golbeck and coworkers showed that several foreign quinones could be incorporated into the \( A_1 \) site of the \textit{menB} mutant by supplementation of the growth
medium with these quinones.\textsuperscript{61} They were able to prove incorporation using spin-polarized transient EPR (X- and Q-band) as well as time-resolved optical kinetics. Several of these quinones are shown in Figure 86. With the ability to incorporate foreign quinones into PS I, we envisioned our synthesized quinones could be incorporated as well. Using quinones of the type \textbf{5-4} it was postulated that incorporation into the native, \textit{A}$_1$ quinone site would occur in an orientation which avoids interaction of the RX group with the backbone of the protein (\textbf{5-4a}), keeping the native H-bond intact (Figure 87). Achieving this orientation would allow for investigating the effect of symmetry on quinone reduction potential directly in a biological system. Incorporating various quinones with differing H-bond strengths would effectively allow for a tunable symmetry in the H-bonding the quinone experiences.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{quiones.png}
\caption{Some foreign quinones incorporated into the \textit{A}$_1$ site of the \textit{menB} mutant.}
\end{figure}
5.3 Synthesis of Internally Hydrogen Bonded Naphthoquinones.

Synthesis of asymmetrically hydrogen-bonded naphthoquinones began with conversion of pentadienoic acid (5-7) to tert-butyl trans-1,3-butadiene-1-carbamate\(^{62}\) (5-8) via a Curtius rearrangement (Figure 88).\(^{63}\) Diene 5-8 was reacted with 2,3-dimethylhydroquinone (5-9a), oxidized in situ to the corresponding quinone (5-9), in a [4 + 2] cycloaddition. Cycloadduct 5-10 (not isolated) aromatized in the presence of excess MnO\(_2\) giving naphthoquinone 5-11a in a one pot procedure in good yield. Internal hydrogen bonding of 5-11a was evident by \(^1\)H NMR. The NH proton was observed at 11.8 ppm, independent of concentration.
Deprotection of 5-11a with TFA gave 5-amino-2,3-dimethylnaphthoquinone (5-11b) (Figure 89). Substitution of this amine using standard methods produced N-acetyl quinone 5-11c, N-trifluoroacetyl quinone 5-11d, N-methyl quinone 5-11e. NH protons for quinones 5-11c-e all appeared downfield (> 9 ppm) independent of concentration, indicating internal hydrogen bonding was present in all compounds. Single crystal X-ray analysis confirmed the structure for naphthoquinone 5-11c, which clearly indicates internal hydrogen bonding.

Figure 88: One pot synthesis of quinone 5-11a via [4+2] cycloaddition/oxidation.
In an effort to probe the relative contribution of the hydrogen bond, we decided to synthesize analogues missing this feature. Asymmetric naphtoquinones lacking internal hydrogen-bonds were synthesized using methyl groups to replace the NH protons. Acetylation and trifluoroacetylation of N-methyl quinone 5-11e gave quinones 5-12a and 5-12b, respectively (Figure 90).

Figure 89: Functionalization of amine 5-11b.

Figure 90: Synthesis of quinones lacking an internal hydrogen bond.
Synthesis of symmetrically hydrogen-bonded naphthoquinones began with conversion of commercially available trans,trans-muconic acid (5-7a) into corresponding bis-carbamate 5-8a via a Curtius rearrangement (Figure 91). Diene 5-10a was reacted with quinone 5-9a, oxidized in situ from the corresponding dihydroquinone 5-9, in a [4 + 2] cycloaddition, followed by oxidation of cycloadduct 5-10a (not isolated) with DDQ to give 5,8-dicarbamate 5-13a in one pot.

Deprotection of 5-13a with TFA gave 5,8-diamino-2,3-dimethylnaphthoquinone (5-13b, Figure 92). Substitution of this amine 5-13b proceeded using standard methods to give N-acetyl naphthoquinone 5-13c, and N-trifluoroacetyl naphthoquinone 5-13d.
5.4 Properties of Synthesized Quinones.

With the eleven synthesized quinones in hand, a thorough investigation of relative hydrogen bond strength was warranted. To accomplish this task, we collected some salient properties known to scale with H-bond strength (IR frequency and $^1$H NMR) of the NH within these quinones as well as the half-wave reduction potential in an aprotic solvent. Reduction potentials measurements were obtained in CH$_2$Cl$_2$ (2 mM in quinone, 100 mM in Bu$_4$NClO$_4$) with a sweep rate of 3 V/s over a range of 0 to -2496 mV at 20 °C. Measurements were converted to SHE via the formula: $E_{\text{SHE}} = E_{(\text{Ag}/\text{Ag}^+)} + 541$ mV. As a reference, the ferrocene/ferrocenium reduction was observed at +200 mV (lit. 206 mV vs. Ag/AgPF$_6$). This data is shown in Table 15.
To probe the relative contributions of the hydrogen bond as well as the contributions of the nitrogen’s lone pair via resonance with the carbonyl, we examined control compounds 5-11b, 5-11e, 5-12a, and 5-12b. Without any amide carbonyl function, the nitrogen’s lone pair has the expected effect on the quinones reduction potential, making it harder to reduce by 98 mV; compare entry a (R = H) with entry b (R = NH₂). In this case, the NH--O=C bond can be described as modest at best, and so this comparison is close to the case where H-bonding is minimized, whereas the nitrogen’s lone pair contribution is elevated. A complimentary control wherein H-bonding is turned

Table 15: Reduction potentials, IR frequencies, and ¹H NMR signal positions of quinones.

<table>
<thead>
<tr>
<th>entry</th>
<th>compound</th>
<th>R</th>
<th>R₁</th>
<th>red. pot. vs. SHEᵃ (mV)</th>
<th>N-H IR freq.ᵇ (cm⁻¹)</th>
<th>N-H ¹H NMRᶜ (δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>5-14</td>
<td>H</td>
<td>H</td>
<td>-623</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>b</td>
<td>5-11b</td>
<td>NH₂</td>
<td>H</td>
<td>-721</td>
<td>3339</td>
<td>not obs.</td>
</tr>
<tr>
<td>c</td>
<td>5-11e</td>
<td>NHCH₃</td>
<td>H</td>
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</tr>
<tr>
<td>d</td>
<td>5-11a</td>
<td>NHBoc</td>
<td>H</td>
<td>-551</td>
<td>3263</td>
<td>11.77</td>
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<tr>
<td>e</td>
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<td>NHAc</td>
<td>H</td>
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</tr>
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<td>H</td>
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<td>13.08</td>
</tr>
<tr>
<td>g</td>
<td>5-12a</td>
<td>N(CH₃)Ac</td>
<td>H</td>
<td>-560</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>h</td>
<td>5-12b</td>
<td>N(CH₃)TFA</td>
<td>H</td>
<td>-554</td>
<td>--</td>
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<td>5-13b</td>
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<td>-819</td>
<td>3288</td>
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<tr>
<td>l</td>
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<td>NHTFA</td>
<td>NHTFA</td>
<td>-108</td>
<td>3076</td>
<td>13.18</td>
</tr>
</tbody>
</table>

ᵃ Conditions: 2 mM in quinone, 100 mM in Bu₄NClO₄ in CH₂Cl₂ at 20 °C, reference electrode: Ag/AgNO₃ (0.01 M in MeCN), working electrode: Pt disc (1.6 mm).
ᵇ Measured in CCl₄. ᶜ Measured in C₆D₆.
off and nitrogen lone pair elevated cannot be assured in this system due to uncertainty in the degree of overlap between the quinone π system and the lone pair of the nitrogen. Compounds 5-12a-b, where H-bonding cannot occur by methyl incorporation, comes close to approximating this goal. In these cases, the quinones reduction potential is lowered compared to the H-bonded analogues 5-11c-d by 76 mV (5-11c vs 5-12a) and 207 mV (5-11d vs 5-12b), respectively. The large difference between these values appears to be attributable to the increased H-bond strength in the NHTFA quinone 5-11c, noting that the reduction potentials of the two H-bond incapable quinones are essentially equal. These data suggest that the nitrogen’s lone pair does contribute to the (lowering of) quinone reduction potential, its effect is relatively smaller than the H-bond effect and consistent throughout the substrates examined within this work. Thus, the differences in reduction potential between the differently substituted amino-quinones should largely reflect the impact of the H-bond.

The data for quinones 5-11a, 5-11c-d, and 5-13a-b support the hypothesis that quinone reduction potential correlates with the strength of the H-bond. However, the less than perfect measurements of H-bond strength used for this correlation do little to encourage a linear trend. Double activation of the quinone function leads to expected increases in the reduction potentials, however, the amount of increase does not scale with the increased H-bond strength. An additional H-bond in the Boc species leads to an increase in reduction potential of 132 mV (entries d vs j), whereas in the NHAc species (stronger H-bond), the difference is 125 mV (entries e vs k) and in the NHTFA species (strongest H-bond), 239 mV (entries f vs l).
Although no linear correlation to H-bond strength and quinone reduction potential was observed, our data did support the premise that a stronger H-bond makes quinones more easily reduced and that simultaneous H-bonding to both quinones carbonyls makes the quinones even more easily reduced than additivity might suggest.

5.5 Biological Incorporation.

With the data collected on the synthesized quinones in hand, we sought to incorporate these quinones into the A₁ site of the menB mutant of PS I. Unfortunately, all attempts at incorporation failed to displace the weakly bound quinone 5-2 from the site. However, the quinone lacking peri-substitution (2,3-dimethylnaphthoquinone, 5-14) used as a reference compound in Table 15, entry a did incorporate into the A₁ site (experiments performed by Nithya Srinivasan). We speculate the substitutions at the peri positions of the quinones offer too much steric bulk to allow any of these quinones entry into the A₁ environment.

5.6 Conclusions.

During the course of these investigations, a new mutant was developed by Nithya Srinivasan in which a single point mutation of the Leu A722 to a Trp residue. Is it presumed that this mutation should effectively block H-bonding to the backbone of the residue previously experienced by phylloquinone 5-1. This theory was testing using incorporated quinone 5-14. The spin density distribution about the quinone in the A₁ site
is unavoidably asymmetric due, in large part, to the asymmetrical H-bond experienced by
the quinone (as measured by transient EPR). However, with the Trp mutant, the spin
density becomes more symmetric, indicative of the diminished or non-existant H-bond.
Additionally, the quinone reduction potential was found to be more negative, as expected
for a non-H-bonded quinone. Using the measured rate of electron transfer (by time-
resolved optical spectroscopy) allowed calculation of quinone reduction potential through
Marcus theory. This data indicates that the single H-bond in PS I is worth about 100 mV.
Although the data presented in Table 15 does not definitively place a numerical value on
the a hydrogen bond, the data from the Trp single-point mutant does fall in the range of
the data collected in solution with the synthesized quinones.

5.7 References.


56 Sétif, P.; Bottin, H.; Biochemistry 1989, 28, 2689.


Chapter 6

Experimentals

6.1 General Experimental.

Moisture and oxygen sensitive reactions were carried out in flame-dried glassware under a nitrogen atmosphere. Photolysis was carried out using a Rayonet model RPR-100 reactor with cooling fan. Solvents were dried by passage through an activated alumina column under nitrogen. All organic reagents were used as purchased unless otherwise noted. Flash chromatography was performed using 32 – 63 µm silica gel (unless otherwise noted) with the indicated solvent systems. Melting points are uncorrected. Infrared spectra were obtained using a Perkin-Elmer 1600 FTIR. Low and high resolution mass spectra were obtained according to the specified technique and were performed at the Proteomics and Mass Spectrometry Core Facility at the Pennsylvania State University. X-ray data was obtained at the Department of Chemistry X-ray Crystallography Facility at the Pennsylvania State University, University Park, PA. Optical rotations were recorded on an AUTOPOL II polarimeter at the specified temperature (concentration in grams/mL solvent). Microwave irradiation reactions were performed on a CEM Discover microwave reactor. Cyclic voltammetry measurements were performed on a BAS 100B Electrochemical Workstation using a 1.6 mm diameter Pt disc working electrode, Ag/AgNO₃ (0.01 M in CH₃CN) reference electrode.
6.2 Allenyl Azide Cycloaddition Studies.

**General Procedure 1. Thermolysis of Crude Phenyl-Substituted Allenyl Azides.** To a stirring solution of propargyl acetate 2-5 (1 equiv) and Pd(PPh₃)₄ (10 mol%) in THF (0.3 M in acetate) was added dropwise the appropriate arylzinc reagent (1.5 equiv.) and the reaction mixture was stirred for 1 h at rt, then brought to reflux and held there for 14 h. The reaction mixture was allowed to cool to room temperature and added to 30 mL of ice-cold saturated NH₄Cl solution. The mixture was extracted with Et₂O (3 X 30 mL), and the combined organic layers were washed with water (3 X 90 mL) and brine (3 X 90 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (5% EtOAc/hexanes).

**General Procedure 2. Sonagashira Coupling.** To a 0.5 M solution of alkenyl iodide in THF was added PdCl₂(PPh₃)₂ (10 mol%), 1-(2-azidophenyl)-prop-2-ynyl acetate (2-25) (1.6 equiv.), Et₃N (7 equiv.), and CuI (3 mol%). The mixture was stirred at rt under a nitrogen atmosphere for 16 h unless otherwise noted. The reaction solution was then diluted with an equivalent volume of Et₂O and an equivalent volume of saturated NH₄Cl solution was added. The organic layer was washed (3 X H₂O, 3 X brine), dried over MgSO₄, and evaporated under reduced pressure. The resulting oil was purified by flash chromatography (1% Et₂O/hexanes → 15% Et₂O/hexanes).

**General Procedure 3. Allenyl Azide Formation.** MeMgBr (3.0 M in Et₂O, 10 equiv.) was added dropwise to an ice-cold 0.1 M solution of CuI (10 equiv.) and LiBr (10 equiv.) in THF, and the resulting solution was stirred at that temperature for 30 min. A solution of the alkynyl azide in THF (0.1 M) was added slowly via cannula. The ice-cold
solution was stirred for 30 min (monitored by TLC for starting material consumption). Ice-cold saturated NH₄Cl solution was then added dropwise until gas evolution ceased, and then the reaction mixture was diluted with an equivalent volume of Et₂O. The organic layer was washed (3 X ice-cold H₂O, 3 X ice-cold brine), dried over MgSO₄ and evaporated under reduced pressure maintaining a water bath temperature below 40 °C. The resulting oil was purified by flash chromatography (hexanes → 2% Et₂O/hexanes).

**General Procedure 4. Allenyl Azide Formation.** To a solution of ZnCl₂ (2.5 equiv.) in THF (0.3 M solution) was added the appropriate Grignard reagent (2.5 equiv.) and the mixture was stirred at room temperature for 1 h. Pd(PPh₃)₄ (5 mol%) and the propargylic acetate (1 equiv.) in THF (0.1 M solution) were added sequentially. The reaction mixture was allowed to stir at room temperature for 20 min (monitored by TLC for starting material consumption). After addition of an equal volume of a saturated NH₄Cl solution, the organic layer was extracted into Et₂O and washed with water and brine, dried over Na₂SO₄ and evaporated under reduced pressure maintaining a water bath temperature below 40 °C. The resulting oil was purified by flash chromatography (hexanes → 2% Et₂O/hexanes).

**General Procedure 5. Thermolysis of Allenyl Azides.** A flame-dried round-bottomed flask or sealed tube containing a 0.1 M solution of allenyl azide in the specified solvent was refluxed for a minimum of 30 min under a N₂ atmosphere with monitoring by TLC for starting material consumption. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (2% Et₂O/hexanes → 10% Et₂O/hexanes).
**General Procedure 6. Photolysis of Allenyl Azides.** A flame-dried quartz vessel containing a 5 mM solution of allenyl azide in MeCN (and 1.5 equiv. CuI for copper-mediated reactions) was vigorously purged with N₂ or Ar for 5 min. The vessel was irradiated at the specified wavelength for a minimum of 1 h with monitoring by TLC for starting material consumption. For reactions containing CuI, the reaction solution was diluted with an equivalent volume of Et₂O and washed 2 X with ice-cold 10% NH₄OH in saturated NH₄Cl (1:4), 3 X with ice-cold H₂O (until aq. pH = 7), and 3 X with brine, dried over Na₂SO₄ and evaporated under reduced pressure. An alternative aqueous workup was also found to be effective: ice-cold 1 M Na₂S₂O₃, 2 X ice-cold 1 N H₃PO₄, 3 X ice-cold H₂O and 3 X ice-cold brine. The residue was purified by flash chromatography (2% Et₂O/hexanes → 10% Et₂O/hexanes).

**General Procedure 7. Azidophenyl Alkynyl Acetate Synthesis.** To a -78 °C stirring solution of the indicated alkyne (1.0 equiv.) in THF (0.1 M solution) was added dropwise n-BuLi (2.45 M in hexanes, 1.0 equiv.) and the reaction mixture was stirred for 1 h. A 1.0 M solution of 2-azidobenzaldehyde (2-11) in THF was then added via cannula and the reaction solution was stirred at -78 °C for 1.5 h. Ac₂O (1.5 equiv.) was then added and the reaction solution was allowed to warm to rt. An equal volume of ice-cold saturated NH₄Cl was added and the mixture was diluted with an equal volume of Et₂O. The organic layer was washed with an equal volume of H₂O and brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography using the specified eluent.
**1-Azido-2-(3-phenylbuta-1,2-dienyl)-benzene (2-7).** Following general procedure 3, 400 mg (1.37 mmol) of acetate 2-12 produced 275 mg (81%) of 2-7 as a yellow oil: IR (neat): 2122, 1931 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.36 – 7.33 (m, 2H), 7.31 (dd, $J = 8.5$, 0.7 Hz, 1H), 7.25 – 7.20 (m, 2H), 7.15 – 7.10 (m, 2H), 7.03 (ddd, $J = 8.1$, 1.3, 0.4 Hz, 1H), 6.94 (m, 1H), 6.65 (q, $J = 2.9$ Hz, 1H), 2.12 (d, $J = 3.0$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 207.5, 136.4, 136.1, 128.4, 128.2, 128.1, 127.0, 125.80, 125.77, 124.8, 118.5, 104.5, 91.0, 16.7; ES+ m/z (relative intensity) 220.2 (M – N$_2$ + H, 20%), 248.1 (M + H, 10%); HRMS Calcd for C$_{16}$H$_{14}$N: 220.1126, Found: 220.1122.

**2-(1-Phenylvinyl)-1H-indole (2-8a).** Following general procedure 1, 77 mg (0.34 mmol) of 2-5 and phenylzinc bromide (0.50 M in THF, 1.0 mL, 0.50 mmol) produced 25 mg (34%) of 2-8a as a yellow oil: IR (neat): 3416 cm$^{-1}$; $^1$H NMR (400 MHz, (CD$_3$)$_2$CO) $\delta$ 10.30 (br s, 1H), 7.51-7.48 (m, 3H), 7.42-7.36 (m, 4H), 7.10 (m, 1H), 6.99 (m, 1H), 6.30 (dd, $J = 2.2$, 0.8 Hz, 1H), 5.76 (s, 1H), 5.33 (d, $J = 0.6$ Hz, 1H); $^{13}$C NMR (100 MHz, (CD$_3$)$_2$CO) $\delta$ 143.0, 141.5, 138.8, 138.3, 129.5, 129.3, 129.1, 128.9, 123.1, 121.3, 120.3, 112.7, 111.9, 104.0; AP+ m/z (relative intensity) 220.1 (M + H, 100%); HRMS Calcd for C$_{16}$H$_{14}$N: 220.1126, Found: 220.1121.
2-[1-(4-Methoxyphenyl)-vinyl]-1H-indole (2-8b). Following general procedure
1, 78 mg (0.34 mmol) of 2-5 and 4-methoxyphenylzinc iodide (0.50 M in THF, 1.0 mL,
0.51 mmol) produced 30 mg (35%) of 2-8b as a yellow solid: mp 145 - 146 °C; IR
(neat): 3429 cm\(^{-1}\); \(^1\)H NMR (300 MHz, (CD\(_3\))\(_2\)CO) \(\delta\) 10.35 (br s, 1H), 7.49 (dd, \(J = 6.8,
1.0 \text{ Hz}, 1\text{H}), 7.42 (dd, \(J = 6.7, 2.2 \text{ Hz}, 2\text{H}), 7.37 (dq, \(J = 8.1, 0.9 \text{ Hz}, 1\text{H}), 7.10 (td, \(J =
7.1, 1.2 \text{ Hz}, 1\text{H}), 7.01-6.94 (m, 3\text{H}), 6.32 (dd, \(J = 2.2, 0.8 \text{ Hz}, 1\text{H}), 5.66 (d, \(J = 0.7, 1\text{H}),
5.27 (d, \(J = 0.8 \text{ Hz}, 1\text{H}), 3.84 (s, 3\text{H}); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 159.7, 141.0, 138.1,
136.3, 132.4, 129.6, 128.6, 122.6, 120.7, 120.0, 113.7, 111.7, 110.7, 103.1, 55.3; AP+
m/z (relative intensity) 250.1 (M + H, 100%); HRMS Calcd for C\(_{17}\)H\(_{16}\)NO: 250.1232,
Found: 250.1226.

2-[1-(3-Methoxyphenyl)-vinyl]-1H-indole (2-8c). Following general procedure
1, using a reflux time of 4 h and 6% Et\(_2\)O/hexanes as chromatography eleuent, 81 mg
(0.35 mmol) of 2-8c and 3-methoxyphenylzinc iodide (0.50 M in THF, 1.8 mL, 0.88
mmol) produced 20 mg (23%) of 2-8c as a yellow oil: IR (neat): 3413 cm\(^{-1}\); \(^1\)H NMR
(400 MHz, (CD\(_3\))\(_2\)CO) \(\delta\) 10.40 (br s, 1H), 7.49 (dd, \(J = 7.9, 0.8 \text{ Hz}, 1\text{H}), 7.37 (dq, \(J =

8.2, 0.8 Hz, 1H), 7.32 (t, $J = 7.9$ Hz, 1H), 7.10 (m, 1H), 7.07-7.03 (m, 2H), 7.00-6.96 (m, 2H), 6.35 (dd, $J = 5.1$, 0.8 Hz, 1H), 5.76 (s, 1H), 5.34 (s, 1H), 3.82 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 159.5, 141.5, 141.4, 137.6, 136.4, 129.4, 128.6, 122.7, 121.0, 120.8, 120.1, 114.0, 113.9, 112.8, 110.8, 103.2, 55.3; ES$^+$ m/z (relative intensity) 250.1 (M +H, 100%); HRMS Calcd for C$_{17}$H$_{16}$NO: 250.1232, Found: 250.1230.

2-[1-(3-Fluorophenyl)-vinyl]-1H-indole (2-8d). Following general procedure 1, 82 mg (0.36 mmol) of 2-5 and 3-fluorophenylzinc iodide (0.50 M in THF, 1.1 mL, 0.54 mmol) produced 45 mg (53%) of 2-8d as an orange solid: mp 74 - 75 °C; IR (neat): 3415 cm$^{-1}$; $^1$H NMR (300 MHz, (CD$_3$)$_2$CO) δ 10.48 (br s, 1H), 7.52 (d, $J = 7.9$ Hz, 1H), 7.48-7.33 (m, 3H), 7.26 (d, $J = 10.2$ Hz, 1H), 7.21-7.11 (m, 2H), 7.01 (t, $J = 7.5$ Hz, 1H), 6.35 (s, 1H), 5.82 (s, 1H), 5.41 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 162.7 (d, $J_{CF} = 244.7$ Hz), 142.2 (d, $J_{CF} = 7.6$ Hz), 140.6 (d, $J_{CF} = 2.2$ Hz), 137.1, 136.5, 129.8 (d, $J_{CF} = 8.2$ Hz), 128.5, 124.2 (d, $J_{CF} = 2.9$ Hz), 122.9, 120.9, 120.2, 115.4 (d, $J_{CF} = 25.6$ Hz), 115.1 (d, $J_{CF} = 24.7$ Hz), 113.2, 110.8, 103.7; CI$^+$ m/z (relative intensity) 238.0 (M +H, 100%); HRMS Calcd for C$_{16}$H$_{13}$NF: 238.1032, Found: 238.1027.
Acetic Acid 1-(2-Azidophenyl)-3-phenylprop-2-ynyl Ester (2-12). To a -40 °C stirring solution of 2-azidobenzaldehyde (500 mg, 3.40 mmol) in 34 mL of THF was added dropwise phenylethynylmagnesium bromide (1.0 M in THF, 5.1 mL, 5.1 mmol). The cold bath was allowed to warm slowly to rt over 20 h, then ice-cold saturated NH₄Cl solution (10 mL) was added slowly to the reaction. The mixture was diluted with 34 mL of Et₂O and the organic layer was washed with H₂O (3 X 70 mL), brine (3 X 70 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (5% Et₂O/hexanes → 20% Et₂O/hexanes) to remove phenylacetylene providing 692 mg of the crude alcohol as a yellow oil which was immediately dissolved in 25 mL of CH₂Cl₂ and cooled to 0 °C. DMAP (848 mg, 6.94 mmol) and Ac₂O (394 µL, 4.17 mmol) were added sequentially and the reaction was warmed to rt. Ice-cold saturated NH₄Cl (10 mL) was added slowly and then the mixture was diluted with Et₂O (60 mL). The organic layer was washed with H₂O (2 X 100 mL), brine (3 X 100 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (10% Et₂O/hexanes) to provide 780 mg (79%) of the title compound as a white solid: mp 49 – 50 °C; IR (neat): 2125, 1743 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) δ 7.76 (d, \(J = 7.8\) Hz, 1H), 7.47 – 7.45 (m, 2H), 7.40 (td, \(J = 7.8, 1.1\) Hz, 1H), 7.32 – 7.28 (m, 3H), 7.22 – 7.17 (m, 2H), 6.86 (s, 1H), 2.12 (s, 3H); \(^13\)C NMR (75 MHz, CDCl₃) δ 169.5, 137.9, 131.9, 130.3, 129.4, 128.8, 128.2, 128.1, 125.0, 122.0, 118.3, 86.9, 85.0, 61.3, 21.0; ES+ m/z (relative intensity) 292.3 (M + H, 10%), 314.1 (M + Na, 100%); HRMS (ES+) Calcd for C₁₇H₁₃N₃O₂Na: 314.0905, Found: 314.0918.
Carbonic Acid 1-(2-Azidophenyl)-3-trimethylsilylprop-2-ynyl Ester Ethyl Ester (2-12a). To a -30 °C stirring solution of trimethylsilylacetylene (484 µL, 3.40 mmol) in 34 mL of THF was added 1.37 mL of n-BuLi (2.48 M in hexanes, 3.40 mmol) and the reaction mixture was stirred at that temperature for 1 h. A solution of 2-azidobenzaldehyde (2-11) (500 mg, 3.40 mmol) in 14 mL of THF was added via cannula and stirring was continued at -30 °C for 10 min with TLC monitoring for starting material consumption. Ethyl chloroformate (330 µL, 3.45 mmol) was added and the reaction mixture was allowed to warm to rt. Ice-cold saturated NH₄Cl solution (100 mL) was added and the reaction mixture was diluted with 50 mL of Et₂O. The organic layer was washed with H₂O (3 X 100 mL), and brine (3 X 100 mL), dried over MgSO₄ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (3% Et₂O/hexanes) to provide 1.03 g (96%) of the title compound as a white solid: mp 84 - 85 °C; IR (neat): 2130, 1751 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.66 (d, J = 7.7 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.10 (m, 2H), 6.49 (s, 1H), 4.17 (q, J = 7.1 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H), 0.15 (s, 9H); ¹³C NMR (90 MHz, CDCl₃) δ 153.7, 137.8, 130.4, 129.2, 127.2, 124.8, 118.0, 100.0, 93.1, 64.4, 64.2, 14.0, -0.5; ES+ m/z (relative intensity) 318.1 (M + H, 10%), 340.1 (M + Na, 100%); HRMS (ES+) Calcd for C₁₅H₁₉N₃O₅SiNa: 340.1093, Found: 340.1092.
3-[3-(2-Azidophenyl)-1-methylpropa-1,2-dienyl]-6,6-dimethylcyclohex-2-enone (2-21). To a stirring solution of alcohol 2-31 (57 mg, 0.20 mmol) in 1 mL of CH$_2$Cl$_2$ was added a solution of Dess-Martin periodinane (170 mg, 0.40 mmol) in 2 mL of CH$_2$Cl$_2$ and the reaction mixture was stirred for 1 min. Saturated NaHCO$_3$ (3 mL) was added and the organic layer was washed with H$_2$O (3 X 5 mL) and brine (3 X 5 mL), dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (5% EtOAc/hexanes) to provide 24 mg (41%) of 2-21 as a yellow oil: IR (neat): 2124, 1927, 1664 cm$^{-1}$; $^1$H NMR (360 MHz, C$_6$D$_6$) $\delta$ 7.21 (dd, $J = 7.3, 1.7$ Hz, 1H), 6.84 – 6.76 (m, 2H), 6.70 – 6.66 (m, 2H), 6.07 (d, $J = 1.1$ Hz, 1H), 2.20 (app pent, $J = 6.1$ Hz, 2H), 1.68 (d, $J = 2.7$ Hz, 3H), 1.46 (t, $J = 6.2$ Hz, 2H), 1.06 (s, 3H), 1.04 (s, 3H); $^{13}$C NMR (90 MHz, C$_6$D$_6$) $\delta$ 210.4, 202.7, 153.5, 136.9, 129.0, 128.4, 125.2, 124.9, 123.3, 118.9, 106.4, 91.5, 40.6, 36.4, 24.9, 24.3, 15.5; ES+ m/z (relative intensity) 316.1 (M + Na, 100%); HRMS (ES+) Calcd for C$_{18}$H$_{19}$N$_3$ONa: 316.1426, Found: 316.1429.

3-Iodo-6,6-dimethylcyclohex-2-enone (2-24) To a stirring suspension of iodine (9.970 g, 39.28 mmol) in 200 mL of MeCN was added PPh$_3$ (10.31 g, 39.31 mmol), Et$_3$N
(5.460 mL, 39.28 mmol), and 4,4-dimethyl-1,3-cyclohexanedione (2-23) (5.00 g, 35.7 mmol). The reaction mixture was heated at reflux for 72 h, and then concentrated under reduced pressure. The resulting oil was purified by flash chromatography (5% Et₂O/hexanes) to give 8.22 g (92%) of the title compound as a colorless oil: IR (neat): 1677 cm⁻¹; ¹H NMR (400 MHz, C₆D₆) δ 6.61 (t, J = 1.5 Hz, 1H), 2.33 (td, J = 6.1, 1.6 Hz, 2H), 1.16 (t, J = 6.1 Hz, 2H), 0.82 (s, 6H); ¹³C NMR (100 MHz, C₆D₆) δ 198.5, 139.2, 123.8, 40.4, 38.3, 37.4, 23.7; ESI m/z (relative intensity) 251.0 (M + H, 100%), 283.0 (M+ Na, 25%); HRMS (ES+) Calcd for C₈H₁₂O₁: 250.9933, Found: 250.9955.

1-(2-Azidophenyl)-prop-2-ynyl Acetate (2-25). To a solution of 2-azidobenzaldehyde (2-11) (3.00 g, 20.4 mmol) in 204 mL of THF at -40 °C was added ethynylmagnesium bromide (0.5 M in THF, 61.2 mL, 30.6 mmol) and the mixture was stirred for 30 min with TLC monitoring. When the starting aldehyde was consumed, Ac₂O (3.47 mL, 36.7 mmol) was added and the reaction solution was warmed to rt. Ice-cold saturated NH₄Cl solution (200 mL) was added slowly and the mixture was diluted with Et₂O (100 mL). The organic layer was washed (3 X H₂O, 3 X brine), dried over Na₂SO₄, and evaporated under reduced pressure. The resulting oil was purified by flash chromatography (10% Et₂O/hexanes) to give 3.60 g (82%) of 6 as a yellow solid: mp 58 - 59 °C; IR (CCl₄): 2124, 1750 cm⁻¹; ¹H NMR (400 MHz, C₆D₆) δ 7.70 (dd, J = 7.1, 1.8 Hz, 1H), 6.94 (d, J = 2.3 Hz, 1H), 6.79 (m, 2H), 6.51 (dd, J = 7.0, 1.9 Hz, 1H), 2.11 (d, J
= 2.2 Hz, 1H), 1.58 (s, 3H); $^{13}$C NMR (100 MHz, C$_6$D$_6$) δ 168.7, 138.2, 130.5, 129.4, 128.1, 125.0, 118.4, 80.3, 75.6, 60.6, 20.2; APCI+ m/z (relative intensity) 216.1 (M +H 30%); HRMS (ES+) Calcd for C$_{11}$H$_9$N$_3$O$_2$Na: 238.0592, Found: 238.0589.

3-Iodo-6,6-dimethylcyclohex-2-enol (2-27). To an ice-cold solution of 2-24 (5.02 g, 20.1 mmol), and CeCl$_3$$\cdot$7H$_2$O (9.35 g, 25.1 mmol) in 400 mL of MeOH was added slowly NaBH$_4$ (949 mg, 25.1 mmol). The reaction mixture was warmed to rt and stirred for an additional 10 min. The solvent was removed under reduced pressure. 300 mL of 1N HCl solution was added to the residue, and this mixture was extracted with EtOAc (3 X 200 mL), the combined organic layers were washed (3 X 200 mL H$_2$O, 3 X 200 mL brine), dried over Na$_2$SO$_4$, and concentrated under reduced pressure to give 5.0 g (99%) of the title compound as a white solid: mp 56 - 57 °C; IR (neat): 3346, 1633 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) δ 6.30 (m, 1H), 3.71 (m, 1H), 2.50 (m, 2H), 1.52 (m, 1H), 1.43 (m, 1H), 0.95 (s, 3H), 0.90 (s, 3H); $^{13}$C NMR (75 MHz, C$_6$D$_6$) δ 140.4, 99.3, 75.9, 37.7, 35.4, 32.9, 26.0, 21.0; AP+ m/z (relative intensity) 235.0 (M – OH, 100%); HRMS (AP+) Calcd for C$_8$H$_{12}$I: 234.9984, Found: 235.0002.

**tert-Butyl-(3-iodo-6,6-dimethylcyclohex-2-enyloxy)-dimethylsilane (2-28a).**

To a stirred solution of 2-27 (8.327 g, 33.03 mmol), and 2,6-lutidine (9.60 mL, 82.6
mmol) in 200 mL of CH₂Cl₂ was added TBSOTf (11.4 mL, 49.6 mmol). The reaction mixture was stirred at rt for 16 h, and then the solvent was removed under reduced pressure. The resulting oil was purified by flash chromatography (hexanes) to yield 12.10 g (100%) of 2-28a as a colorless oil: IR (neat): 1634 cm⁻¹; ¹H NMR (300 MHz, C₆D₆) δ 6.25 (m, 1H), 3.55 (q, J = 2.5 Hz, 1H), 2.27 (m, 2H), 1.24 (m, 1H), 1.06 (m, 1H), 0.90 (s, 9H), 0.82 (s, 3H), 0.75 (s, 3H), -0.04 (s, 6H); ¹³C NMR (75 MHz, C₆D₆) δ 140.9, 98.6, 76.8, 37.8, 35.7, 33.6, 26.6, 26.0, 21.2, 18.3, -4.1, -4.9; EI+ m/z (relative intensity) 351.1 (M - CH₃, 100%), 365.1 (M – H, 10%); HRMS (EI+) Calcd for C₁₃H₂₄OISi: 351.0641, Found: 351.0634.

(3-Iodo-6,6-dimethylcyclohex-2-enyloxy)-triisopropylsilane (2-28b). To a stirred solution of 2-27 (5.00 g, 19.9 mmol), and 2,6-lutidine (5.75 mL, 49.5 mmol) in 190 mL of CH₂Cl₂ was added TIPSOTf (8.00 mL, 29.7 mmol). The reaction mixture was stirred at rt for 1.5 h, and then the solvent was removed under reduced pressure. The resulting oil was purified by flash chromatography (hexanes) to yield 7.60 g (94%) of the title compound as a colorless oil: IR (neat): 1633 cm⁻¹; ¹H NMR (400 MHz, C₆D₆) δ 6.36 (m, 1H), 3.76 (t, J = 1.7 Hz, 1H), 2.34 (m, 1H), 2.27 (m, 1H), 1.39 (m, 1H), 1.05 – 0.95 (m, 22H), 0.87 (s, 3H), 0.80 (s, 3H); ¹³C NMR (90 MHz, CDCl₃) δ 140.5, 99.2, 76.8, 37.6, 35.1, 33.9, 26.1, 22.1, 18.3, 18.2, 12.9; APCI m/z (relative intensity) 234.9 (M – TIPSOH, 100%), 281.2 (M - I, 25%); HRMS (AP+) Calcd for C₁₇H₃₃OSi: 281.2301, Found: 281.2293.
(3-Iodo-6,6-dimethylcyclohex-2-enyloxymethyl)-benzene (2-28c). To a stirring solution of alcohol 2-27 (3.12 g, 12.4 mmol) in 100 mL of THF was added portionwise NaH (372 mg, 15.5 mmol) and BnBr (2.35 mL, 19.8 mmol). The reaction mixture was stirred for 16 h, and then the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes → 10% Et₂O/hexanes) to yield 3.95 g (93%) of 2-28c as a colorless oil: IR (neat): 1632 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.19 (m, 5H), 6.29 (m, 1H), 4.56 (d, J = 11.8 Hz, 1H), 4.37 (d, J = 11.8 Hz, 1H), 3.36 (m, 1H), 2.45 – 2.30 (m, 2H), 1.44 (m, 1H), 1.35 (m, 1H), 0.86 (s, 3H), 0.84 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 138.4, 137.0, 128.2, 127.6, 127.5, 99.7, 82.7, 71.7, 37.5, 36.0, 33.0, 26.5, 21.5; EI⁺ m/z (relative intensity) 215.1 (M – I, 60%); HRMS (EI⁺) Calcd for C₁₅H₁₉O: 215.1436, Found: 215.1434.

[2-(3-Iodo-6,6-dimethylcyclohex-2-enyloxymethoxy)-ethyl]-trimethylsilane (2-28d). To a stirring solution of alcohol 2-27 (355 mg, 1.41 mmol) in 5 mL of CH₂Cl₂ was added Bu₄NI (624 mg, 1.69 mmol), N,N-diisopropylethylamine (dried over Na₂SO₄ and decolorized with charcoal) (279 µL, 1.69 mmol), and SEMCl (tech. grade, 499 µL, 2.82 mmol). The reaction mixture was stirred for 16 h and then the solvent was removed under reduced pressure. The resulting oil was dissolved in Et₂O (10 mL) and washed (3
X 10 mL H₂O, 3 X 10 mL brine), dried over MgSO₄, and then the solvent was removed under reduced pressure. The resulting oil was purified by flash chromatography (hexanes → 10% Et₂O/hexanes) to yield 515 mg (96%) of 2-28d as a colorless oil: IR (neat): 1635 cm⁻¹; ¹H NMR (360 MHz, C₆D₆) δ 6.45 (m, 1H), 4.61 – 4.45 (m, 2H), 3.66 – 3.45 (m, 3H), 2.40 – 2.15 (m, 2H), 1.28 (m, 1H), 1.06 (m, 1H), 0.95 – 0.85 (m, 5H), 0.80 – 0.72 (m, 3H), 0.00 - -0.05 (m, 9H); ¹³C NMR (90 MHz, C₆D₆) δ 138.8, 99.3, 94.6, 81.4, 65.2, 37.7, 35.9, 32.8, 26.3, 21.8, 18.2, -1.2; EI+ m/z (relative intensity) 309.0 (M – SiMe₃, 40%); HRMS (EI+) Calcd for C₁₁H₁₈O₂I: 309.0352, Found: 309.0360.

1-((tert-Butyldimethylsilyloxy)-3-iodo-6,6-dimethylcyclohex-2-enecarbonitrile (2-28e). To a stirring solution of 2-24 (864 mg, 3.45 mmol) in 6 mL of MeCN was added TBSCN (975 mg, 6.90 mmol) and ZnI₂ (30 mg, 0.09 mmol). The reaction mixture was stirred at rt for 24 h. The crude mixture was diluted with 25 mL of Et₂O, washed with H₂O (3 X 30 mL) and brine (3 X 30 mL), dried over MgSO₄ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (3% Et₂O/hexanes) to provide 1.30 g (96%) of the title compound as a colorless oil: IR (neat): 1632 -¹; ¹H NMR (360 MHz, CDCl₃) δ 6.31 (t, J = 1.9 Hz, 1H), 2.55 (td, J = 6.1, 1.9 Hz, 2H), 1.73 (m, 1H), 1.49 (m, 1H), 1.09 (s, 3H), 1.01 (s, 3H), 0.87 (s, 9H), 0.24 (s, 3H), 0.17 (s, 3H); ¹³C NMR (90 MHz, CDCl₃) δ 135.6, 119.5, 103.8, 75.3, 37.2, 36.9, 33.2, 25.4, 23.3, 22.6, 18.2, -3.3, -4.0; APCI+ m/z (relative intensity)
392.1 (M + H, 40%), 409.1 (M + NH₄, 100%); HRMS (APCI+) Calcd for C₁₅H₂₇NOSi:\n392.0907, Found: 392.0894.

1-(2-Azidophenyl)-3-[3-(tert-butyldimethylsilanyloxy)-4,4-dimethylcyclohex-1-enyl]-prop-2-ynyl Acetate (2-29a). Following general procedure 2, 1.13 g (3.08 mmol) of 2-28a and 1.06 g (4.94 mmol) of 2-25 produced 1.10 g (79%) of 2-29a as a yellow oil (mixture of diastereomers): IR (neat): 2125, 1749 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.61 (dd, J = 7.7, 1.5 Hz, 1H), 7.28 (td, J = 7.7, 1.6 Hz, 1H), 7.05 (m, 2H), 6.69 (s, 1H), 5.81 (d, J = 2.2 Hz, 1H), 3.74 (d, J = 2.1 Hz, 1H), 2.16 – 1.91 (m, 2H), 1.99 (s, 3H), 1.42 (m, 1H), 1.30 (m, 1H), 0.83 (s, 12H), 0.77 (s, 3H), 0.00 (s, 3H), -0.02 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 169.4, 138.69, 138.68, 137.8, 130.2, 129.4, 128.2, 124.9, 120.1, 118.2, 87.6, 83.5, 74.3, 61.3, 33.6, 33.3, 27.2, 26.9, 25.8, 21.0, 20.3, 18.0, -4.1, -5.0; ES⁺ m/z (relative intensity) 476.1 (M + Na, 100%); HRMS (ES+) Calcd for C₂₅H₃₅N₃O₃NaSi: 476.2345, Found: 476.2357.

1-(2-Azidophenyl)-3-(4,4-dimethyl-3-triisopropylsilanyloxy-cyclohex-1-enyl)-prop-2-ynyl Acetate (2-29b). Following general procedure 2, using 3 equiv. of 2-25, 18
mol% PdCl$_2$(PPh$_3$)$_2$, and 6 mol% CuI, 354 mg (0.867 mmol) of 2-28b and 566 mg (2.63 mmol) of 2-25 produced 395 mg (92%) of the title compound (mixture of diastereomers) as a yellow oil: IR (neat): 2126, 1748 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.73 (d, $J = 7.8$ Hz, 1H), 7.43 (dt, $J = 7.8$, 1.4 Hz, 1H), 7.21 (m, 2H), 6.80 (s, 1H), 6.06 (d, $J = 2.0$ Hz, 1H), 4.04 (d, $J = 2.0$ Hz, 1H), 2.20 (m, 1H), 2.13 (s, 3H), 2.13 – 2.08 (m, 1H), 1.60 (dt, $J = 13.4$, 5.7 Hz, 1H), 1.38 (m, 1H), 1.15 – 1.10 (br s, 21H), 0.98 (s, 3H), 0.94 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 169.4, 138.4, 138.3, 137.8, 130.2, 129.4, 128.2, 124.9, 120.5, 118.2, 87.73, 87.71, 83.5, 74.5, 61.3, 34.0, 32.8, 26.9, 26.7, 21.3, 20.9, 18.2, 18.1, 12.9; APCI+ m/z (relative intensity) 518.2 (M + Na, 70%); HRMS (ES+) Calcd for C$_{28}$H$_{41}$N$_3$O$_3$NaSi: 518.2815, Found: 518.2820.

1-(2-Azidophenyl)-3-(3-benzyloxy-4,4-dimethylcyclohex-1-enyl)-prop-2-ynyl Acetate (2-29c). Following general procedure 2, 509 mg (1.49 mmol) of iodide 2-28c and 512 mg (2.38 mmol) of alkyne 2-25 produced 490 mg (77%) of 2-29c as a yellow oil (mixture of diastereomers): IR (neat): 2125, 1744 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.73 (d, $J = 7.2$ Hz, 1H), 7.48 – 7.25 (m, 6H), 7.24 – 7.15 (m, 2H), 6.79 (s, 1H), 6.23 (s, 1H), 4.71 (d, $J = 10.8$ Hz, 1H), 4.53 (d, $J = 10.8$ Hz, 1H), 3.57 (s, 1H), 2.30 – 2.15 (m, 2H), 2.13 (s, 3H), 1.57 (m, 1H), 1.43 (m, 1H), 0.98 (s, 6H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 169.4, 138.6, 137.7, 134.7, 130.2, 129.3, 128.2, 128.0, 127.5, 127.4, 124.9, 121.4, 118.2, 87.5, 83.8, 80.4, 71.7, 61.18, 61.15, 33.4, 33.1, 26.9, 26.8, 21.2, 20.9; ES+ m/z (relative
intensity) 452.1 (M + Na, 100%); HRMS (ES+) Calcd for C_{26}H_{27}N_{3}O_{3}Na: 452.1950, Found: 452.1959.

![Structure of 1-(2-Azidophenyl)-3-[4,4-dimethyl-3-(2-trimethylsilanylethoxymethoxy)-cyclohex-1-enyl]-prop-2-ynyl Acetate (2-29d).]

Following general procedure 2, 515 mg (1.35 mmol) of 2-28d and 464 mg (2.16 mmol) of 2-25 produced 400 mg (63%) of 2-29d as a yellow oil (mixture of diastereomers): IR (neat): 2126, 1748 cm^{-1}; \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) δ 7.65 (d, J = 7.6 Hz, 1H), 7.36 (td, J = 7.7, 1.5 Hz, 1H), 7.20 – 7.10 (m, 2H), 6.72 (s, 1H), 6.06 (d, J = 1.4 Hz, 1H), 4.74 (d, J = 7.0 Hz, 1H), 4.63 (d, J = 7.1 Hz, 1H), 3.70 (br s, 1H), 3.65 – 3.58 (m, 2H), 2.20 – 2.05 (m, 2H), 2.06 (s, 3H), 1.50 (m, 1H), 1.37 (m, 1H), 0.92 – 0.88 (m, 2H), 0.92 (s, 3H), 0.88 (s, 3H), -0.01 (s, 9H); \textsuperscript{13}C NMR (90 MHz, CDCl\textsubscript{3}) δ 169.3, 137.8, 135.5, 130.2, 129.3, 128.1, 124.9, 121.4, 118.2, 94.3, 87.4, 83.8, 78.63, 78.60, 65.0, 61.1, 33.1, 32.8, 26.8, 26.5, 21.5, 20.9, 18.0, -1.5; ES+ m/z (relative intensity) 492.2 (M + Na, 100%); HRMS (ES+) Calcd for C_{25}H_{35}N_{3}O_{4}NaSi: 492.2295, Found: 492.2289.
Acetic Acid 1-(2-Azidophenyl)-3-[3-(tert-butyldimethylsilanyloxy)-3-cyano-4,4-dimethylcyclohex-1-enyl]-prop-2-ynyl Ester (2-29e). Following general procedure 2, using 100% hexanes $\rightarrow$ 7% Et$_2$O/hexanes as the eluent for flash chromatography, 195 mg of 2-28e (0.498 mmol) and 172 mg of 2-25 (0.797 mmol) produced 180 mg (76%) of the title compound as a yellow oil (mixture of diastereomers): IR (neat): 2126, 1749 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.63 (dd, $J = 7.6, 1.1$ Hz, 1H), 7.40 (td, $J = 7.7, 1.3$ Hz, 1H), 7.17 (m, 2H), 6.74 (s, 1H), 5.98 (d, $J = 2.0$ Hz, 1H), 2.18 (t, $J = 5.8$ Hz, 2H), 2.09 (s, 3H), 1.66 (m, 1H), 1.53 (m, 1H), 1.09 (s, 3H), 1.01 (s, 3H), 0.87 (s, 9H), 0.26 (s, 3H), 0.17 (s, 3H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 169.3, 137.8, 132.7, 132.6, 130.4, 129.2, 127.6, 125.0, 124.7, 119.9, 118.3, 86.8, 85.57, 85.55, 73.3, 60.9, 37.0, 30.6, 26.8, 25.4, 23.5, 22.3, 20.9, 18.2, -3.2, -3.99; ES$^+$ m/z (relative intensity) 496.3 (M + NH$_4^+$, 100%), 501.3 (M + Na, 85%); HRMS (ES$^+$) Calcd for C$_{26}$H$_{34}$N$_4$O$_3$NaSi: 501.2298, Found: 501.2307.

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[3-[3-(2-Azidophenyl)-1-methylpropa-1,2-dienyl]-6,6-dimethylcyclohex-2-enyloxy]-tert-butyldimethylsilane (2-30a). Following general procedure 3, 453 mg (0.999 mmol) of 2-29a produced 375 mg (92%) of 2-30a as a yellow oil: IR (neat): 2123, 1930 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33 (m, 1H), 7.21 (t, $J = 7.6$ Hz, 1H), 7.11 (d, $J = 7.8$ Hz, 1H), 7.06 (m, 1H), 6.55 (s, 1H), 5.53 (s, 1H), 3.93 (s, 1H), 2.18 – 2.03 (m, 2H), 1.94 (d, $J = 2.6$ Hz, 3H), 1.51 (m, 1H), 1.37 (m, 1H), 0.92 (m, 12H), 0.84 (m, 3H), 0.10 (m, 3H), 0.08 (m, 3H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 207.8, 207.7, 136.2, 136.1,
133.5, 133.4, 128.02, 127.96, 127.9, 126.7, 126.6, 126.42, 126.40, 124.83, 124.77, 118.4, 105.7, 90.2, 75.54, 75.47, 34.2, 34.1, 33.8, 33.7, 27.3, 25.9, 24.7, 24.6, 20.5, 20.3, 18.19, 18.17, 15.9, -3.9, -4.8; ES+ $m/z$ (relative intensity) 432.2 (M + Na, 35%); HRMS (ES+) Calcd for C$_{24}$H$_{35}$N$_{3}$ONaSi: 432.2447, Found: 432.2464.

[3-[3-(2-Azidophenyl)-1-methylpropa-1,2-dienyl]-6,6-dimethylcyclohex-2-enyloxy]-triisopropylsilane (2-30b). Following general procedure 3, 230 mg (0.464 mmol) of 2-29b produced 180 mg (89%) of 2-30b as a yellow oil (mixture of diastereomers): IR (neat): 2123, 1931 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.30 (d, $J$ = 7.7 Hz, 1H), 7.19 (m, 1H), 7.10 – 7.02 (m, 2H), 6.53 (s, 1H), 5.63 (s, 1H), 4.09 (d, $J$ = 7.3 Hz, 1H), 2.20 – 1.95 (m, 2H), 1.93 (d, $J$ = 2.6 Hz, 3H), 1.51 (m, 1H), 1.32 (m, 1H), 1.14 – 1.01 (m, 21H), 0.93 (m, 3H), 0.86 (m, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 207.85, 207.76, 136.2, 133.6, 133.5, 128.0, 127.9, 126.8, 126.6, 126.42, 126.38, 124.9, 124.8, 118.4, 105.8, 90.2, 75.9, 75.7, 34.6, 34.5, 33.7, 33.4, 29.7, 27.3, 27.0, 24.6, 24.5, 21.1, 20.7, 18.33, 18.27, 15.9, 13.0; ES+ $m/z$ (relative intensity) 424.2 (M – N$_2$ + H, 100%); HRMS (ES+) Calcd for C$_{27}$H$_{42}$NOSi: 424.3026, Found: 424.3040.
1-Azido-2-[3-(3-benzyloxy-4,4-dimethylcyclohex-1-enyl)-buta-1,2-dienyl]-benzene (2-30c). Following general procedure 3, 490 mg (1.14 mmol) of 2-29c produced 350 mg (80%) of 2-30c as a yellow oil (mixture of diastereomers): IR (neat): 2123, 1931 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.45 – 7.30 (m, 6H), 7.21 (m, 1H), 7.15 – 7.02 (m, 2H), 6.60 (s, 1H), 5.80 (s, 1H), 4.76 (d, $J = 11.9$ Hz, 1H), 4.62 (dd, $J = 11.9$, 2.3 Hz, 1H), 3.68 (d, $J = 9.8$ Hz, 1H), 2.30 – 2.04 (m, 2H), 2.00 – 1.97 (m, 3H), 1.58 (m, 1H), 1.41 (m, 1H), 1.01 (s, 3H), 1.00 (s, 3H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 207.83, 207.77, 139.0, 136.1, 136.0, 134.8, 134.6, 128.2, 127.94, 127.86, 127.5, 127.3, 126.23, 126.15, 124.8, 124.7, 122.6, 122.4, 118.4, 118.3, 105.81, 105.75, 90.2, 82.2, 81.90, 81.88, 72.1, 72.0, 33.8, 33.7, 27.1, 26.9, 24.7, 24.6, 21.6, 21.0, 15.9; APCI+ m/z (relative intensity) 386.1 (M + H, 40%); HRMS (AP+) Calcd for C$_{25}$H$_{28}$N$_3$O: 386.2232, Found: 386.2216.

(2-{3-[3-(2-Azidophenyl)-1-methylpropa-1,2-dienyl]-6,6-dimethylcyclohex-2-enyloxymethoxy}-ethyl)-trimethylsilane (2-30d). Following general procedure 3, 354 mg (0.754 mmol) of 2-29d produced 275 mg (86%) of 2-30d as a yellow oil (mixture of diastereomers): IR (neat): 2124, 1930 cm$^{-1}$; $^1$H NMR (300 MHz, C$_6$D$_6$) $\delta$ 7.36 (m, 1H), 6.85 – 6.65 (m, 4H), 5.91 (s, 1H), 4.83 (d, $J = 6.9$ Hz, 1H), 4.68 (d, $J = 6.8$ Hz, 1H), 3.86 (d, $J = 8.5$ Hz, 1H), 3.80 – 3.60 (m, 2H), 2.30 – 2.05 (m, 2H), 1.94 (d, $J = 2.6$ Hz, 3H), 1.51 (m, 1H), 1.31 (m, 1H), 1.08 – 0.90 (m, 2H), 1.03 (s, 3H), 0.96 (s, 3H), -0.01 (s, 9H);
$^{13}$C NMR (75 MHz, C$_6$D$_6$) $\delta$ 208.3, 208.2, 136.7, 136.6, 134.7, 134.6, 126.71, 126.65, 125.1, 125.0, 124.7, 124.5, 118.74, 118.70, 106.3, 106.2, 95.1, 90.9, 80.9, 80.6, 65.2, 34.2, 33.9, 33.74, 33.66, 27.1, 26.9, 25.2, 25.1, 21.9, 21.5, 18.4, 16.1, -1.3; ES+ m/z (relative intensity) 448.2 (M + Na, 100%); HRMS (ES+) Calcd for C$_{24}$H$_{35}$N$_3$O$_2$NaSi: 448.2396, Found: 448.2403.

![Chemical structure](image)

3-[3-(2-Azidophenyl)-1-methylpropa-1,2-dienyl]-1-(tert-butyldimethylsilanyl-oxy)-6,6-dimethylcyclohex-2-enecarbonitrile (2-30e). Following general procedure 3, 1.09 g of 2-29e produced 800 mg (81%) of 2-30e (mixture of diastereomers) as a yellow oil: IR (neat): 2123, 1932 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.31 – 7.22 (m, 2H), 7.14 – 7.04 (m, 2H), 6.61 (d, $J$ = 2.9 Hz, 1H), 5.70 (d, $J$ = 8.4 Hz, 1H), 2.26 – 2.18 (m, 1H), 2.14 – 2.04 (m, 1H), 1.97 (d, $J$ = 2.6 Hz, 3H), 1.73 – 1.64 (m, 1H), 1.57 – 1.47 (m, 1H), 1.11 (m, 3H), 1.03 (m, 3H), 0.91 (s, 9H), 0.30 (s, 3H), 0.19 (m, 3H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 208.4, 208.3, 138.2, 138.0, 136.4, 136.3, 128.32, 128.28, 128.1, 128.0, 125.3, 124.9, 124.8, 121.6, 121.5, 120.9, 118.54, 118.48, 104.88, 104.84, 90.9, 74.6, 74.5, 37.42, 37.36, 31.0, 30.8, 25.5, 24.3, 23.7, 23.5, 22.7, 22.4, 18.2, 15.8, -2.9, -3.0, -3.8; ES+ m/z (relative intensity) 407.3 (M − N$_2$ + H, 15%), 452.3 (M + NH$_4$, 100 %), 457.3 (M + Na, 80%); HRMS (ES+) Calcd for C$_{25}$H$_{35}$N$_2$OSi: 407.2519, Found: 407.2523.
3-[3-(2-Azidophenyl)-1-methylpropa-1,2-dienyl]-6,6-dimethylcyclohex-2-enol (2-31). To a 0 °C stirring solution of 2-30a (429 mg, 1.05 mmol) in 10 mL of THF was added TBAF (1.0 M in THF, 10 mL, 10 mmol). The reaction mixture was stirred at 0 °C for 54 h (monitored by TLC for starting material consumption). Ice-cold saturated NaHCO$_3$ solution (10 mL) was added and then the reaction mixture was diluted with Et$_2$O (10 mL). The organic layer was washed with ice-cold brine (2 X 20 mL), dried over Na$_2$SO$_4$ and evaporated under reduced pressure maintaining a water bath temperature below 40 °C. The resulting oil was purified by flash chromatography (neutral alumina, 25% EtOAc/hexanes) to give 289 mg (93%) of 2-31 as an orange oil (mixture of diastereomers): IR (neat): 3393, 2124, 1930 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.31 (m, 1H), 7.21 (m, 1H), 7.11 (dd, $J = 8.0$, 0.9 Hz, 1H), 7.05 (t, $J = 7.8$ Hz, 1H), 6.57 (s, 1H), 5.68 (m, 1H), 3.89 (d, $J = 7.9$ Hz, 1H), 2.11 – 2.03 (m, 2H), 1.96 (d, $J = 2.7$ Hz, 3H), 1.73 (br s, 1H), 1.50 (m, 1H), 1.39 (m, 1H), 0.98 – 0.96 (m, 3H), 0.92 – 0.88 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 207.9, 207.8, 136.11, 136.09, 135.1, 135.0, 127.93, 127.91, 126.1, 125.0, 124.8, 124.7, 118.4, 105.6, 90.2, 74.9, 74.6, 33.6, 33.5, 33.3, 32.9, 26.5, 26.2, 24.6, 24.5, 21.2, 20.7, 15.9; ES+ m/z (relative intensity) 318.1 (M + Na, 100%), 296.2 (M + H, 10%); HRMS (ES+) Calcd for C$_{18}$H$_{21}$N$_3$ONa: 318.1582, Found: 318.1585.
10-(tert-Butyldimethylsilanyloxy)-6,9,9-trimethyl-5,7,8,9,10,10a-hexahydro-indeno[2,1-b]indole (2-32a). Following general procedure 6, 43 mg of 2-30a (0.11 mmol) produced 25 mg of 2-32a (62 %) and 2 mg of 2-34 (8%). 9: Crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of an Et₂O/hexanes solution of 2-32a over a period of 24 h at rt. (brown solid): mp 63 - 64 °C; IR (neat): 3406 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.89 (br s, 1H), 7.66 (d, J = 7.2 Hz, 1H), 7.30 (dd, J = 7.0, 1.7 Hz, 1H), 7.08 – 6.99 (m, 2H), 3.36 (d, J = 10.1 Hz, 1H), 3.04 (d, J = 10.3 Hz, 1H), 2.57 (ddd, J = 14.2, 5.4, 1.7 Hz, 1H), 2.41 – 2.37 (m, 1H), 2.03 (s, 3H), 1.66 (ddd, J = 13.1, 5.5, 1.6 Hz, 1H), 1.38 – 1.27 (m, 1H), 1.19 (s, 3H), 1.07 (s, 3H), 1.01 (s, 3H), -0.02 (s, 3H), -0.44 (s, 3H); ¹³C NMR (100 MHz, C₆D₆) δ 150.0, 146.8, 139.8, 126.9, 122.5, 121.7, 120.9, 119.9, 119.4, 112.0, 83.4, 50.1, 40.7, 37.9, 30.4, 26.9, 23.1, 18.8, 18.5, 10.3, -1.7, -2.5; APCI+ m/z (relative intensity) 382.3 (M + H, 100%); HRMS (ES+) Calcd for C₂₄H₃₆NOSi: 382.2566, Found: 382.2564.

X-Ray Analysis (2-32a).

A colorless block shaped crystal of 2-32a (C₂₄H₃₅NOSi) with approximate dimensions 0.06 x 0.15 x 0.20 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 128(2) K, cooled by Rigaku-MSC X-Stream 2000, on a Bruker SMART APEX CCD area detector system equipped with a graphite
monochromator and a MoKα fine-focus sealed tube (λ = 0.71073Å) operated at 1600 watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal.

A total of 1850 frames were collected with a scan width of 0.3° in ω and an exposure time of 10 seconds/frame. The total data collection time was about 8 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm. The integration of the data using a Triclinic unit cell yielded a total of 10873 reflections to a maximum θ angle of 28.34° (0.90 Å resolution), of which 11043 were independent, completeness = 94.9 %, R_{int} = 0.0536, R_{sig} = 0.1644 and 5107 were greater than 2σ(I). The final cell constants: a = 9.437(8)Å, b = 13.537(9)Å, c = 19.104(9)Å, α = 101.43(4)°, β = 97.13(4)°, γ = 99.38(4)°, volume = 2328.0(26)Å³, are based upon the refinement of the XYZ-centroids of 1755 reflections above 20σ(I) with 2.230° < θ < 28.348°. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.069.

The structure was solved and refined using the Bruker SHELXTL (Version 6.1)
Software Package, using the space group P-1, with Z = 2 for the formula unit, C_{48}H_{70}N_{2}O_{2}Si_{2}. The final anisotropic full-matrix least-squares refinement on F^2 with 503 variables converged at R1 = 10.20%, for the observed data and wR2 = 30.66% for all data. The goodness-of-fit was 0.984. The largest peak on the final difference map was 0.388 e/Å^3 and the largest hole was -0.724 e/Å^3. Based on the final model, the calculated density of the crystal is 1.088 g/cm^3 and F(000) amounts to 832 electrons.

![Image of TIPS-OH]

6,9,9-Trimethyl-10-triisopropylsilanyloxy-5,7,8,9,10,10a-hexahydro-indeno[2,1-b]indole (2-32b). Following general procedure 6, 100 mg (0.221 mmol) of 15a produced 60 mg (64%) of 2-32b and 3 mg (5%) of 2-34. 2-32b: (brown oil): IR (neat): 3403 cm^{-1}; ^1H NMR (400 MHz, CDCl_3) δ 7.89 (br s, 1H), 7.61 (d, J = 6.3 Hz, 1H), 7.29 (d, J = 8.3 Hz, 1H), 7.02 (m, 2H), 3.37 (d, J = 9.4 Hz, 1H), 3.31 (d, J = 9.2 Hz, 1H), 2.54 (dd, J = 13.7, 5.1 Hz, 1H), 2.02 (s, 3H), 1.68 (dd, J = 12.8, 5.8 Hz, 1H), 1.32 (dd, J = 13.0, 5.5 Hz, 1H), 1.20 – 1.16 (m, 1H), 1.18 (s, 3H), 1.06 – 1.02 (m, 12H), 1.00 (s, 3H), 0.92 – 0.89 (m, 9H); ^13C NMR (100 MHz, CDCl_3) δ 149.6, 147.6, 139.2, 126.2, 121.8, 121.6, 119.5, 119.4, 118.8, 111.2, 85.1, 50.9, 40.6, 37.9, 29.0, 22.9, 19.1, 18.7, 18.3, 14.1, 10.2; ES+ m/z (relative intensity) 424.2 (M + H, 100%); HRMS (ES+) Calcd for C_{27}H_{42}NOSi: 424.3036, Found: 424.3039.
10-Benzyl-6,9,9-trimethyl-5,7,8,9,10,10a-hexahydroinden[2,1-b]indole (2-32c). Following general procedure 5, 55 mg of allene 2-30c produced 18 mg (51%) of 2-34 and 12 mg (24%) of 2-32c as a brown solid: mp 69 °C (dec.); IR (neat): 3404 cm⁻¹; ¹H NMR (300 MHz, C₆D₆) δ 7.81 (d, J = 7.3 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.25 (t, J = 7.5 Hz, 2H), 7.22 – 7.16 (m, 3H), 7.11 (m, 1H), 6.81 (br s, 1H), 4.77 (d, J = 11.7 Hz, 1H), 4.30 (d, J = 11.6 Hz, 1H), 3.47 (dd, J = 10.8, 1.3 Hz, 1H), 2.53 (d, J = 10.9 Hz, 1H), 2.39 (ddd, J = 14.1, 5.0, 2.0 Hz, 1H), 2.20 (m, 1H), 1.81 (t, J = 1.6 Hz, 3H), 1.45 (ddd, J = 13.1, 5.1, 2.0 Hz, 1H), 1.22 (s, 3H), 1.13 (m, 1H), 0.98 (s, 3H); ¹³C NMR (90 MHz, CDCl₃) δ 149.0, 145.8, 139.4, 139.3, 128.2, 127.3, 127.2, 125.1, 122.3, 120.9, 119.9, 119.4, 119.2, 111.6, 90.5, 74.8, 48.3, 40.9, 37.6, 28.4, 22.7, 18.6, 10.2; ES⁺ m/z (relative intensity) 380.1 (M + Na, 100%), 358.2 (M+ H, 75%); HRMS (ES⁺) Calcd for C₂₅H₂₈NO: 358.2171, Found: 358.2186.
6,9,9-Trimethyl-10-(2-trimethylsilylethoxymethoxy)-5,7,8,9,10,10a-hexahydroindeno[2,1-b]indole (2-32d). Following general procedure 6, 84 mg (0.197 mmol) of allene 2-30d produced 47 mg (60%) of 2-32d as a yellow solid: mp 139 – 140 °C; IR (neat): 3405 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.99 (br s, 1H), 7.55 (d, \(J = 7.8\) Hz, 1H), 7.32 (d, \(J = 7.8\) Hz, 1H), 7.09 (t, \(J = 7.1\) Hz, 1H), 7.03 (t, \(J = 7.6\) Hz, 1H), 4.91 (d, \(J = 6.8\) Hz, 1H), 4.61 (d, \(J = 6.8\) Hz, 1H), 3.87 (m, 1H), 3.52 (m, 1H), 3.38 (d, \(J = 10.5\) Hz, 1H), 2.73 (d, \(J = 10.7\) Hz, 1H), 2.54 (m, 1H), 2.36 (m, 1H), 2.01 (s, 3H), 1.66 (m, 1H), 1.30 (m, 1H), 1.21 (s, 3H), 1.08 (s, 3H), 0.91 (m, 1H), 0.00 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 149.2, 145.9, 139.3, 125.3, 122.3, 120.1, 120.0, 119.4, 118.6, 111.7, 96.8, 89.7, 65.8, 48.7, 41.3, 36.5, 28.7, 22.7, 18.7, 18.0, 10.2, -1.5; ES+ \(m/z\) (relative intensity) 398.7 (M + H, 100%), 420.7 (M + Na, 40%); HRMS (ES+) Calcd for C\(_{24}\)H\(_{36}\)NO\(_2\)Si: 398.2515, Found: 398.2521.

10-(\textit{tert}-Butyldimethylsilyloxy)-6,9,9-trimethyl-5,7,8,9,10,10a-hexahydroindeno[2,1-b]indole-10-carbonitrile (2-32e). Following general procedure 6, using neutral alumina (deactivated with 10 % H\(_2\)O by weight) for column chromatography (5% Et\(_2\)O/hexanes \(\rightarrow\) 50% Et\(_2\)O/hexanes), 223 mg (0.513 mmol) of 2-30e produced 130 mg (62%) of 2-32e and 14 mg (7%) of 2-33e. 2-32e: Crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of an Et\(_2\)O/benzene solution.
of 2-32e over a period of 24 h at rt. (white solid): mp 195 °C (dec.); IR (neat): 3358, 1611 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.27 (br s, 1H), 7.65 (m, 1H), 7.31 (m, 1H), 7.05 (m, 2H), 3.56 (d, \(J = 1.4\) Hz, 1H), 2.62 (ddd, \(J = 14.4, 5.3, 1.7\) Hz, 1H), 2.44 – 2.34 (m, 1H), 1.89 (t, \(J = 1.6\) Hz, 3H), 1.80 (dd, \(J = 13.4, 5.5\) Hz, 1H), 1.68 (ddd, \(J = 13.9, 6.1, 1.7\) Hz, 1H), 1.31 (s, 3H), 1.22 (s, 3H), 1.11 (s, 9H), 0.29 (s, 3H), -0.11 (s, 3H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 151.1, 142.7, 139.4, 126.2, 125.3, 120.0, 119.9, 119.10, 119.06, 117.6, 111.8, 83.8, 51.2, 41.3, 38.4, 27.7, 26.5, 22.2, 19.03, 18.97, 10.2, -0.7, -2.3; ES+ \(m/\ell\) (relative intensity) 407.3 (M + H, 100%), 429.3 (M + Na, 40%); HRMS (ES+) Calcd for C\(_{25}\)H\(_{35}\)N\(_2\)OSi: 407.2519, Found: 407.2523.

X-Ray Analysis (2-32e).

A colorless block shaped crystal of 2-32e (C\(_{25}\)H\(_{34}\)N\(_2\)OSi) with approximate dimensions 0.20 x 0.30 x 0.40 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 129(2) K, cooled by Rigaku-MSC X-Stream 2000, on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a MoK\(\alpha\) fine-focus sealed tube (\(\lambda = 0.71073\)Å) operated at 1600 watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal.
A total of 1850 frames were collected with a scan width of 0.3° in ω and an exposure time of 5 seconds/frame. The total data collection time was about 6 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm. The integration of the data using a Triclinic unit cell yielded a total of 11778 reflections to a maximum θ angle of 28.34° (0.90 Å resolution), of which 5913 were independent, completeness = 97.7%, R_{int} = 0.0152, R_{sig} = 0.0250 and 4820 were greater than 2σ(I). The final cell constants: a = 9.779(3)Å, b = 10.939(3)Å, c = 11.635(4)Å, α = 89.483(6)°, β = 77.658(5)°, γ = 85.916(5)°, volume = 1212.8(7)Å³, are based upon the refinement of the XYZ-centroids of 4583 reflections above 20σ(I) with 2.137° < θ < 27.994°. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.8805.

The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package, using the space group P-1, with Z = 2 for the formula unit, C_{25}H_{34}N_{2}OSi. The final anisotropic full-matrix least-squares refinement on F² with 270 variables converged at R1 = 4.77%, for the observed data and wR2 = 14.44% for all data. The goodness-of-fit was 1.037. The largest peak on the final difference map was 0.384 e⁻/Å³ and the largest hole was -0.174 e⁻/Å³. Based on the final model, the calculated density of the crystal is 1.113 g/cm³ and F(000) amounts to 440 electrons.
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**6,9,9-Trimethyl-5,7,8,9,10,10a-hexahydroindeno[2,1-b]indol-10-ol (2-32f).**

Following general procedure 6, 109 mg (0.369 mmol) of allene 2-31 produced 59 mg (60%) of 2-32f as a brown solid: mp 76 °C (dec.); IR (neat): 3400, 3301 cm⁻¹; ¹H NMR (400 MHz, C₆D₆) δ 7.94 (d, J = 7.7 Hz, 1H), 7.29 – 7.20 (m, 3H), 6.99 (br s, 1H), 3.26 (d, J = 10.7 Hz, 1H), 2.56 (dd, J = 10.7, 4.8 Hz, 1H), 2.34 (dd, J = 14.2, 3.0 Hz, 1H), 2.16 (td, J = 14.2, 3.2 Hz, 1H), 1.77 (m, 1H), 1.77 (s, 3H), 1.44 (dd, J = 13.1, 3.2 Hz, 1H), 1.08 (s, 3H), 1.05 (m, 1H), 0.91 (s, 3H); ¹³C NMR (90 MHz, CDCl₃) δ 148.9, 145.5, 139.3, 125.0, 122.5, 120.7, 120.1, 119.5, 118.3, 111.8, 82.6, 49.1, 40.7, 36.2, 28.0, 22.7, 17.5, 10.2; APCI+ m/z (relative intensity) 268.2 (M + H, 100%); HRMS (ES+) Calcd for C₁₈H₂₂NO: 268.1701, Found: 268.1714.

**4-(tert-Butyldimethylsilanyloxy)-3,3,11-trimethyl-2,3,4,4a-tetrahydro-1H-indolo[1,2-a]indole-4-carbonitrile (2-33e).** Yellow solid: mp 166 – 167 °C; ¹H NMR (360 MHz, CDCl₃) δ 7.55 (m, 1H), 7.48 (m, 1H), 7.10 – 7.00 (m, 2H), 6.26 (s, 1H), 4.72
(s, 1H), 2.66 (ddd, $J = 14.4, 5.3, 1.6$ Hz, 1H), 2.41 – 2.32 (m, 1H), 2.07 (t, $J = 1.6$ Hz, 3H), 1.79 (td, $J = 13.7, 5.5$ Hz, 1H), 1.66 (ddd, $J = 13.9, 6.0, 1.6$ Hz, 1H), 1.28 (s, 3H), 1.21 (s, 3H), 1.11 (s, 9H), 0.30 (s, 3H), -0.33 (s, 3H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 151.4, 138.6, 136.7, 132.7, 126.9, 121.3, 120.2, 119.5, 117.3, 111.9, 91.9, 84.4, 67.1, 41.6, 37.0, 27.8, 26.6, 21.6, 19.1, 18.9, 9.9, -0.8, -2.6; ES+ m/z (relative intensity) 407.3 (M + H, 100%), 429.3 (M + Na, 45%); HRMS (ES+) Calcd for C$_{25}$H$_{35}$N$_2$OSi: 407.2519, Found: 407.2523.

3,3,11-Trimethyl-2,3-dihydro-1H-indolo[1,2-a]indole (2-34). The title compound was formed upon exposure of crude thermosylates or photosylates of 2-30 to SiO$_2$ during flash chromatography (2% Et$_2$O/hexanes). Yellow oil: IR (neat): 1649, 1641, 1560, 1452 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.47 (m, 1H), 7.37 (m, 1H), 7.11 (m, 1H), 6.99 (m, 1H), 6.08 (s, 1H), 5.73 (s, 1H), 2.58 (t, $J = 6.5$ Hz, 2H), 2.01 (s, 3H), 1.67 (t, $J = 6.5$ Hz, 2H), 1.18 (s, 6H); $^{13}$C NMR (90 MHz, C$_6$D$_6$) $\delta$ 147.9, 137.7, 134.3, 134.1, 133.3, 123.9, 122.7, 122.2, 120.5, 115.5, 110.4, 92.8, 37.9, 32.6, 29.5, 19.8, 9.6; ES+ m/z (relative intensity) 250.1 (M + H, 100%); HRMS (ES+) Calcd for C$_{18}$H$_{20}$N: 250.1596, Found: 250.1593.
[5-(2-Azidophenyl)-3-methylpenta-1,3,4-trienyl]-\textit{tert}-butyldimethylsilane (2-38e). Following general procedure 3, 66 mg (0.19 mmol) of acetate 2-43a produced 34 mg (59%) of 2-38e as a yellow oil: IR (neat): 2121, 1929 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.31 (d, \(J = 7.6\) Hz, 1H), 7.22 (t, \(J = 7.7\) Hz, 1H), 7.11 (d, \(J = 7.9\) Hz, 1H), 7.06 (t, \(J = 7.3\) Hz, 1H), 6.54 (d, \(J = 18.9\) Hz, 1H), 6.51 (s, 1H), 5.84 (d, \(J = 19.0\) Hz, 1H), 1.91 (d, \(J = 2.5\) Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 210.8, 142.3, 136.3, 128.5, 128.0, 126.8, 125.9, 124.8, 118.4, 105.4, 88.6, 26.4, 16.7, 14.6, -6.0, -6.1; ES\(^+\) m/z (relative intensity) 283.2 (M – N\(_2\), 50%).

1-Azido-2-(4-methyl-3-phenylpenta-1,2,4-trienyl)-benzene (38f). Following general procedure 4, isopropenylmagnesium bromide (0.5 M in THF, 3.3 mL, 1.6 mmol) and acetate 2-12 (190 mg, 0.652 mmol) provided 123 mg (69%) of 38f as a yellow oil: IR (neat): 2121, 1921 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.37 (d, \(J = 7.7\) Hz, 1H), 7.05 – 6.97 (m, 2H), 6.72 (s, 1H), 5.04 (s, 1H), 4.86 (s, 1H), 1.91 (s, 3H); \(^{13}\)C NMR (90 MHz, CDCl\(_3\)) \(\delta\) 208.4, 139.6, 136.4, 136.0, 128.9, 128.27, 128.26, 127.4, 125.6, 124.9, 118.5, 115.5, 115.2, 91.32, 91.30, 22.0; ES\(^+\) m/z (relative intensity) 246.1 (M – N\(_2\) + H, 100%); HRMS (ES+) Calcd for C\(_{18}\)H\(_{16}\)N: 246.1283, Found: 246.1276.
1-Azido-2-(3-methyl-4,5,5-triphenylpenta-1,2,4-trienyl)-benzene  \((38g)\).

Following general procedure 3, allowing the reaction mixture to warm to rt for 1h (as monitored by TLC for starting material consumption), 1.043 g (2.221 mmol) of 2-43b produced 357 mg (38%) of 2-38g as a yellow foam: IR (neat): 2123, 1943 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.36 – 7.29 (m, 8H), 7.24 – 7.20 (m, 3H), 7.12 – 7.09 (m, 4H), 7.02 – 6.99 (m, 2H), 6.95 (td, \(J = 7.4, 1.4\) Hz, 1H), 6.71 (dd, \(J = 7.8, 1.4\) Hz, 1H), 6.06 (q, \(J = 2.9\) Hz, 1H), 1.86 (d, \(J = 3.0\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 207.9, 144.3, 142.8, 141.1, 140.5, 137.5, 135.9, 131.2, 130.4, 129.7, 128.7, 128.1, 127.9, 127.52, 127.46, 126.7, 126.6, 126.4, 126.3, 124.8, 118.2, 105.9, 87.4, 19.7; ES\(^+\) \(m/z\) (relative intensity) 398.2 (M – N\(_2\) + H, 100%), 426.2 (M + H, 20%); HRMS (ES\(^+\)) Calcd for C\(_{30}\)H\(_{24}\)N\(_3\): 426.1970, Found: 426.1965.

[3-(2-Azidophenyl)-1-isopropenylpropa-1,2-dienyl]-trimethylsilane  \((38i)\).

Following general procedure 4, isopropenylmagnesium bromide (0.5 M in THF, 16 mL, 7.8 mmol) and carbonate 2-12a (990 mg, 3.12 mmol) provided 520 mg (62%) of 2-38i as a yellow oil: IR (neat): 2123, 1903 cm\(^{-1}\); \(^1\)H NMR (360 MHz, C\(_6\)D\(_6\)) \(\delta\) 7.35 (m, 1H), 6.79 (m, 2H), 6.68 (m, 1H), 6.49 (s, 1H), 5.03 (s, 1H), 4.93 (t, \(J = 1.2\) Hz, 1H), 1.88 (s, 3H); \(^{13}\)C NMR (75 MHz, C\(_6\)D\(_6\)) \(\delta\) 210.6, 140.2, 136.0, 127.7, 127.3, 126.8, 125.1, 118.8,
114.4, 106.3, 86.3, 23.4, -0.1; ES+ m/z (relative intensity) 242.2 (M – N2 + H, 25%);

[6-(2-Azidophenyl)-4-methylhexa-2,4,5-trienyloxy]-tert-butyldimethylsilane (2-38k). Following general procedure 3, 263 mg (0.682 mmol) of acetate 2-43k produced 167 mg (72%) of 2-38k as a yellow oil: IR (neat): 2123, 1929 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.35 (dd, J = 7.7, 1.4 Hz, 1H), 7.24 (td, J = 7.2, 1.3 Hz, 1H), 7.13 (dd, J = 8.0, 1.0 Hz, 1H), 7.08 (td, J = 7.6, 1.0 Hz, 1H), 6.53 (s, 1H), 6.28 (dd, J = 15.6, 0.7 Hz, 1H), 5.78 (dtd, J = 15.6, 5.3, 1.2 Hz, 1H), 4.30 (dt, J = 5.3, 1.4 Hz, 2H), 1.96 (s, 3H), 0.95 (s, 9H), 0.12 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 209.7, 136.3, 128.9, 128.4, 128.0, 127.3, 126.0, 124.8, 118.4, 103.3, 88.6, 63.9, 25.9, 18.4, 15.3, -5.2; ES+ m/z (relative intensity) 314.2 (M – N₂ + H), 80%); HRMS (AP+) Calcd for C₁₉H₂₈NOSi: 314.1940, Found: 314.1936.

1-Azido-2-(3-methylundeca-1,2,4-trienyl)-benzene (2-38l). Following general procedure 3, 164 mg (0.504 mmol) of 2-43l produced 83 mg (59%) of 2-38l as a colorless oil: IR (neat): 2119, 1931 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.30 (dd, J = 7.7, 1.2 Hz, 1H), 7.18 (t, J = 7.7 Hz, 1H), 7.07 (d, J = 7.3 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.46 (s, 1H), 6.02 (d, J = 15.6 Hz, 1H), 5.64 (dt, J = 15.6, 6.9 Hz, 1H), 2.10 (app q, J = 7.1 Hz,
2H), 1.89 (d, J = 2.7 Hz, 3H), 1.40 – 1.35 (m, 2H), 1.29 – 1.24 (m, 6H), 0.87 (m, 3H); $^{13}$C NMR (90 MHz, CDCl$_3$) δ 209.1, 136.2, 130.9, 128.3, 127.8, 126.8, 126.4, 124.7, 118.3, 103.8, 88.4, 33.0, 31.7, 29.4, 28.9, 22.6, 15.3, 14.1; ES+ m/z (relative intensity) 254.2 (M – N$_2$ + H, 100%); HRMS (ES+) Calcd for C$_{18}$H$_{24}$N: 254.1909, Found: 254.1920.

[7-(2-Azidophenyl)-5-methylhepta-3,5,6-trienyloxy]-tert-butyldimethylsilane (2-38m). Following general procedure 3, 778 mg of acetate 2-43m produced 216 mg (31%) of 2-38m as a yellow oil: IR (neat): 2119, 1931 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) δ 7.31 (dd, J = 7.6, 1.1 Hz, 1H), 7.21 (m, 1H), 7.11 (d, J = 7.9 Hz, 1H), 7.05 (t, J = 7.9 Hz, 1H), 6.48 (s 1H), 6.10 (d, J = 15.8 Hz, 1H), 5.67 (dt, J = 15.5, 7.2 Hz, 1H), 3.68 (t, J = 6.5 Hz, 2H), 2.35 (app q, J = 6.8 Hz, 2H), 1.91 (d, J = 2.5 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); $^{13}$C NMR (90 MHz, CDCl$_3$) δ 209.3, 136.3, 128.8, 128.4, 127.9, 126.9, 126.3, 124.7, 118.4, 103.7, 88.5, 62.9, 36.5, 25.9, 18.3, 15.2, -5.3; ES+ m/z (relative intensity) 328.2 (M – N$_2$ + H, 100%); HRMS (ES+) Calcd for C$_{20}$H$_{30}$NOSi: 328.2097, Found: 328.2080.

[6-(2-Azidophenyl)-3,4-dimethylhexa-2,4,5-trienyloxy]-tert-butyldimethylsilane (2-38n). Following general procedure 3, 1.22 g (3.05 mmol) of acetate 2-43n produced 810 mg (75%) of 2-38n as a yellow oil: IR (neat): 2121, 1928 cm$^{-1}$; $^1$H NMR
(360 MHz, CDCl$_{3}$) $\delta$ 7.31 (dd, $J = 7.7$, 1.4 Hz, 1H), 7.16 (td, $J = 7.6$, 1.5 Hz, 1H), 7.06 (dd, $J = 8.0$, 1.0 Hz, 1H), 7.02 (td, $J = 7.5$, 1.1 Hz, 1H), 6.57 (s, 1H), 5.62 (tt, $J = 6.1$, 1.1 Hz, 1H), 4.35 (d, $J = 6.1$ Hz, 2H), 1.96 (d, $J = 2.9$ Hz, 3H), 1.74 (s, 3H), 0.93 (s, 9H), 0.10 (s, 6H); $^{13}$C NMR (90 MHz, CDCl$_{3}$) $\delta$ 208.2, 136.1, 131.5, 128.0, 127.8, 126.3, 126.2, 124.7, 118.3, 107.4, 90.2, 60.9, 25.9, 18.3, 16.2, 15.2, -5.1; ES+ m/z (relative intensity) 328.3 (M – N$_2$ + H, 25%), 378.3, (M + Na, 20%); HRMS (ES+) Calcd for C$_{20}$H$_{30}$NOSi: 328.2097, Found: 328.2090.

1-Azido-2-penta-1,2,4-trienyl-benzene (2-38o). Following general procedure 4, vinylmagnesium bromide (1.0 M in THF, 230 µL, 0.23 mmol) and acetate 2-25 (50 mg, .23 mmol) produced 21 mg (49%) of 2-38o as a yellow oil: IR (neat): 2123, 1931 cm$^{-1}$; $^1$H NMR (360 MHz, C$_6$D$_6$) $\delta$ 7.32 (dd, $J = 7.2$, 1.6 Hz, 1H), 6.80 – 6.71 (m, 3H), 6.63 (m, 1H), 6.24 – 6.06 (m, 2H), 5.06 (dt, $J = 16.2$, 1.5 Hz, 1H), 4.87 (m, 1H); $^{13}$C NMR (90 MHz, C$_6$D$_6$) $\delta$ 210.4, 136.8, 132.1, 128.63, 128.59, 125.4, 125.0, 118.6, 117.0, 98.7, 91.0; ES+ m/z (relative intensity) 184.1 (M + H, 45%), 206.1 (M + Na, 10%); HRMS (ES+) Calcd for C$_{11}$H$_{10}$N$_3$: 184.0875, Found: 184.0877.

1-Azido-2-(4-methylpenta-1,2,4-trienyl)-benzene (2-38p). Following general procedure 4, isopropenylmagnesium bromide (0.5 M in THF, 4.6 mL, 2.3 mmol) and
acetate 2-25 (200 mg, 0.929 mmol) produced 90 mg (49%) of 2-38p as a yellow oil: IR (neat): 2123, 1925 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.40 (dd, \(J = 7.8, 1.5\) Hz, 1H), 7.24 (td, \(J = 7.7, 1.5\) Hz, 1H), 7.13 (dd, \(J = 8.0, 1.1\) Hz, 1H), 7.08 (td, \(J = 7.5, 1.1\) Hz, 1H), 6.70 (d, \(J = 6.4\) Hz, 1H), 6.34 (d, \(J = 6.5\) Hz, 1H), 5.02 (d, \(J = 0.6\) Hz, 1H), 4.93 (q, \(J = 1.5\) Hz, 1H), 1.82 (t, \(J = 0.6\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 208.5, 138.5, 136.3, 128.2, 128.1, 125.5, 124.9, 118.4, 114.6, 101.5, 91.8, 19.7; EI+ \(m/z\) (relative intensity) 169.1 (M – N\(_2\), 70%); HRMS (EI+) Calcd for C\(_{12}\)H\(_{11}\)N: 169.0891, Found: 169.0973.

[6-(2-Azidophenyl)-2-bromo-4-methylhexa-2,4,5-trienyloxy]-\textit{tert}-butyl-dimethylsilane (2-38q). Following general procedure 3, 133 mg (0.286 mmol) of acetate 2-62 produced 71 mg (59%) of 2-38q as a yellow oil: IR (neat): 2124,1934 cm\(^{-1}\); \(^1\)H NMR (300 MHz, C\(_6\)D\(_6\)) δ 7.56 (m, 1H), 6.85 – 6.77 (m, 3H), 6.65 (m, 1H), 6.44 (d, \(J = 1.5\) Hz, 1H), 4.19 (s, 2H), 1.83 (d, \(J = 3.0\) Hz, 3H), 0.91 (s, 9H), -0.03 (s, 6H); \(^{13}\)C NMR (75 MHz, C\(_6\)D\(_6\)) δ 208.5, 137.3, 129.6, 128.7, 127.4, 126.7, 125.3, 123.5, 119.0, 101.7, 91.4, 69.3, 26.3, 20.2, 18.9, -5.0; ES+ \(m/z\) (relative intensity) 420.0 (M + H, 50%); HRMS (ES+) Calcd for C\(_{19}\)H\(_{27}\)ON\(_3\)Si\(_{79}\)Br: 420.1107, Found: 420.1121.
1-Azido-2-[3-(2-phenylethynylcyclopent-1-enyl)-buta-1,2-dienyl]-benzene (2-38r). Following general procedure 3, 160 mg (0.419 mmol) of acetate 2-64 produced 57 mg (40%) of 2-38r as a yellow oil: IR (neat): 2121, 1922 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.26 – 7.24 (m, 2H), 7.18 – 7.14 (m, 3H), 7.10 – 7.05 (m, 2H), 6.96 (d, \(J = 7.8\) Hz, 1H), 6.92 (t, \(J = 7.4\) Hz, 1H), 6.43 (s, 1H), 2.58 (td, \(J = 7.0, 1.3\) Hz, 2H), 2.45 – 2.36 (m, 2H), 2.22 (d, \(J = 2.7\) Hz, 3H), 1.74 (app pent, \(J = 7.6\) Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 210.3, 142.9, 136.3, 131.0, 128.35, 128.27, 128.0, 127.9, 126.1, 123.8, 119.4, 118.4, 104.2, 95.8, 89.1, 87.8, 39.7, 36.3, 22.3, 17.6; ES+ \(m/z\) (relative intensity) 310.1 (M – N\(_2\) + H, 100%); HRMS (ES+) Calcd for C\(_{23}\)H\(_{20}\)N: 310.1596, Found: 310.1592.

1-(tert-Butyldimethylsilanyl)-3-methyl-1,4-dihydrocyclopenta[b]indole (2-39e). Following general procedure 6, with the modification of column chromatography performed at -78 °C, 84 mg (0.27 mmol) of allene 2-38e produced 34 mg (44%) of 2-39e as a yellow oil: IR (neat): 3410 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.95 (br s, 1H), 7.57 (m, 1H), 7.37 (m, 1H), 7.10 – 7.05 (m, 2H), 6.35 (app pent, \(J = 1.8\) Hz, 1H), 1H), 3.43
(app pent, $J = 1.8$ Hz, 1H), 2.21 (t, $J = 1.8$ Hz, 3H), 0.87 (s, 9H), 0.24 (s, 3H), -0.36 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 147.6, 140.3, 133.2, 127.9, 124.6, 123.2, 119.9, 119.3, 119.2, 111.7, 38.0, 27.3, 18.0, 12.8, -4.5, -8.1; ES+ $m/z$ (relative intensity) 284.2 (M + H, 90%), 567.4 (2M + H, 100%), 850.6 (3M + H, 25%); HRMS (ES+) Calcd for C$_{18}$H$_{26}$NSi: 284.1835, Found: 284.1837.

**2-Methyl-3-phenyl-1,4-dihydro-cyclopenta[b]indole (2-39f).** Following general procedure 6, using spherical silica gel (20 - 45 µm) for flash chromatography, 48 mg (0.18 mmol) of 2-38f produced 30 mg (69%) of 2-39f as a yellow oil: IR (neat): 3412 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) δ 8.0 (br s, 1H), 7.55 – 7.47 (m, 5H), 7.39 – 7.33 (m, 2H), 7.14 – 7.05 (m, 2H), 3.38 (s, 2H), 2.29 (s, 3H); $^{13}$C NMR (90 MHz, CDCl$_3$) δ 147.6, 143.2, 139.3, 134.8, 131.0, 128.9, 128.0, 127.2, 124.8, 120.0, 119.8, 117.7, 117.0, 111.8, 37.1, 15.8; ES+ $m/z$ (relative intensity) 246.1 (M + H, 100%); HRMS (ES+) Calcd for C$_{18}$H$_{16}$N: 246.1283, Found: 246.1276.

**3-Methyl-1,1,2-triphenyl-1,4-dihydro-cyclopenta[b]indole (2-39g).** Following general procedure 5, 95 mg (0.22 mmol) of 2-38g produced 47 mg (53%) of 2-39g and 23 mg (26%) of 2-40g. 2-39g: (yellow solid): mp 92 °C (dec.); IR (neat): 3413 cm$^{-1}$; $^1$H
NMR (300 MHz, CDCl$_3$) $\delta$ 8.20 (br s, 1H), 7.48 (d, $J = 8.0$ Hz, 1H), 7.33 – 7.28 (m, 9H), 7.24 – 7.22 (m, 6H), 7.12 – 7.08 (m, 3H), 2.27 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 161.9, 160.0, 153.5, 145.1, 141.9, 139.8, 136.7, 130.1, 129.7, 127.8, 127.6, 126.9, 126.3, 123.8, 120.6, 120.3, 118.1, 111.9, 12.1; ES+ $m/z$ (relative intensity) 398.2 (M + H, 100%), 420.2 (M + Na, 70%); HRMS (ES+) Calcd for C$_{30}$H$_{24}$N: 398.1909, Found: 398.1922.

2-Methyl-3-trimethylsilyl-1,4-dihydrocyclopenta[b]indole (2-39i).

Following general procedure 6 without copper, and employing flash chromatography at -78 °C (1% Et$_2$O/hexanes $\rightarrow$ 5% Et$_2$O/hexanes $\rightarrow$ 15% Et$_2$O/hexanes), 118 mg (0.438 mmol) of 2-38i produced 5 mg (6%) of 2-47b, 30 mg (28%) of 2-39i, and 37 mg (35%) of 2-40i. 2-39i: (yellow oil): IR (neat): 3378, 1682 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.91 (br s, 1H), 7.46 (d, $J = 7.6$ Hz, 1H), 7.34 (d, $J = 7.3$ Hz, 1H), 7.09 -7.00 (m, 2H), 3.24 (s, 2H), 2.29 (s, 3H), 0.37 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.5, 151.7, 139.4, 128.0, 124.3, 119.8, 119.4, 117.5, 117.1, 111.6, 39.3, 18.4, -0.1; ES+ $m/z$ (relative intensity) 242.2 (M + H, 100%); HRMS (ES+) Calcd for C$_{15}$H$_{20}$NSi: 242.1365, Found: 242.1369.
1-Methyl-2,3,3-triphenyl-3H-3a-azacyclopenta[a]indene (2-40g). Crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of an Et₂O/pentane solution of 2-40g over a period of 24 h at rt. (yellow solid): mp 144 - 145 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.75 (dd, \(J = 7.9, 1.0\) Hz, 1H), 7.36 - 7.29 (m, 9H), 7.22 - 7.20 (m, 3H), 7.15 - 7.10 (m, 2H), 7.05 - 6.96 (m, 3H), 6.87 (d, \(J = 8.1\) Hz, 1H), 6.57 (s, 1H), 2.28 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 149.6, 147.2, 138.4, 134.3, 133.9, 133.1, 130.2, 128.5, 128.0 (2 signals), 127.9, 127.7, 127.6, 121.4, 121.2, 119.2, 110.4, 91.3, 78.6, 11.3; ES+ m/z (relative intensity) 398.2 (M + H, 100%), 420.2 (M + Na, 10%); HRMS (ES+) Calcd for C\(_{30}\)H\(_{24}\)N: 398.1909, Found: 398.1901.

X-Ray Analysis (2-40g).

A colorless rod shaped crystal of 2-40g (2(C\(_{30}\)H\(_{23}\)N), C\(_5\)H\(_{12}\)) with approximate dimensions 0.13 x 0.14 x 0.29 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 298(2) K, cooled by Rigaku-MSC X-Stream 2000, on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a MoK\(_\alpha\) fine-focus sealed tube (\(\lambda = 0.71073\)Å) operated at 1600 watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal.
A total of 1850 frames were collected with a scan width of 0.3° in $\omega$ and an exposure time of 20 seconds/frame. The total data collection time was about 14 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm. The integration of the data using a Triclinic unit cell yielded a total of 9890 reflections to a maximum $\theta$ angle of 28.48° (0.90 Å resolution), of which 5970 were independent, completeness = 97.1%, $R_{int} = 0.0364$, $R_{sig} = 0.0778$ and 2909 were greater than $2\sigma(I)$. The final cell constants: $a = 10.254(8)$ Å, $b = 10.743(8)$ Å, $c = 12.090(9)$ Å, $\alpha = 97.948(13)^\circ$, $\beta = 106.727(13)^\circ$, $\gamma = 102.782(13)^\circ$, volume = 1214.5(16) Å$^3$, are based upon the refinement of the XYZ-centroids of 2876 reflections above 20$\sigma(I)$ with 2.310° < $\theta$ < 27.366°. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.3513.

The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package, using the space group P-1, with $Z = 2$ for the formula unit, C32.50 H28.5 N. The final anisotropic full-matrix least-squares refinement on $F^2$ with 310 variables converged at $R_1 = 7.21\%$, for the observed data and $wR_2 = 24.36\%$ for all data.
The goodness-of-fit was 0.958. The largest peak on the final difference map was 0.571 e/Å³ and the largest hole was -0.190 e/Å³. Based on the final model, the calculated density of the crystal is 1.186 g/cm³ and F(000) amounts to 462 electrons.

2-Methyl-1-trimethylsilanyl-8H-3a-azacyclopa[a]indene (2-40i). Yellow oil: ¹H NMR (360 MHz, CDCl₃) δ 7.27 (d, J = 7.3 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.07 (d, J = 7.7 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.88 (s, 1H), 3.74 (s, 2H), 2.19 (s, 3H), 0.24 (s, 9H); ¹³C NMR (90 MHz, CDCl₃) δ 142.4, 140.8, 134.4, 129.4, 127.3, 125.5, 122.5, 109.5, 109.4, 109.2, 30.5, 13.9, 0.2; ES+ m/z (relative intensity) 242.2 (M + H, 100%); HRMS (ES+) Calcd for C₁₅H₂₀NSi: 242.1365, Found: 242.1362.

tert-Butyl-(2-iodovinyl)-dimethylsilane (2-42). To an ice-cold stirring solution of Zr(Cp)₂Cl₂ (1.82 g, 6.22 mmol) in 20 mL of THF was added DIBAL-H (1.0 M in hexanes, 6.2 mL, 6.2 mmol). The reaction was stirred at that temperature for 30 min, and then a solution of (tert-butyldimethylsilyl)acetylene (1.06 mL, 5.66 mmol) in 3 mL of THF was added slowly and the reaction mixture was allowed to warm to room temperature. Upon warming, the reaction mixture turned green and then red. The reaction solution was cooled to -78 °C and a solution of I₂ (1.87 g, 7.36 mmol) in 5 mL of THF was added slowly and stirring was continued at that temperature for 1 h. The
reaction solution was then allowed to warm to room temperature and stirring was continued for 2.5 h. At that time, ice-cold 1 M HCl (35 mL) was slowly added and the mixture diluted with Et₂O (50 mL). The organic layer was washed with 1 M HCl (50 mL), 1 M Na₂S₂O₃ solution (2 X 50 mL), saturated NaHCO₃ solution (50 mL), H₂O (3 X 50 mL), brine (3 X 50 mL), dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes) to provide 1.14 g (75%) of the title compound as a pale yellow oil: \(^1\)H NMR (360 MHz, CDCl₃) \(\delta\) 7.04 (d, \(J = 16.1\) Hz, 1H), 6.65 (d, \(J = 16.2\) Hz, 1H), 0.86 (s, 9H), 0.02 (s, 6H); \(^{13}\)C NMR (90 MHz, CDCl₃) \(\delta\) 147.6, 90.1, 26.2, 16.6, -6.3; EI+ m/z (relative intensity) 141.1 (M – I, 20%), 210.9 (M – t-Bu, 100%), 268.0 (M⁺, 20%); HRMS (EI+) Calcd for C₈H₁₇Si: 260.0144, Found: 268.0146.

![Acetic Acid 1-(2-Azidophenyl)-5-(tert-butyldimethylsilanyl)-pent-4-en-2-ynyl Ester (2-43a)](image)

Following general procedure 2 using 20 mol% PdCl₂(PPh₃)₂, 1.14 g (4.25 mmol) of iodide 2-42 and 1.46 g (6.80 mmol) of alkyne 2-25 produced 332 mg (22%) of the title compound as a yellow oil: IR (neat): 2127, 1746 cm⁻¹; \(^1\)H NMR (360 MHz, CDCl₃) \(\delta\) 7.67 (dd, \(J = 7.6, 1.4\) Hz, 1H), 7.37 (td, \(J = 7.8, 1.5\) Hz, 1H), 7.19 – 7.13 (m, 2H), 6.75 (d, \(J = 1.7\) Hz, 1H), 6.50 (d, \(J = 19.4\) Hz, 1H), 5.98 (dd, \(J = 19.3, 1.8\) Hz, 1H), 2.08 (s, 3H), 0.86 (s, 9H), 0.01 (s, 6H); \(^{13}\)C NMR (90 MHz, CDCl₃) \(\delta\) 169.3, 144.9, 137.7, 130.2, 129.2, 128.0, 124.9, 123.5, 118.2, 87.0, 85.1, 61.2, 26.3, 20.9, 16.5, -6.5;
Acetic Acid 1-(2-azidophenyl)-4,5,5-triphenylpent-4-en-2-ynyl Ester (2-43b).

To a -78 °C stirring solution of 2-45 (802 mg, 2.86 mmol) in 29 mL of THF was added n-BuLi (2.40 M in hexanes, 1.19 mL, 2.86 mmol) and the reaction solution was stirred at that temperature for 1 h. A solution of 2-azidobenzaldehyde (2-11) (421 mg, 2.86 mmol) in 29 mL of THF was added dropwise and stirring was continued at -78 °C for 1 h. Ac₂O (284 µL, 3.00 mmol) then was added dropwise and the reaction warmed to 0 °C. Sat’d NH₄Cl solution (60 mL) was added and the mixture was diluted with Et₂O (60 mL). The organic layer was washed with H₂O (3 X 120 mL) and brine (3 X 120 mL), dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by flash chromatography (1% Et₂O/hexanes → 10% Et₂O/hexanes) providing 1.05 g (78%) of the title compound as a yellow foam: IR (neat): 2126, 1743 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.45 – 7.43 (m, 2H), 7.40 – 7.36 (m, 2H), 7.32 – 7.25 (m, 5H), 7.19 – 7.07 (m, 8H), 7.00 – 6.97 (m, 2H), 6.72 (s, 1H), 2.05 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.0, 150.1, 142.2, 140.8, 138.7, 137.5, 130.7, 130.0, 129.9, 129.7, 129.4, 127.7 (2 signals), 127.6 (2 signals), 127.5, 127.2, 126.9, 124.6, 120.3, 117.9, 89.0, 88.1, 61.3, 20.6; ES+ m/z (relative intensity) 492.1 (M + Na, 40%); HRMS (ES+) Calcd for C₃₁H₂₃N₃O₂Na: 492.1688, Found: 492.1694.
Acetic Acid 1-(2-Azidophenyl)-6-(tert-butyldimethylsilyl oxy)-hex-4-en-2-ynyl Ester (2-43k). Following general procedure 2, with a reaction time of 4 h, 2.40 g (11.2 mmol) of 2-25 and 2.08 g (6.97 mmol) of tert-butyldimethylsilyl-(E)-3-iodo-2-propenyl ether produced 1.99 g (74%) of the title compound as a yellow oil: IR (neat): 2127, 1747 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.66 (dd, J = 7.6, 1.6 Hz, 1H), 7.37 (td, J = 7.7, 1.6 Hz, 1H), 7.20 – 7.10 (m, 2H), 6.73 (d, J = 1.8 Hz, 1H), 6.25 (dt, J = 15.8, 4.1 Hz, 1H), 5.79 (dq, J = 15.8, 2.2 Hz, 1H), 4.20 (ddd, J = 4.0, 2.2, 0.4 Hz, 1H), 2.07 (s, 3H), 0.89 (s, 9H), 0.03 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 169.3, 143.9, 137.7, 130.1, 129.2, 128.1, 124.9, 118.2, 107.5, 85.3, 85.0, 62.6, 61.2, 25.7, 20.9, 18.2, -5.5; ES⁺ m/z (relative intensity) 408.1 (M + Na, 100%); HRMS (ES⁺) Calcd for C₂₀H₂₇N₃O₃NaSi: 408.1719, Found: 408.1729.

Acetic Acid 1-(2-Azidophenyl)-undec-4-en-2-ynyl Ester (2-43l). Following general procedure 2, 674 mg (3.13 mmol) of alkyne 2-25 and 466 mg (1.96 mmol) of (E)-1-iodooct-1-ene produced 165 mg (26%) of 2-43l as a yellow oil: IR (neat): 2125, 1744 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.67 (d, J = 7.5 Hz, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.18 – 7.12 (m, 2H), 6.72 (d, J = 1.2 Hz, 1H), 6.20 (dt, J = 15.9, 7.0 Hz, 1H), 5.48 (dd, J
\[ \text{Acetic Acid 1-(2-Azidophenyl)-7-(\text{tert-butyldimethylsilyloxy})-hept-4-en-2-yny} \text{yl Ester (2-43m). Following general procedure 2 with a reaction time of 4 h, 1.14 g (5.28 mmol) of alkyne 2-25 and 1.03 g (3.30 mmol) of (E)-\text{tert-Butyl-(4-iodobut-3-enyloxy)}-dimethylsilane produced 778 mg (59%) of 2-43m as a yellow oil: IR (neat): 2127, 1746 cm}^{-1}; ^1\text{H NMR (360 MHz, CDCl}_3\text{)} \delta 7.66 (dd, J = 7.7, 1.2 Hz, 1H), 7.36 (td, J = 7.9, 1.5 Hz, 1H), 7.16 – 7.11 (m, 2H), 6.71 (d, J = 1.6 Hz, 1H), 6.19 (dt, J = 15.9, 7.2 Hz, 1H), 5.55 (dd, J = 16.0, 1.7 Hz, 1H), 3.61 (t, J = 6.6 Hz, 2H), 2.29 (dd, J = 13.5, 6.5, 1.2 Hz, 2H), 2.06 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^13\text{C NMR (90 MHz, CDCl}_3\text{)} \delta 169.3, 142.8, 137.7, 130.1, 129.2, 128.1, 124.8, 118.1, 110.3, 85.6, 83.7, 61.9, 61.2, 36.5, 25.8, 20.8, 18.2, -5.4; \text{ES}^+ \text{ m/z (relative intensity) 298.2 (M – N}_2\text{ + H, 10%), 422.2 (M + Na, 100%); HRMS (ES+) Calcd for C}_{21}\text{H}_{29}\text{N}_3\text{O}_3\text{NaSi: 422.1876, Found: 422.1892.} \]
Acetic Acid 1-(2-Azidophenyl)-6-(tert-butyldimethylsilanyloxy)-4-methylhex-4-en-2-ynyl Ester (2-43n). Following general procedure 2, 1.55 g (7.22 mmol) of alkyne 2-25 and 1.41 g (4.52 mmol) of (E)-tert-Butyl-(3-iodobut-2-enyloxy)-dimethylsilane produced 1.22 g (68%) of 2-43n as a yellow oil: IR (neat): 2126, 1746 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.64 (dd, , J = 6.6, 1.2 Hz, 1H), 7.32 (td, J = 7.8, 1.4 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 7.7 (d, J = 8.0 Hz, 1H), 6.70 (s, 1H), 5.94 (td, J = 5.6, 1.2 Hz, 1H), 4.18 (d, J = 6.2 Hz, 2H), 2.01 (s, 3H), 1.74 (s, 3H), 0.85 (s, 9H), 0.20 (s, 6H); ¹³C NMR (90 MHz, CDCl₃) δ 168.9, 138.2, 137.5, 130.0, 129.1, 128.0, 124.7, 117.9, 117.4, 88.9, 82.3, 60.9 59.5, 25.6, 20.6, 18.0, 17.1, -5.5; ES⁺ m/z (relative intensity) 422.2 (M + Na, 100%); HRMS (ES⁺) Calcd for C₂₁H₂₉N₃O₃SiNa: 422.1876, Found: 422.1865.

3-Isopropenyl-4H-[1,2,3]triazolo[1,5-a]indole (2-47b). Yellow solid: mp 152 – 153 °C; IR (neat):1473, 1396 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.83 (d, J = 7.8 Hz, 1H), 7.53 – 7.43 (m, 2H), 7.33 (td, J = 7.6, 1.0 Hz, 1H), 5.52 (s, 1H), 5.18 (t, J = 1.4 Hz, 1H), 3.95 (s, 2H), 2.26 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 141.5, 137.1, 135.6, 135.1, 134.3, 128.2, 126.7, 126.5, 112.6, 112.4, 27.6, 20.4; APCI+ m/z (relative intensity) 198.1 (M + H, 100%); HRMS (APCI+) Calcd for C₁₂H₁₂N₅: 198.1031, Found: 198.1030.
1-(3-Isopropenyl-[1,2,3]triazolo[1,5-a]indol-4-ylidene)-ethylamine (2-48).

Following general procedure 5, 169 mg (0.627 mmol) of 2-38i produced 65 mg (53%) of 2-47b and 54 mg (23%) of 2-48 as a yellow solid. Crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of a CH₂Cl₂ solution of 2-48 over a period of 24 h at rt. mp 144 °C (dec.); IR (neat): 3413, 3338, 3206, 1644 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.88 (m, 1H), 7.56 (m, 1H), 7.23 – 7.18 (m, 2H), 5.55 (br s, 1H), 5.48 (t, J = 1.5 Hz, 1H), 4.56 (t, J = 0.7 Hz, 1H), 2.50 (s, 3H), 2.33 (t, J = 0.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 149.0, 138.7, 136.4, 133.7, 133.1, 131.3, 125.6, 123.2, 121.7, 116.8, 111.9, 92.7, 23.4, 21.8; ES+ m/z (relative intensity) 239.1 (M + H, 100%); HRMS (APCI+) Calcd for C₁₄H₁₄N₄: 239.1297, Found: 239.1286.

X-Ray Analysis (2-48).

A colorless plate shaped crystal of 2-48 (C₁₄H₁₄N₄) with approximate dimensions 0.09 x 0.20 x 0.28 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 123(2) K, cooled by Rigaku-MSC X-Stream 2000, on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a MoKα fine-focus sealed tube (λ = 0.71073Å) operated at 1600 watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal.
A total of 1850 frames were collected with a scan width of 0.3° in ω and an exposure time of 10 seconds/frame. The total data collection time was about 8 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm. The integration of the data using a Monoclinic unit cell yielded a total of 20935 reflections to a maximum θ angle of 28.33° (0.90 Å resolution), of which 6098 were independent, completeness = 98.6%, R_int = 0.0440, R_sig = 0.0492 and 3664 were greater than 2σ(I). The final cell constants: a = 9.8894(16) Å, b = 21.213(3)Å, c = 11.8512(19) Å, α = 90°, β = 93.758(3)°, γ = 90°, volume = 2480.9(7) Å³, are based upon the refinement of the XYZ-centroids of 5397 reflections above 20σ(I) with 2.275° <θ <28.319°. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.8135.

The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package, using the space group P2(1)/c, with Z = 8 for the formula unit, C_{14}H_{14}N_{4}. The final anisotropic full-matrix least-squares refinement on F² with 329 variables converged at R1 = 6.79%, for the observed data and wR2 = 19.85% for all data. The goodness-of-fit was 0.963. The largest peak on the final difference map was 0.201 e⁻
and the largest hole was -0.213 e/Å³. Based on the final model, the calculated density of the crystal is 1.276 g/cm³ and F(000) amounts to 1008 electrons.

\[
\text{Br} \quad \text{OTBS}
\]

(Z)-(2-Bromo-3-iodoallyloxy)-tert-butyl(dimethyl)silane (2-61). To a stirring solution of (Z)-2-Bromo-3-iodoacrylic Acid Ethyl Ester (2-65) (2.138 g, 7.012 mmol) in 25 mL of Et₂O at -78 °C was added dropwise DIBAL-H (1.0 M in hexanes, 15 mL, 15 mmol) and stirring was continued for 15 min at that temperature. At that time, the solution was warmed to 0 °C and stirred for 30 min (monitored by TLC for starting material consumption). MeOH was added dropwise at 0 °C until gas evolution ceased, and then the reaction mixture was diluted with Et₂O (25 mL) and 10% HCl solution (50 mL) was added. The organic layer was washed with 10% HCl solution (2 X 50 mL), water (3 X 50 mL), and brine (3 X 50 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ (20 mL) and imidazole (716 mg, 10.5 mmol) and TBSCl (1.59 g, 10.5 mmol) were added sequentially and the mixture was stirred for 20 min. The reaction solution was then concentrated under reduced pressure and the residue was dissolved in Et₂O (50 mL) and H₂O (50 mL). The organic layer was washed with H₂O (3 X 50 mL) and brine (3 X 50 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (10% Et₂O/hexanes) to provide 2.47 g (94%) of 2-61 as a colorless oil: \(^1\)H NMR (300 MHz, CDCl₃) δ 7.19 (t, J = 1.7 Hz, 1H), 4.25 (d, J = 1.7 Hz, 2H), 0.89 (s, 9H), 0.08 (s, 6H); \(^13\)C NMR (75 MHz, CDCl₃) δ 138.0, 79.8, 68.4, 25.7, 18.2, -5.4; EI+ m/z (relative
intensity) 318.9 (M − t-Bu, 100%); HRMS (EI+) Calcd for C_{5}H_{9}O_{5}Si^{79}Br: 318.8651, Found: 318.8645.

Acetic Acid 1-(2-Azidophenyl)-5-bromo-6-(tert-butyldimethylsilyloxy)-hex-4-en-2-ynyl Ester (2-62). Following general procedure 2, using 1 equiv. of vinyl iodide, 760 mg (3.53 mmol) of alkyne 2-25 and 1.33 g (3.53 mmol) of 2-61 produced 135 mg (8%) of 2-62 as a yellow oil: IR (neat): 2126, 1747 cm⁻¹; \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 7.80 (d, \(J = 7.7\) Hz, 1H), 7.39 (t, \(J = 7.7\) Hz, 1H), 7.24 – 7.14 (m, 2H), 6.77 (s, 1H), 6.40 (d, \(J = 1.5\) Hz, 1H), 4.28 (s, 2H), 2.09 (s, 3H), 0.89 (s, 9H), 0.07 (s, 6H); \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta\) 169.4, 137.94, 137.87, 130.3, 129.7, 127.5, 124.9, 118.2, 107.9, 90.6, 83.4, 67.4, 61.3, 25.7, 20.9, 18.2, -5.5; ES⁺ m/z (relative intensity) 406.0 (M − t-Bu, 100%), 486.0 (M + Na, 60%); HRMS (ES⁺) Calcd for C_{20}H_{26}O_{3}N_{3}Si^{79}BrNa: 486.0825, Found: 486.0837.

Acetic Acid 1-(2-Azidophenyl)-3-(2-phenylethynylcyclopent-1-enyl)-prop-2-ynyl Ester (2-64). Following general procedure 7 using 5% Et₂O/hexanes as the eluent for flash chromatography, 129 mg (0.671 mmol) of alkyne 2-63 provided 161 mg (63%)
of 2-64 as a yellow oil: IR (neat): 2125, 1744 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta \) 7.76 (dd, \(J = 7.7, 1.5 \text{ Hz}, 1\)H), 7.34 – 7.30 (m, 2H), 7.25 (m, 1H), 7.23 – 7.19 (m, 3H), 7.04 (dd, \(J = 8.1, 0.9 \text{ Hz}, 1\)H), 6.94 (td, \(J = 7.6, 1.0 \text{ Hz}, 1\)H), 6.78 (s, 1H), 2.56 – 2.48 (m, 4H), 1.99 (s, 3H), 1.86 (app pent, \(J = 7.6 \text{ Hz}, 2\)H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta \) 169.4, 137.8, 132.3, 131.6, 130.2, 129.6, 129.2, 128.3, 128.2, 127.9, 124.9, 123.0, 118.1, 96.6, 91.7, 85.8, 83.7, 61.3, 36.8, 36.5, 23.0, 20.9; ES\(^+\) m/z (relative intensity) 404.1 (M + Na, 25%); HRMS (ES\(^+\)) Calcd for C\(_{24}\)H\(_{19}\)N\(_3\)O\(_2\): 404.1375, Found: 404.1390.

\(\text{(E)}\)-3-Iodo-2-phenylprop-2-en-1-ol (2-66b). A solution of (Z)-3-Iodo-2-phenylprop-2-en-1-ol (2-66a) (1.12 g, 4.31 mmol) in 160 mL of MeCN was irradiated at 254 nm for 2 h and then concentrated under reduced pressure. \(^1\)H NMR analysis of the reaction mixture indicated that a 5 : 1 mixture of the E and Z isomers were present. The residue was purified by flash chromatography (hexanes → 4% EtOAc/hexanes → 8% EtOAc/hexanes) to provide 157 mg (14%) of the starting material and 400 mg (36%) of 2-66b as a white solid: mp 58 – 59 °C; IR (neat): 3321 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta \) 7.28 – 7.21 (m, 3H), 7.11 – 7.09 (m, 2H), 6.49 (s, 1H), 4.19 (s, 2H), 2.27 (br s, 1H); \(^{13}\)C NMR (90 MHz, CDCl\(_3\)) \(\delta \) 151.7, 139.5, 128.5, 128.1, 128.0, 78.3, 67.3; EI\(^+\) m/z (relative intensity) 260.3 (M\(^+\), 100%); HRMS (EI\(^+\)) Calcd for C\(_9\)H\(_9\)OI: 259.9698, Found: 259.9704.
(E)-tert-Butyldimethyl-(2-phenylpent-2-en-4-ynyloxy)-silane (2-67). To a stirring solution of alcohol 2-66b (395 mg, 1.52 mmol) in 10 mL of Et$_3$N was added trimethylsilylacetylene (433 µL, 3.04 mmol), PdCl$_2$(PPh$_3$)$_2$ (21 mg, 0.30 mmol), and CuI (3 mg, 0.02 mmol), and the reaction mixture was stirred for 24 h at rt and then diluted with Et$_2$O (50 mL). The mixture was washed with saturated NH$_4$Cl solution (3 X 50 mL), H$_2$O (3 X 50 mL) and brine (3 X 50 mL), dried over MgSO$_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography (hexanes $\rightarrow$ 5% Et$_2$O/hexanes $\rightarrow$ 25% Et$_2$O/hexanes) to provide 215 mg (54%) of the corresponding TMS-alkyne. TBAF (1.0 M in THF, 1 mL, 1 mmol) was added slowly to a solution of the above TMS-alkyne (215 mg, 0.933 mmol) in 10 mL of THF and stirred for 20 min. Saturated NaHCO$_3$ (10 mL) was added and the organic layer was washed with H$_2$O (3 X 30 mL) and brine (3 X 30 mL), dried over MgSO$_4$, and concentrated under reduced pressure. The residue was dissolved in CH$_2$Cl$_2$ (6 mL). Imidazole (95 mg, 1.4 mmol) and TBSCl (211 mg, 1.40 mmol) were added sequentially and the reaction solution was stirred for 20 min. At that time, H$_2$O (10 mL) was added slowly and the reaction mixture was diluted with Et$_2$O (50 mL). The organic layer was washed with H$_2$O (3 X 50 mL), and brine (3 X 50 mL), dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes $\rightarrow$ 5% Et$_2$O/hexanes) to provide 228 mg (90%) of 2-67 as a yellow oil: IR (neat): 3294 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.49 – 7.46 (m, 2H), 7.39 – 7.29 (m, 3H), 5.94 (app q, $J = 2.3$ Hz, 1H), 4.45 (dd, $J = 2.0$, 0.7 Hz, 2H), 2.90 (d, $J = 2.5$ Hz, 1H), 0.94 (s, 9H), 0.10 (s, 6H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 153.1, 137.0, 128.2, 128.1, 127.7, 103.5, 81.6, 80.6, 65.4, 25.8, 18.3, -5.4; ES+...
m/z (relative intensity) 273.2 (M + H, 100%); HRMS (ES+) Calcd for C_{17}H_{25}OSi: 273.1675, Found: 273.1664.

![Chemical Structure](image)

**Acetic Acid 1-(2-Azidophenyl)-6-(tert-butyldimethysilyloxy)-5-phenylhex-4-en-2-ynyl Ester (2-68a).** To a -30 °C stirring solution of alkyne 2-67 (278 mg, 0.837 mmol) in 8 mL of THF was added slowly n-BuLi (2.5 M in hexanes, 340 µL, 0.84 mmol) and stirring was continued for 1 h. At that time, a solution of 2-azidobenzaldehyde (123 mg, 0.837 mmol) in 8 mL of THF was added. Stirring was continued for 20 min (as monitored by TLC for starting material consumption) and then Ac_2O (119 µL, 1.26 mmol) was added and the reaction solution was allowed to warm to rt. At that point, ice-cold, saturated NH_4Cl (10 mL) was added dropwise and the mixture was diluted with Et_2O (25 mL). The organic layer was washed with H_2O (3 X 25 mL) and brine (3 X 25 mL), dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (5% Et_2O/hexanes → 15% Et_2O/hexanes) to provide 320 mg (83%) of 2-68a as a yellow oil: IR (neat): 2126, 1746 cm^{-1}; ^1H NMR (360 MHz, CDCl_3) δ 7.35 – 7.32 (m, 2H), 7.30 (dd, J = 7.7, 1.1 Hz, 1H), 7.24 (td, J = 7.9, 1.4 Hz, 1H), 7.21 – 7.18 (m, 3H), 7.00 – 6.92 (m, 2H), 6.59 (d, J = 1.5 Hz, 1H), 5.91 (app q, J = 2.0 Hz, 1H), 4.37 (d, J = 1.7 Hz, 2H), 1.94 (s, 3H), 0.84 (s, 9H), 0.00 (s, 6H); ^13C NMR (90 MHz, CDCl_3) δ 169.3, 153.1, 137.6, 137.0, 130.0, 129.4, 128.02, 127.95, 127.8, 127.7, 124.7, 118.0, 103.6, 88.0, 85.3, 65.3, 61.4, 25.8, 20.8, 18.2, -5.5; ES+ m/z (relative
intensity) 484.1 (M + Na, 80%), 507.2 (M + 2Na, 70%); HRMS (ES+) Calcd for C_{26}H_{31}N_{3}O_{3}SiNa: 484.2032, Found: 484.2033.

Acetic Acid 1-(2-Azidophenyl)-6-(tert-butyldimethylsilanyloxy)-5-methylhex-4-en-2-ynyl Ester (2-68b). Following general procedure 2, 480 mg (2.22 mmol) of alkyne 2-25 and 435 mg (1.39 mmol) of iodide 2-72 produced 95 mg (17%) of 2-68b as a red oil: IR (neat): 2126, 1748 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.65 (dd, \(J = 8.1, 1.1\) Hz, 1H), 7.37 (td, \(J = 7.8, 1.5\) Hz, 1H), 7.17 – 7.14 (m, 2H), 6.75 (d, \(J = 1.7\) Hz, 1H), 5.33 (s, 1H), 4.33 (s, 2H), 2.07 (s, 3H), 1.83 (d, \(J = 0.9\) Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); \(^13\)C NMR (90 MHz, CDCl\(_3\)) \(\delta\) 169.4, 153.1, 137.7, 130.2, 129.2, 128.3, 124.9, 118.3, 104.2, 88.4, 83.7, 63.9, 61.4, 25.8, 20.9, 19.8, 18.2, -5.4; ES+ \(m/z\) (relative intensity) 422.2 (M + Na, 100%); HRMS (ES+) Calcd for C_{21}H_{29}N_{3}O_{3}SiNa: 422.1876, Found: 422.1894.

[4-(2-Azidobenzyl)-3-methylnaphthalen-1-ylmethoxy]-tert-butyldimethylsilane (2-69). Following general procedure 3, 320 mg (0.693 mmol) of 2-68a produced 120 mg (41%) of 2-69 as a tacky yellow solid: IR (neat): 2120 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.73 (dd, \(J = 7.5, 1.7\) Hz, 1H), 7.54 (dd, \(J = 7.6, 1.8\) Hz, 1H), 7.17 – 7.13 (m,
2H), 6.97 – 6.90 (m, 3H), 6.56 (td, \(J = 7.1, 2.0\ Hz, 1H\)), 6.23 (d, \(J = 7.8\ Hz, 1H\)), 4.96 (s, 2H), 4.08 (s, 2H), 2.17 (s, 3H), 0.74 (s, 9H), -0.08 (s, 6H); \(^{13}\)C NMR (90 MHz, CDCl\(_3\)) \(\delta\) 137.7, 135.2, 134.2, 132.9, 131.53, 131.48, 129.9, 129.0, 127.28, 127.25, 127.1, 125.9, 124.8, 124.6, 123.7, 117.6, 63.4, 28.9, 26.0, 20.4, 18.5, -5.2; ES\(^+\) m/z (relative intensity) 418.3 (M + H, 100%), 435.3 (M + NH\(_4\), 70%), 440.3 (M + Na, 70%); HRMS (ES+) Calcd for C\(_{25}\)H\(_{32}\)N\(_3\)OSi: 418.2315, Found: 418.2322.

**Acetic Acid 1-(2-Azidophenyl)-3-(2-hex-1-ynylcyclopent-1-enyl)-prop-2-ynyl Ester (2-74a).** Following general procedure 7 using 2% Et\(_2\)O/hexanes \(\rightarrow\) 7% Et\(_2\)O/hexanes as the eluent for flash chromatography, 819 mg (4.75 mmol) of alkyne 2-73a produced 1.08 g (63%) of 2-74a as a yellow oil: IR (neat): 2125, 1745 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.84 (d, \(J = 7.6\ Hz, 1H\)), 7.40 (t, \(J = 7.4\ Hz, 1H\)), 7.20 – 7.15 (m, 2H), 6.86 (s, 1H), 2.58 – 2.45 (m, 4H), 2.40 (t, \(J = 6.9\ Hz, 2H\)), 2.09 (s, 3H), 1.89 (app pent, \(J = 7.5\ Hz, 2H\)), 1.55 – 1.41 (m, 4H), 0.91 (t, \(J = 7.2\ Hz, 3H\)); \(^{13}\)C NMR (90 MHz, CDCl\(_3\)) \(\delta\) 169.0, 137.6, 132.8, 130.0, 129.4, 127.9, 126.9, 124.6, 117.9, 98.0, 90.3, 83.7, 76.8, 61.1, 37.0, 36.1, 30.5, 22.7, 21.6, 20.6, 19.1, 13.3; ES\(^+\) m/z (relative intensity) 384.2 (M + Na, 40%); HRMS (ES+) Calcd for C\(_{22}\)H\(_{23}\)N\(_3\)O\(_2\)Na: 384.1688, Found: 384.1696.
Acetic Acid 1-(2-Azidophenyl)-3-(2-phenylethynylcyclohex-1-enyl)-prop-2-ynyl Ester (2-74b). Following general procedure 7, using 1% Et₂O/hexanes → 7% Et₂O/hexanes as the eluent for flash chromatography, 1.02 g (4.94 mmol) of alkyne 2-73b provided 1.66 g (85%) of 2-74b as a yellow solid: mp 80 – 81 °C; IR (neat): 2124, 1742 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.73 (dd, J = 7.7, 1.3 Hz, 1H), 7.30 – 7.27 (m, 2H), 7.20 – 7.13 (m, 4H), 6.95 (d, J = 7.6 Hz, 1H), 6.83 (d, J = 7.6 Hz, 1H), 6.77 (s, 1H), 2.20 – 2.10 (m, 4H), 1.90 (s, 3H), 1.55 – 1.45 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 169.9, 137.4, 131.3, 129.9, 129.3, 127.9, 127.83, 127.77, 127.6, 125.0, 124.6, 123.0, 117.8, 93.2, 89.7, 88.6, 87.4, 61.0, 29.7, 29.5, 21.4, 21.3, 20.5; ES⁺ m/z (relative intensity) 418.2 (M + Na, 40%); HRMS (ES⁺) Calcd for C₂₅H₂₁N₃O₂Na: 418.1531, Found: 418.1546.

Acetic Acid 1-(2-azidophenyl)-3-(2-trimethylsilanylethynylcyclohex-1-enyl)-prop-2-ynyl Ester (2-74c). Following general procedure 7, using 3% Et₂O/hexanes → 10% Et₂O/hexanes as the eluent for flash chromatography, 586 mg (2.90 mmol) of alkyne 2-73c produced 658 mg (58%) of 2-74c as a yellow oil: IR (neat): 2126, 1745 cm⁻¹; ¹H
NMR (360 MHz, C₆D₆) δ 7.94 (dd, J = 7.5, 1.8 Hz, 1H), 7.05 (s, 1H), 6.83 (td, J = 7.4, 1.3 Hz, 1H), 6.78 (td, J = 7.4, 1.7 Hz, 1H), 6.48 (dd, J = 7.7, 1.3 Hz, 1H), 1.97 – 1.94 (m, 2H), 1.91 – 1.88 (m, 2H), 1.57 (s, 3H), 1.02 – 0.99 (m, 4H), 0.14 (s, 9H); ¹³C NMR (90 MHz, C₆D₆) δ 168.8, 138.4, 134.9, 130.4, 130.2, 129.0, 126.8, 125.0, 118.4, 106.4, 98.6, 89.9, 88.0, 61.6, 30.2, 30.1, 21.7 (X2), 20.5, 0.2; ES+ m/z (relative intensity) 414.1 (M + Na, 25%); HRMS (ES+) Calcd for C₂₂H₂₅N₃O₂NaSi: 414.1614, Found: 414.1622.

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1-Azido-2-[3-[3-(tert-butyldimethylsilanyloxy)-4,4-dimethylcyclohex-1-enyl]-4-trimethylsilanylobuta-1,2-dienyl]-benzene (2-84a). Following general procedure 3, using TMSCH₂MgCl (1.0 M in Et₂O), 115 mg (0.251 mmol) of 2-29a produced 115 mg (95%) of 2-84a as a yellow oil (mixture of diastereomers): IR (neat): 2123, 1919 cm⁻¹; ¹H NMR (300 MHz, C₆D₆) δ 7.45 (m, 1H), 6.85 – 6.75 (m, 3H), 6.71 (m, 1H), 5.68 (d, J = 1.2 Hz, 1H), 3.96 (s, 1H), 2.25 – 2.10 (m, 2H), 1.80 – 1.70 (m, 2H), 1.43 (m, 1H), 1.31 (m, 1H), 1.00 (s, 9H), 0.97 – 0.95 (m, 3H), 0.94 (s, 3H), 0.16 – 0.15 (m, 3H), 0.10 (s, 9H + 3H); ¹³C NMR (75 MHz, CDCl₃) δ 208.1, 207.9, 136.2, 133.2, 133.0, 128.0, 127.7, 127.6, 127.5, 126.7, 124.8, 124.7, 118.4, 108.21, 108.18, 90.71, 90.65, 75.8, 75.7, 34.3, 34.23, 34.18, 34.1, 27.72, 27.66, 25.9, 24.9, 19.9, 19.7, 18.2, 18.1, 17.6, -0.8, -4.2, -4.9; APCI+ m/z (relative intensity) 454.3 (M + H – N₂, 100%), 482.3 (M + H, 15%); HRMS (AP+) Calcd for C₂₇H₄₄NOSi₂: 454.2961, Found: 454.2979.
2-{1-[3-(tert-Butyldimethylsilanyloxy)-4,4-dimethylcyclohex-1-enyl]-vinyl}-1H-indole (2-89). Following general procedure 5, 135 mg (0.280 mmol) of 2-84a produced 45 mg (35%) of 2-90 and 44 mg (41%) of 2-89 as a brown oil: IR (neat): 3412 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.05 (br s, 1H), 7.56 (dd, \(J = 8.2, 1.1\) Hz, 1H), 7.31 (dd, \(J = 8.0, 0.8\) Hz, 1H), 7.16 (td, \(J = 7.0, 1.2\) Hz, 1H), 7.08 (td, \(J = 7.1, 1.2\) Hz, 1H), 6.52 (dd, \(J = 2.1, 0.9\) Hz, 1H), 5.79 (pent, \(J = 1.6\) Hz, 1H), 5.34 (s, 1H), 5.22 (s, 1H), 5.22 (s, 1H), 3.88 (dd, \(J = 4.9, 2.0\) Hz, 1H), 2.30 – 2.22 (m, 2H), 1.65 (m, 1H), 1.45 (m, 1H), 0.96 (s, 3H), 0.92 (s, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 142.3, 137.4, 136.4, 136.0, 131.2, 128.6, 122.2, 120.6, 119.9, 111.9, 110.6, 102.4, 74.7, 33.8, 33.3, 26.8, 25.9, 25.4, 21.4, 18.2, -4.1, -4.9; ES+ m/z (relative intensity) 382.2 (M + H, 100%); HRMS (ES+) Calcd for C\(_{24}\)H\(_{36}\)NOSi: 382.2566, Found: 382.2555.

4-(tert-Butyldimethylsilanyloxy)-3,3-dimethyl-11-trimethylsilanylmethyl-2,3,4,4a-tetrahydro-1H-indolo[1,2-a]indole (2-90). White solid: Crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of an Et\(_2\)O/hexanes solution of 2-90 over a period of 24 h at rt. mp 105 – 106 °C; IR (neat): 1456 cm\(^{-1}\); \(^1\)H
NMR (300 MHz, CDCl$_3$) $\delta$ 7.55 – 7.45 (m, 2H), 7.05 – 6.95 (m, 2H), 6.08 (s, 1H), 4.55 (d, $J$ = 9.3 Hz, 1H), 3.10 (d, $J$ = 9.4 Hz, 1H), 2.48 (dd, $J$ = 14.2, 5.5 Hz, 1H), 2.31 (td, $J$ = 12.9, 5.1 Hz, 1H), 1.87 (s, 2H), 1.63 (dd, $J$ = 13.4, 4.0 Hz, 1H), 1.33 (m, 1H), 1.15 (s, 3H), 1.00 (s, 9H + 3H), 0.06 (s, 9H), -0.06 (s, 3H), -0.84 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 151.3, 139.6, 137.0, 132.3, 125.0, 120.7, 119.7, 118.8, 112.3, 90.8, 84.1, 65.6, 39.1, 37.8, 29.9, 26.6, 22.7, 18.5, 18.4, 15.5, -0.9, -2.3, -3.7; ES+ $m/z$ (relative intensity) 454.3 (M + H, 100%); HRMS (ES+) Calcd for C$_{27}$H$_{44}$NOSi$_2$: 454.2961, Found: 454.2949.

**X-Ray Analysis (2-90).**

A colorless block shaped crystal of 2-90 (C$_{27}$H$_{43}$NOSi$_2$) with approximate dimensions 0.13 x 0.18 x 0.25 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 123(2)K, cooled by Rigaku-MSC X-Stream 2000, on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a MoK$\alpha$ fine-focus sealed tube ($\lambda$ = 0.71073Å) operated at 1600 watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal.

A total of 1850 frames were collected with a scan width of 0.3° in $\omega$ and an exposure time of 10 seconds/frame. The total data collection time was about 8 hours. The frames were integrated with the Bruker SAINT software package using a narrow-
frame integration algorithm. The integration of the data using a Monoclinic unit cell yielded a total of 24148 reflections to a maximum θ angle of 29.13° (0.90 Å resolution), of which 7027 were independent, completeness = 94.3%, $R_{\text{int}} = 0.0910$, $R_{\text{sig}} = 0.0928$ and 4448 were greater than 2σ(I). The final cell constants: $a = 11.869(2)$ Å, $b = 10.874(2)$ Å, $c = 22.010(4)$ Å, $α = 90°$, $β = 93.52(3)$°, $γ = 90°$, volume $= 2835.2(10)$ Å$^3$, are based upon the refinement of the XYZ-centroids of 9371 reflections above 20σ(I) with 2.534° <θ <28.570°. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.4338.

The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package, using the space group P2(1)/c, with $Z = 4$ for the formula unit, C27 H₄₃NOSi₂. The final anisotropic full-matrix least-squares refinement on $F^2$ with 290 variables converged at $R1 = 7.38\%$, for the observed data and $wR2 = 19.39\%$ for all data. The goodness-of-fit was 1.022. The largest peak on the final difference map was 0.681 e⁻/Å$^3$ and the largest hole was -0.620 e⁻/Å$^3$. Based on the final model, the calculated density of the crystal is 1.063 g/cm$^3$ and F(000) amounts to 992 electrons.

**Acetic Acid 3-Phenyl-4H-[1,2,3]triazolo[1,5-a]indol-4-yl Ester (2-91).** A 10 mL microwave vessel containing a solution of acetate 2-12 (96 mg, 0.33 mmol) and PtCl₂ (4.4 mg, 0.016 mmol) in 3 mL of MeCN was subjected to microwave irradiation (300 W,
150 °C, 250 PSI max) for 1 h. The reaction solution was then diluted with Et₂O (25 mL) and washed with saturated NH₄Cl solution (25 mL), and brine (2 X 25 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (10% Et₂O/hexanes → 30% Et₂O/hexanes) to provide 60 mg (63%) of 2-91 as a yellow solid. Crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of an Et₂O/CH₂Cl₂/hexanes solution of 2-91 over a period of 24 h at rt. mp 155 – 156 °C; IR (neat): 1747 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.87 – 7.82 (m, 3H), 7.65 (dd, J = 7.6, 0.4 Hz, 1H), 7.53 (td, J = 7.6, 0.9 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.39 – 7.32 (m, 2H), 7.09 (s, 1H), 2.19 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.8, 143.2, 136.9, 135.5, 134.0, 130.9, 129.6, 129.0, 128.7, 128.1, 126.2, 112.7, 65.4, 20.7;

X-Ray Analysis (2-91).

A yellow block shaped crystal of 2-91 (C₁₇H₁₃N₃O₂) with approximate dimensions 0.19 x 0.30 x 0.32 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 133(2)K, cooled by Rigaku-MSC X-Stream 2000, on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a MoKα fine-focus sealed tube (λ = 0.71073Å) operated at 1600 watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal.
A total of 1850 frames were collected with a scan width of 0.3° in \( \omega \) and an exposure time of 10 seconds/frame. The total data collection time was about 8 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm. The integration of the data using a Monoclinic unit cell yielded a total of 11712 reflections to a maximum \( \theta \) angle of 28.33° (0.90 Å resolution), of which 3461 were independent, completeness = 99.7%, \( R_{\text{int}} = 0.0235 \), \( R_{\text{sig}} = 0.0207 \) and 3077 were greater than 2\( \sigma(I) \). The final cell constants: \( a = 5.7985(11) \) Å, \( b = 16.815(3) \) Å, \( c = 14.272(3) \) Å, \( \alpha = 90^\circ \), \( \beta = 91.443(4)^\circ \), \( \gamma = 90^\circ \), volume = 1391.1(5) Å\(^3\), are based upon the refinement of the XYZ-centroids of 7318 reflections above 20\( \sigma(I) \) with 2.422° < \( \theta \) < 28.289°. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.8787.

The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package, using the space group \( P2(1)/c \), with \( Z = 4 \) for the formula unit, \( \text{C}_{17}\text{H}_{13}\text{N}_{3}\text{O}_{2} \). The final anisotropic full-matrix least-squares refinement on \( F^2 \) with 200 variables converged at \( R1 = 4.98\% \), for the observed data and \( \text{wR}2 = 13.44\% \) for all data. The goodness-of-fit was 1.073. The largest peak on the final difference map was 0.516 e\(^-\).
and the largest hole was -0.233 e/Å³. Based on the final model, the calculated density of the crystal is 1.391 g/cm³ and F(000) amounts to 608 electrons.

**6,9,9-Trimethyl-8,9-dihydro-7H-indeno[2,1-b]indole-5-carboxylic Acid tert-Butyl Ester (2-92a).** To a 0 °C stirring solution of alcohol 2-32f (198 mg, 0.741 mmol) in 7.5 mL of CH₂Cl₂ was added DMAP (904 mg, 7.41 mmol) and Boc₂O (403 mg, 1.85 mmol) sequentially and then the reaction mixture was warmed to rt and stirred for 1 h. The solvent then was removed under reduced pressure and the residue was dissolved in Et₂O (15 mL) and washed with H₂O (3 X 15 mL), and brine (3 X 15 mL), dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by flash chromatography (5% Et₂O/hexanes) to provide 150 mg (58%) of 2-92a as an orange oil:

- IR (neat): 1736 cm⁻¹;
- ¹H NMR (400 MHz, CDCl₃) δ 8.01 (dd, J = 8.3, 0.8 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.17 (td, J = 7.5, 1.0 Hz, 1H), 7.10 (ddd, J = 8.5, 7.3, 1.4 Hz, 1H), 6.58 (s, 1H), 2.64 (td, J = 6.0, 1.3 Hz, 2H), 2.23 (s, 3H), 1.75 (t, J = 6.7 Hz, 2H), 1.69 (s, 9H), 1.20 (s, 6H);
- ¹³C NMR (100 MHz, CDCl₃) δ 150.2, 148.7, 141.9, 139.7, 133.6, 132.4, 125.5, 124.8, 123.0, 121.7, 117.6, 116.8, 116.3, 83.9, 38.6, 33.7, 28.4, 28.3, 20.5, 14.0; ES⁺ m/z (relative intensity) 350.2 (M + H, 100%); HRMS (ES⁺) Calcd for C₂₃H₂₈NO₂: 350.2120, Found: 350.2124.
10-Cyano-6,9,9-trimethyl-8,9-dihydro-7H-indeno[2,1-b]indole-5-carboxylic Acid tert-Butyl Ester (2-92b). To a 0 °C stirring solution of indole 2-32e (31 mg, 0.076 mmol) in 1 mL of CH₂Cl₂ was added DMAP (93 mg, 0.76 mmol) and Boc₂O (50 mg, 0.23 mmol), and stirring was continued for 25 min. At that time, the solution was warmed to rt and stirred for 1 h. The solvent was removed under reduced pressure and the residue was dissolved in 15 mL of Et₂O and washed with H₂O (3 X 15 mL), and brine (3 X 15 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (5% Et₂O/hexanes) to provide 28 mg (98%) of 2-92b as a purple solid. Crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of an Et₂O/hexanes solution of 2-92b over a period of 24 h at rt. mp 177 – 179 °C; IR (neat): 1729 cm⁻¹; ¹H NMR (300 MHz, CD₂Cl₂) δ 8.29 (m, 1H), 8.00 (m, 1H), 7.22 (td, J = 7.2, 1.2 Hz, 1H), 7.16 (m, 1H), 2.62 – 2.57 (m, 2H), 2.19 (t, J = 1.7 Hz, 3H), 1.81 (t, J = 6.4 Hz, 2H), 1.70 (s, 9H), 1.34 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 151.0, 149.6, 145.0, 139.6, 133.0, 130.5, 124.1, 123.8, 122.7, 120.4, 119.5, 119.3, 115.8, 114.5, 84.9, 38.0, 35.3, 28.2, 27.5, 19.9, 14.3; ES+ m/z (relative intensity) 305.2 (M – Boc + MeOH, 100%), 317.0 (M – t-Bu, 55%), 349.2 (M – CN + H, 75%); HRMS (ES+) Calcd for C₂₃H₂₇NO₂: 349.2042, Found: 349.2039.

X-Ray Analysis (2-92b).
Note regarding the structure refinement (R-cryst=0.14): The poor structure refinement may be because of a very large unit cell dimension (~50 Å) and a very high space group (16 a.u.) with 16 molecules per unit cell. Consequently, there are some parameters which are just above acceptable cutoff.

An opaque plate shaped crystal of 2-92b (C_{24}H_{26}N_{2}O_{2}) with approximate dimensions 0.07 x 0.14 x 0.18 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 298(2) K, on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a MoK $\alpha$ fine-focus sealed tube ($\lambda = 0.71073$ Å) operated at 1600 watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal. Efforts to freeze the crystal in paratone oil were not successful as the crystal was falling apart in the oil rapidly.

A total of 1850 frames were collected with a scan width of 0.3° in $\omega$ and an exposure time of 10 seconds/frame. The total data collection time was about 8 hours. The frames were integrated with the Bruker SAINT software package using a narrow-
frame integration algorithm. The integration of the data using a Tetragonal unit cell yielded a total of 24341 reflections to a maximum $\theta$ angle of $28.33^\circ$ (0.90 Å resolution), of which 4963 were independent, completeness = 97.5%, $R_{\text{int}} = 0.0578$, $R_{\text{sig}} = 0.0557$ and 2697 were greater than $2\sigma(I)$. The final cell constants: $a = 12.5780(14)$ Å, $b = 12.5780(14)$ Å, $c = 52.005(12)$ Å, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 90^\circ$, volume = $8227(2)$ Å$^3$, are based upon the refinement of the XYZ-centroids of 5148 reflections above $20\sigma(I)$ with $2.420^\circ < \theta < 28.332^\circ$. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.5995.

The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package, using the space group $I4(1)cd$, with $Z = 16$ for the formula unit, $C_{24}H_{26}N_2O_2$. The final anisotropic full-matrix least-squares refinement on $F^2$ with 259 variables converged at $R1 = 14.24\%$, for the observed data and $wR2 = 38.97\%$ for all data. The goodness-of-fit was 1.278. The largest peak on the final difference map was 0.699 e/Å$^3$ and the largest hole was -0.333 e/Å$^3$. Based on the final model, the calculated density of the crystal is 1.209 g/cm$^3$ and $F(000)$ amounts to 3200 electrons.

![Chemical structure](image)

6,9,9-Trimethyl-5,7,8,9-tetrahydro-indeno[2,1-b]indole (2-92c). A 10 mL microwave vessel containing a solution of indole 2-32d (207 mg, 0.521 mmol) and
TBAF (1.0 M in THF, 1.0 mL, 1.0 mmol) in 3 mL of THF was subjected to microwave irradiation (300 W, 80 °C, 250 psi max) for 5 min. The reaction solution was then concentrated under reduced pressure. The residue was purified by flash chromatography (5% Et₂O/hexanes → 20% Et₂O/hexanes) to provide 100 mg (77%) of 2-92c as a yellow oil: IR (neat): 3398 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.93 (br s, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.09 (td, J = 7.3, 1.0 Hz, 1H), 7.00 (m, 1H), 6.45 (s, 1H), 2.63 (t, J = 5.7 Hz, 2H), 2.03 (s, 3H), 1.75 (t, J = 6.4 Hz, 2H), 1.20 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 150.2, 139.6, 139.0, 133.9, 133.1, 123.3, 121.6, 120.5, 119.4, 117.7, 111.8, 111.0, 38.7, 33.4, 28.7, 20.3, 10.2; ES⁺ m/z (relative intensity) 249.2 (M⁺, 100%), 250.2 (M + H, 90%); HRMS (ES⁺) Calcd for C₁₈H₂₀N: 250.1596, Found: 250.1608.

6,6,9,9-Tetramethyl-7,8,9,10-tetrahydro-6H-indeno[2,1-b]indole-5-carboxylic Acid tert-Butyl Ester (2-97). To a -40 °C stirring solution of fulvene 2-92a (27 mg, 0.077 mmol) in 4 mL of THF was added LiAlH₄ (1.0 M in THF, 120 µL, 0.12 mmol) and the reaction solution was allowed to warm to rt. MeI (15 µL, 0.24 mmol) was then added and stirring was continued for 30 min. At that time, ice-cold saturated NH₄Cl (4 mL) was added slowly and the mixture was diluted with Et₂O (15 mL). The organic layer was washed with H₂O (3 X 15 mL) and brine (3 X 15 mL), dried over MgSO₄ and
concentrated under reduced pressure. The residue was purified by flash chromatography (5% Et₂O/hexanes) to provide 24 mg (85%) of **2-97** as a yellow oil: IR (neat): 1729 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.14 (m, 1H), 7.56 (m, 1H), 7.20 – 7.17 (m, 2H), 2.41 (t, J = 2.3 Hz, 2H), 2.15 – 2.12 (m, 2H), 1.71 (s, 9H), 1.54 (t, J = 6.2 Hz, 2H), 1.39 (s, 6H), 1.00 (s, 6H); ¹³C NMR (90 MHz, CDCl₃) δ 151.8, 150.1, 145.0, 139.5, 127.4, 126.4, 124.4, 122.7, 122.5, 118.6, 116.4, 83.7, 48.5, 37.5, 35.9, 29.7, 28.4, 28.2, 20.6, 19.0; ES⁺ m/z (relative intensity) 366.3 (M + H, 100%); HRMS (ES⁺) Calcd for C₂₄H₃₂NO₂: 366.2433, Found: 366.2446.

**10-(tert-Butyldimethylsilyloxy)-6,9,9-trimethyl-5,6,6a,7,8,9,10,10a-octahydroindeno[2,1-b]indole (2-98a).** A deoxygenated solution of indole **2-32a** (47 mg, 0.11 mmol) and 10% activated Pd/C (47 mg) in 4 mL of THF was stirred under an atmosphere of H₂ at 1 ATM for 2 h. The reaction mixture was then filtered through Celite and concentrated under reduced pressure. The residue was purified by flash chromatography (5% Et₂O/hexanes → 10% Et₂O/hexanes) to provide 47 mg (100%) of **2-98a** as a yellow solid: mp 44 – 45 °C; IR (neat): 3412 cm⁻¹; ¹H NMR (300 MHz, C₆D₆) δ 7.65 (m, 1H), 7.23 – 7.18 (m, 2H), 7.06 (m, 1H), 6.58 (br s, 1H), 4.39 (s, 1H), 3.37 (dt, J = 5.6, 2.3 Hz, 1H), 2.93 (dtd, J = 13.2, 7.1, 2.4 Hz, 1H), 2.79 (app sextet, J = 5.9 Hz, 1H), 1.88 (td, J = 13.4, 3.6 Hz, 1H), 1.50 (qd, J = 13.6, 3.5 Hz, 1H), 1.36 (m, 1H), 1.06
(s, 9H + 3H), 0.99 (d, J = 7.2 Hz, 3H), 0.85 (s, 3H), 0.18 (s, 3H), 0.15 (s, 3H); $^{13}$C NMR (90 MHz, C$_6$D$_6$) $\delta$ 145.5, 140.7, 125.8, 120.6, 120.1, 120.0, 119.2, 111.8, 76.0, 48.5, 44.7, 37.6, 35.1, 32.1, 30.4, 26.2, 24.4, 20.3, 18.4, 12.2, -4.2, -4.4; ES$^+$ m/z (relative intensity) 384.2 (M + H, 100%); HRMS (ES$^+$) Calcd for C$_{24}$H$_{38}$NOSi: 384.2723, Found: 384.2719.

10-Benzyloxy-6,9,9-trimethyl-5,6,6a,7,8,9,10,10a-octahydro-indeno[2,1-b]indole (2-98c). A deoxygenated solution of indole 2-32c (41 mg, 0.11 mmol) and 10% activated Pd/C (41 mg) in 3 mL of THF was stirred under an atmosphere of H$_2$ at 1 ATM for 24 h. The reaction mixture was then filtered through Celite and concentrated under reduced pressure. The residue was purified by flash chromatography (7% Et$_2$O/hexanes $\rightarrow$ 15% Et$_2$O/hexanes) to provide 28 mg (71%) of 2-98c as a purple solid: mp 46 °C (dec.); IR (neat): 3402 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.78 (br s, 1H), 7.45 (d, J = 7.7 Hz, 1H), 7.39 – 7.33 (m, 4H), 7.32 – 7.25 (m, 2H), 7.09 (t, J = 7.2 Hz, 1H), 7.01 (t, J = 7.2 Hz, 1H), 4.53 (d, J = 11.2 Hz, 1H), 4.44 (d, J = 11.2 Hz, 1H), 3.30 (m, 1H), 3.22 (d, J = 8.4 Hz, 1H), 3.17 (app t, J = 7.3 Hz, 1H), 3.10 (m, 1H), 1.81 (m, 1H), 1.66 (m, 1H), 1.52 (m, 1H), 1.39 (m, 1H), 1.30 (d, J = 7.1 Hz, 3H), 1.11 (s, 3H), 1.01 (s, 3H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 147.6, 139.9, 139.6, 128.1, 127.5, 127.1, 125.0, 121.5, 120.5, 120.0, 119.6, 111.2, 89.2, 74.3, 46.2, 42.2, 37.5, 36.9, 35.8, 28.3, 21.4, 20.8, 17.1; ES$^+$ m/z (relative intensity) 360.2 (M + H, 100%), 382.2 (M + Na, 30%); HRMS (ES$^+$) Calcd for C$_{25}$H$_{30}$NO: 360.2327, Found: 360.2343.
10-(tert-Butyldimethylsilanyloxy)-6,9,9-trimethyl-5,6,6a,7,8,9,10,10a-octahydroindeno[2,1-b]indole-10-carbonitrile (2-98e). A deoxygenated solution of indole 2-32e (21 mg, 0.052 mmol) and 10% activated Pd/C (28 mg) in 2 mL of CH$_2$Cl$_2$ was stirred under an atmosphere of H$_2$ at 1 ATM for 2.5 h. The reaction mixture was then filtered through Celite and concentrated under reduced pressure. The residue was purified by flash chromatography (10% Et$_2$O/hexanes) to provide 19 mg (90%) of 2-98e as a white solid. Crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of an Et$_2$O solution of 2-98e over a period of 24 h at rt. mp 110 °C (dec.); IR (neat): 3374 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.24 (d, $J = 6.4$ Hz, 1H), 7.91 (br s, 1H), 7.27 (m, 1H), 7.15 – 7.05 (m, 2H), 3.59 (m, 1H), 3.17 (m, 1H), 2.82 (app sextet, $J = 5.7$ Hz, 1H), 1.81 (td, $J = 13.0$, 4.0 Hz, 1H), 1.56 (m, 1H), 1.49 – 1.38 (m, 2H), 1.26 (d, $J = 7.2$ Hz, 3H), 1.12 (s, 3H), 1.01 (s, 3H), 0.97 (s, 9H), 0.34 (s, 3H), 0.29 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 146.8, 139.9, 124.8, 123.0, 121.3, 120.7, 120.2, 116.4, 111.1, 76.1, 53.0, 45.2, 38.5, 36.3, 32.1, 27.4, 25.8, 22.5, 19.2, 18.6, 11.8, -3.3, -3.9; ES+ $m/z$ (relative intensity) 408.3 (M + H, 100%), 431.3 (M + Na, 15%); HRMS (ES+) Calcd for C$_{25}$H$_{37}$N$_2$OSi: 409.2675, Found: 409.2681.

X-Ray Analysis (2-98e).

A colorless block shaped crystal of 2-98e (C$_{25}$H$_{36}$N$_2$OSi, C$_4$H$_{10}$O) with
approximate dimensions 0.29 x 0.32 x 0.45 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 298(2) K, on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a MoKα fine-focus sealed tube (λ = 0.71073 Å) operated at 1600 watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal.

A total of 1850 frames were collected with a scan width of 0.3° in ω and an exposure time of 5 seconds/frame. The total data collection time was about 6 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm. The integration of the data using a Monoclinic unit cell yielded a total of 22540 reflections to a maximum θ angle of 28.35° (0.90 Å resolution), of which 7304 were independent, completeness = 98.6%, R_{int} = 0.0233, R_{sig} = 0.0292 and 4978 were greater than 2σ(I). The final cell constants: a = 11.144(6) Å, b = 7.400(4) Å, c = 36.078(18) Å, α = 90°, β = 92.101(9)°, γ = 90°, volume = 2973(3) Å³, are based upon the refinement of the XYZ-centroids of 8443 reflections above 20σ(I) with 2.810° < θ < 28.188°. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.8648.
The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package, using the space group P2(1)/c, with Z = 4 for the formula unit, C_{29}H_{46}N_{2}O_{2}Si. The final anisotropic full-matrix least-squares refinement on F^2 with 317 variables converged at R1 = 6.14%, for the observed data and wR2 = 19.11% for all data. The goodness-of-fit was 1.045. The largest peak on the final difference map was 0.313 e^-/Å^3 and the largest hole was -0.233 e^-/Å^3. Based on the final model, the calculated density of the crystal is 1.078 g/cm^3 and F(000) amounts to 1056 electrons.

\[ \text{6,9,9-Trimethyl-5,6,6a,7,8,9,10,10a-octahydroindeno[2,1-b]indol-10-ol (2-98f).} \]

A deoxygenated solution of indole 2-32f (131 mg, 0.490 mmol) and 10% activated Pd/C (20 mg) in 5 mL of THF was stirred under an atmosphere of H\textsubscript{2} at 1 ATM for 24 h. The reaction mixture was then filtered through Celite and concentrated under reduced pressure. The residue was purified by flash chromatography (10% Et\textsubscript{2}O/hexanes) to provide 86 mg (65%) of 2-98f as a purple solid: mp 58 – 60 °C; IR (neat): 3402, 3300 cm\textsuperscript{-1}; \(^1\)H NMR (360 MHz, CDCl\textsubscript{3}) \(\delta\) 7.89 (br s, 1H), 7.61 (m, 1H), 7.28 (m, 1H), 7.10 – 7.08 (m, 2H), 3.24 (d, \(J = 8.1\) Hz, 1H), 3.15 – 3.10 (m, 2H), 1.86 – 1.83 (m, 2H), 1.69 – 1.66 (m, 1H), 1.45 – 1.36 (m, 2H), 1.22 (d, \(J = 6.5\) Hz, 3H), 1.04 (s, 3H), 0.96 (s, 3H); \(^{13}\)C NMR (90 MHz, CDCl\textsubscript{3}) \(\delta\) 147.9, 140.2, 125.1, 121.4, 120.7, 119.9, 119.2, 111.5, 82.9,
46.0, 43.5, 37.6, 37.5, 34.6, 28.6, 20.9, 18.7, 17.8; AP+ m/z (relative intensity) 270.2 (M + H, 100%); HRMS (ES+) Calcd for C\textsubscript{18}H\textsubscript{24}NO: 270.1858, Found: 270.1865.

1-Azido-2-[4-(\textit{tert}-butyldimethylsilanyloxy)-3-[3-(\textit{tert}-butyldimethylsilanyl- oxy)-4,4-dimethylcyclohex-1-enyl]-buta-1,2-dienyl]-benzene (2-106). To a -78 °C solution of iodide 2-28a (2.078 g, 8.243 mmol) in 82 mL of THF was added dropwise \textit{t}-BuLi (1.7 M in pentane, 11 mL, 18 mmol) and stirring was continued at that temperature for 30 min, during which time the solution turned deep yellow. A solution of ZnCl\textsubscript{2} (1.124 g, 8.243 mmol) in 40 mL of THF was then added slowly and the resulting solution was warmed to room temperature during which time the solution turned colorless. Pd(PPh\textsubscript{3})\textsubscript{4} (190 mg, 0.165 mmol) and a solution of acetate 2-103 (1.185 g, 3.297 mmol) in 33 mL of THF were added sequentially and the reaction mixture was stirred for 45 min (monitored by TLC for starting material consumption). Ice-cold saturated NH\textsubscript{4}Cl solution (30 mL) was added slowly and the organic layer was diluted with Et\textsubscript{2}O (30 mL). The organic layer was washed with H\textsubscript{2}O (3 X 30 mL) and brine (3 X 30 mL), dried over MgSO\textsubscript{4} and concentrated under reduced pressure. The residue was purified by flash chromatography (2% Et\textsubscript{2}O/hexanes) to produce 1.132 g (64%) of the title compound as a yellow oil (mixture of diastereomers): IR (neat): 2123, 1929 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (360 MHz, C\textsubscript{6}D\textsubscript{6}) \(\delta\) 7.45 (m, 1H), 6.85 (d, \(J = 5.8\) Hz, 1H), 6.81 – 6.78 (m, 2H), 6.67 (m, 1H), 5.96
(s, 1H), 4.60 – 4.49 (m, 2H), 3.96 (s, 1H), 2.15 – 2.02 (m, 2H), 1.47 (m, 1H), 1.34 – 1.28 (m, 2H), 1.04 – 1.00 (m, 9H), 0.98 (s, 3H), 0.97 – 0.93 (m, 9H + 2H), 0.18 (s, 3H), 0.10 (s, 3H), 0.09 – 0.04 (m, 6H); $^{13}$C NMR (90 MHz, C$_6$D$_6$) $\delta$ 208.1, 208.0, 136.7, 136.6, 131.4, 131.3, 128.5, 128.40, 128.35, 128.1, 126.2, 126.1, 125.03, 124.95, 118.71, 118.67, 111.6, 92.54, 92.49, 76.0, 75.8, 62.7, 62.6, 34.4, 34.3, 34.0, 33.9, 27.7, 27.5, 26.2, 26.0, 25.4, 25.3, 20.8, 20.5, 18.4, -3.7, -4.6, -5.0, -5.1; ES+ m/z (relative intensity) 512.3 (M + H, 35%), 562.3 (M + Na, 100%); HRMS (ES+) Calcd for C$_{30}$H$_{49}$N$_3$O$_2$Si$_2$Na: 562.3261, Found: 562.3242.

10-(tert-Butyldimethylsilyloxy)-6-(tert-butyldimethylsilyloxyethyl)-9,9-dimethyl-5,7,8,9,10,10a-hexahydroindeno[2,1-b]indole (2-107). Following general procedure 6, allene 2-106 (99 mg, 0.18 mmol) produced 54 mg (59%) of 2-107 as a tacky yellow solid: IR (neat): 3483 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.20 (br s, 1H), 7.65 (m, 1H), 7.34 (m, 1H), 7.01 – 7.10 (m, 2H), 4.73 (d, $J$ = 13.2 Hz, 1H), 4.64 (d, $J$ = 13.2 Hz, 1H), 3.41 (d, $J$ = 10.3 Hz, 1H), 3.07 (d, $J$ = 10.3 Hz, 1H), 2.52 (ddd, $J$ = 14.2, 5.6, 1.8 Hz, 1H), 2.40 (m, 1H), 1.67 (ddd, $J$ = 13.1, 5.3, 1.8 Hz, 1H), 1.36 (dd, $J$ = 13.1, 5.6 Hz, 1H), 1.19 (s, 3H), 1.07 (s, 9H), 1.02 (s, 3H), 0.95 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), -0.02 (s, 3H), -0.45 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 148.5, 146.2, 139.2, 127.2, 126.0, 121.8, 120.4, 119.5, 118.7, 111.4, 82.9, 58.6, 50.0, 40.3, 37.7, 29.9, 26.6, 26.0,
23.4, 18.6, 18.4, 18.3, -1.9, -3.0, -5.1, -5.2; ES+ m/z (relative intensity) 512.2 (M + H, 100%); HRMS (ES+) Calcd for C$_{30}$H$_{50}$NO$_2$Si$_2$: 512.3380, Found: 512.3379.

[10-\textit{(}tert\textit{-Butyldimethylsilanyloxy)}-9,9-dimethyl-5,7,8,9,10,10a-hexahydro-indeno[2,1-b]indol-6-yl\textit{-}methanol (2-108). To a 0 °C stirring solution of 2-107 (231 mg, 0.451 mmol) in 10 mL of THF was added dropwise TBAF (1.0 M in THF, 250 µL, 0.45 mmol) and the reaction solution was stirred at that temperature for 15 min. The reacion solution was diluted with Et$_2$O (10 mL) and saturated NH$_4$Cl (20 mL) was added. The organic layer was washed with H$_2$O (3 X 20 mL), and brine (3 X 20 mL), dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (5% EtOAc/hexanes $\rightarrow$ 50% EtOAc/hexanes) to provide 152 mg (85%) of 2-108 as an off-white solid: mp 89 °C (dec.); IR (neat): 3354 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 8.37 (br s, 1H), 7.52 (d, $J$ = 6.2 Hz, 1H), 7.17 (d, $J$ = 8.7 Hz, 1H), 6.95 – 6.85 (m, 2H), 4.54 (d, $J$ = 12.9 Hz, 1H), 4.46 (d, $J$ = 12.8 Hz, 1H), 3.28 (d, $J$ = 9.9 Hz, 1H), 2.94 (d, $J$ = 10.3 Hz, 1H), 2.42 (m, 1H), 2.26 (m, 1H), 1.53 (m, 1H), 1.19 (dd, $J$ = 13.3, 5.5 Hz, 1H), 1.05 (s, 3H), 0.93 (s, 9H), 0.87 (s, 3H), -0.16 (s, 3H), -0.59 (s, 3H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 148.6, 147.8, 128.3, 126.6, 125.9, 122.1, 120.5, 119.7, 118.8, 111.5, 83.0, 57.5, 50.2, 40.4, 37.7, 29.9, 26.6, 23.3, 18.6, 18.3, -1.9, -2.9; ES+ m/z
(relative intensity) 398.2 (M + H, 100%); HRMS (ES+) Calcd for C\textsubscript{24}H\textsubscript{36}NO\textsubscript{2}Si: 398.2515, Found: 398.2519.

10-(\textit{tert}-Butyldimethylsilanyloxy)-6-(\textit{tert}-butyldimethylsilanyloxymethyl)-9,9-dimethyl-5,6,6a,7,8,9,10,10a-octahydroindeno[2,1-b]indole (2-109). A deoxygenated solution of indole 2-107 (132 mg, 0.258 mmol) and 10% activated Pd/C (100 mg) in 4 mL of THF was stirred under an atmosphere of H\textsubscript{2} at 1 ATM for 24 h. The reaction mixture was then filtered through Celite and concentrated under reduced pressure. The residue was purified by flash chromatography (5% Et\textsubscript{2}O/hexanes) to provide 100 mg (75%) of 2-109 as a white solid: mp 46 °C (dec.); IR (neat): 3483 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (360 MHz, C\textsubscript{6}D\textsubscript{6}) \delta 7.72 (br s, 1H), 7.67 (d, \textit{J} = 7.7 Hz, 1H), 7.22 (td, \textit{J} = 7.0, 1.2 Hz, 1H), 7.15 (td, \textit{J} = 7.5, 1.2 Hz, 1H), 7.08 (d, \textit{J} = 7.9 Hz, 1H), 4.39 (s, 1H), 3.83 (t, \textit{J} = 9.7 Hz, 1H), 3.73 (dd, \textit{J} = 9.5, 6.2 Hz, 1H), 3.43 (dt, \textit{J} = 5.7, 2.2 Hz, 1H), 3.26 (m, 1H), 2.94 (app. sextet, \textit{J} = 6.0 Hz, 1H), 1.86 (td, \textit{J} = 13.1, 3.1 Hz, 1H), 1.62 (qd, \textit{J} = 13.1, 3.2 Hz, 1H), 1.26 (m, 1H), 1.05 (s, 3H), 1.04 (s, 9H), 0.99 (m, 1H), 0.97 (s, 9H), 0.90 (s, 3H), 0.18 (s, 3H), 0.15 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); \textsuperscript{13}C NMR (90 MHz, C\textsubscript{6}D\textsubscript{6}) \delta 143.9, 140.8, 125.5, 121.0, 120.6, 120.1, 119.3, 112.0, 75.9, 62.9, 48.5, 46.2, 42.6, 35.1, 32.1, 30.4, 26.2, 26.1, 24.4, 20.6, 18.42, 18.40, -4.2, -4.4, -5.2, -5.3; ES+ \textit{m/z} (relative
[10-(tert-Butyldimethylsilyloxy)-9,9-dimethyl-5,6,6a,7,8,9,10,10a-octahydroindeno[2,1-b]indol-6-yl]-methanol (2-110). A deoxygenated solution of indole 2-108 (49 mg, 0.12 mmol) and 10% activated Pd/C (50 mg) in 2 mL of THF was stirred under an atmosphere of H₂ at 1 ATM for 16 h. The reaction mixture was then filtered through Celite and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc/hexanes → 50% EtOAc/hexanes) to provide 45 mg (92%) of 2-110 as a yellow oil: IR (neat): 3412, 3350 cm⁻¹; ¹H NMR (360 MHz, C₆D₆) δ 7.98 (br s, 1H), 7.65 (d, J = 7.2 Hz, 1H), 7.22 (dd, J = 7.1, 1.2 Hz, 1H), 7.18 (t, J = 1.7 Hz, 1H), 7.06 (m, 1H), 4.37 (s, 1H), 3.58 (t, J = 10.0 Hz, 1H), 3.49 (dd, J = 9.8, 5.6 Hz, 1H), 3.40 (dt, J = 5.7, 2.2 Hz, 1H), 3.05 (m, 1H), 2.87 (app sextet, J = 5.9 Hz, 1H), 1.83 (td, J = 13.7, 3.3 Hz, 1H), 1.54 (qd, J = 13.4, 3.4 Hz, 1H), 1.22 – 1.14 (m, 2H), 1.05 (s, 9H + 3H), 0.86 (s, 3H), 0.18 (s, 3H), 0.14 (s, 3H); ¹³C NMR (90 MHz, C₆D₆) δ 143.7, 140.9, 125.4, 120.9, 120.4, 120.0, 119.2, 112.0, 75.8, 62.3, 48.4, 46.1, 42.6, 35.0, 32.0, 30.4, 26.2, 24.4, 20.6, 18.4, -4.2, -4.4; ES+ m/z (relative intensity) 400.2 (M + H, 100%); HRMS (ES+) Calcd for C₂₄H₃₈NO₂Si: 400.2672, Found: 400.2653.
6.3 (-)-Kinamycin F Experimental.

6-Bromo-2-methylcyclohex-5-ene-1,2,3,4-tetraol (4-11). TBAF (21 mL, 1 M in THF, 21 mmol) was slowly added via syringe to a stirring solution of TBS protected alcohol 4-9 (3.45 g, 5.94 mmol) in THF (25 mL) at 0 °C, resulting in a dark brown solution. The reaction mixture was stirred at 0 °C for 1 h, after which time it was warmed to room temperature and stirred for an additional 1 h. The solution was then concentrated under reduced pressure to give a brown oil. The dark oil was dissolved in H₂O and extracted with hexanes (3 x 20 mL). The aqueous layer was concentrated to a dark colored oil and purified by flash chromatography (EtOAc → 5% MeOH/EtOAc) to afford the desired tetraol (1.1 g, 78%) as a white solid. Crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of an Et₂O/MeOH solution of 4-11 over a period of 72 h at rt. mp 90 – 92 °C; IR (neat): 3354, 1643 cm⁻¹; ^1H NMR (300 MHz, CD₃OD) δ 6.04 (d, J = 3.3 Hz, 1H), 3.86 (s, 1H), 3.82 (dd, J = 7.4, 3.4 Hz, 1H), 3.62 (d, J = 7.3 Hz, 1H), 1.11 (s, 3H); ^13C NMR (100 MHz, CD₃OD) δ 134.3, 125.5, 79.4, 75.0, 74.6, 73.3, 18.9; ESI m/z (relative intensity) 261.0 (M + Na, 50%); HRMS (AP+) Calcd for C₇H₁₁BrO₄Na: 260.9738, Found 260.9739; [α]D^22 = 2.0° (c = 0.02,
A colorless plate shaped crystal of **4-11** (C$_7$H$_{13}$BrO$_5$) with approximate dimensions 0.07 x 0.23 x 0.28 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 160(2) K, cooled by Rigaku-MSC X-Stream 2000, on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a MoK$\alpha$ fine-focus sealed tube ($\lambda = 0.71073\text{Å}$) operated at 1600 watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal.

A total of 1850 frames were collected with a scan width of 0.3° in $\omega$ and an exposure time of 10 seconds/frame. The total data collection time was about 8 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm. The integration of the data using a Tetragonal unit cell yielded a total of 14089 reflections to a maximum $\theta$ angle of 28.27° (0.90 Å resolution), of which 2566 were independent, completeness = 99.9%, $R_{\text{int}} = 0.0374$, $R_{\text{sig}} = 0.0310$
and 2193 were greater than 2σ(I). The final cell constants: a = 7.2139(8) Å, b = 7.2139(8) Å, c = 39.665(9) Å, α = 90°, β = 90°, γ = 90°, volume = 2064.2(6) Å³, are based upon the refinement of the XYZ-centroids of 3728 reflections above 20σ(I) with 3.005° <θ <23.216°. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.0585.

The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package, using the space group P4(3)2(1)2, with Z = 8 for the formula unit, C₇H₁₃BrO₅ . The final anisotropic full-matrix least-squares refinement on F² with 123 variables converged at R1 = 3.56%, for the observed data and wR2 = 8.94% for all data. The goodness-of-fit was 1.028. The largest peak on the final difference map was 0.634 e⁻/Å³ and the largest hole was -0.234 e⁻/Å³. Based on the final model, the calculated density of the crystal is 1.655 g/cm³ and F(000) amounts to 1024 electrons.

![1-(3,4,5,6-Tetrakisbenzyloxy-5-methylcyclohex-1-enyl)-ethanone (4-15)](image)

1-(3,4,5,6-Tetrakisbenzyloxy-5-methylcyclohex-1-enyl)-ethanone (4-15). To a -100 °C stirring solution of 4-12 (206 mg, 0.343 mmol) in 4 mL of Et₂O was added dropwise t-BuLi (1.7 M in pentane, 0.40 mL, 0.69 mmol). After 15 min at -100 °C, N-methoxy-N-methylacetamide (91 µL, 0.86 mmol) was added dropwise and the solution was allowed to warm to 0 °C over 2 h. Ice-cold saturated NH₄Cl solution (4 mL) was added and the reaction mixture was diluted with 15 mL of Et₂O. The aqueous layer was
extracted with Et₂O (2 X 15 mL) and the combined organic layers were washed with water (3 X 50 mL) and brine (3 X 50 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography (30% Et₂O/hexanes \(\to\) 50% Et₂O/hexanes) to yield 140 mg (72%) of the title compound as a colorless oil: IR (neat): 1674 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 7.57 - 7.30 (m, 20H), 6.71 (d, \(J = 2.9\) Hz, 1H), 5.11 (d, \(J = 11.2\) Hz, 1H), 4.94 - 4.72 (m, 7H), 4.65 (d, \(J = 11.3\) Hz, 1H), 4.49 (d, \(J = 7.7\) Hz, 1H), 4.24 (dd, \(J = 7.7, 3.0\) Hz, 1H), 2.34 (s, 3H), 1.27 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta\) 198.7, 140.2, 140.1, 140.0, 139.6, 139.5, 138.9, 128.9, 128.72, 128.67, 128.6, 128.4, 128.30, 128.28 128.1 (X2), 127.9, 127.7, 127.5, 82.4, 80.7, 80.2, 75.8, 74.7, 74.2, 73.3, 64.6, 26.1, 15.7; ESI+ \(m/z\) (relative intensity) 580.4 (M + NH₄, 100%), 585.4 (M + Na, 30%); HRMS (ES+) Calcd for C₃₇H₄₂O₅N: 580.3063, Found: 580.3041; \([\alpha]_{D}^{22} = -40^\circ\) (c = 0.11, CHCl₃)

\[\text{1-(2,3,4,5-Tetrakisbenzyloxy-3-methyl-6-vinylcyclohexyl)-ethanone (4-17).}\]

To an ice-cold stirring solution of tetravinyltin (172 µL, 0.944 mmol) in 10 mL of Et₂O was added MeLi (1.6 M in Et₂O, 2.4 mL, 3.7 mmol). After 30 min of stirring at that temperature, the reaction mixture was added to a -78 °C stirring solution of CuI (360 mg, 1.89 mmol) in 10 mL of Et₂O. The reaction mixture was warmed to -40 °C for 30 min and then cooled to -78 °C. A solution of 4-15 (531 mg, 0.944 mmol) and TMSCl (242 µL, 1.89 mmol) in 10 mL of Et₂O was added and stirring continued at -78 °C for 15 min
(as monitored by TLC for starting material consumption). Ice-cold saturated NH₄Cl solution (10 mL) was added dropwise and the mixture was allowed to warm until the aqueous layer was completely thawed, then filtered through Celite using Et₂O as eluent. The organic layer was washed with ice-cold saturated NH₄Cl solution, ice-cold water, and ice-cold brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was dissolved in 20 mL of MeOH and cooled to 0 °C. Camphor sulfonic acid (CSA) (22 mg, 0.094 mmol) was then added and the reaction mixture was stirred for 15 min (monitored by TLC for starting material consumption), then concentrated under reduced pressure. The residue was purified by flash chromatography (20% Et₂O/hexanes → 40% Et₂O/hexanes) to provide 399 mg (72%) of the title compound as a colorless oil:

IR (neat): 1698 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.49 – 7.37 (m, 20H), 5.95 (m, 1H), 5.41 – 5.33 (m, 2H), 5.14 (d, J = 11.2 Hz, 1H), 5.06 (m, 2H), 4.97 – 4.94 (m, 2H), 4.82 (d, J = 11.5 Hz, 1H), 4.74 (d, J = 10.4 Hz, 1H), 4.49 (d, J = 10.4 Hz, 1H), 4.39 (d, J = 9.0 Hz, 1H), 4.16 (d, J = 2.2 Hz, 1H), 3.48 (app t, J = 9.7 Hz, 1H), 3.34 (m, 1H), 2.68 (dd, J = 12.4, 2.2 Hz, 1H), 2.26 (s, 3H), 1.61 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 209.4, 139.1, 138.9, 138.3, 138.2, 138.0, 128.12 (X2), 128.08, 128.0, 127.8, 127.6, 127.43, 127.39, 127.36, 127.1, 127.0, 126.7, 117.8, 84.8, 83.2, 81.6, 81.4, 75.5, 75.4, 75.0, 64.3, 54.7, 42.9, 29.2, 16.7; ESI+ m/z (relative intensity) 591.4 (M + H, 100%), 608.4 (M + NH₄, 40%), 613.4 (M + Na, 50%); HRMS (ES+) Calcd for C₃₉H₄₃O₅: 591.3110, Found: 591.3096; [α]D²¹ = -43° (c = 0.02, CHCl₃)
2-Acetyl-3,4,5,6-tetrakisbenzyloxy-4-methylcyclohexanecarbaldehyde (4-18).

To a -90 °C stirring solution of 4-17 (1.18 g, 2.00 mmol) in 25 mL of CH₂Cl₂ was bubbled O₃/O₂ for 1.5 min. Stirring was continued for 5 min and then the reaction mixture was monitored by TLC for starting material consumption. If required, subsequent O₃/O₂ was bubbled for 1 min intervals with TLC monitoring 5 min after each addition until all starting material was consumed. The solution then was purged with N₂ for 2 min, followed by slow addition of Me₂S (1.5 mL, 20 mmol). The solution was warmed to rt and concentrated under reduced pressure. The residue was purified by flash chromatography (30% Et₂O/hexanes → 50% Et₂O/hexanes) to provide 718 mg (61%) of the title compound as a colorless oil: IR (neat): 1714 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 10.1 (s, 1H), 7.34 – 7.21 (m, 18H), 7.16 – 7.13 (m, 2H), 4.94 – 4.91 (m, 2 H), 4.87 – 4.83 (m, 2H), 4.81 (d, J = 6.0 Hz, 1H), 4.70, (d, J = 11.5 Hz, 1H), 4.49 – 4.42 (m, 2H), 4.21 – 4.19 (m, 2H), 3.72 (td, J = 11.4, 1.1 Hz, 1H), 3.64 (dd, J = 11.4, 8.8 Hz, 1H), 2.97 (dd, J = 11.3, 2.1 Hz, 1H), 2.07 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 205.6, 205.3, 139.3, 139.2, 138.5, 138.4, 128.9 (X2), 128.8, 128.7, 128.22, 128.18, 128.1, 128.0, 127.90, 127.86, 127.8, 127.4, 85.6, 82.2, 81.6, 80.0, 76.1, 75.7, 75.2, 65.0, 53.7, 50.1, 28.1, 17.2; ESI+ m/z (relative intensity) 593.4 (M + H, 100%), 615.3 (M + Na, 100%); HRMS (ES+) Calcd for C₃₈H₄₁O₆: 593.2903, Found: 593.2924; [α]D²³ = -46° (c = 0.05, CHCl₃)
4,5,6,7-Tetrakisbenzoyloxy-6-methyl-3a,4,5,6,7,7a-hexahydroinden-1-one (4-19). To a stirring solution of aldehyde 4-18 (315 mg, 0.531 mmol) in 15 mL of C₆H₆ was added pyrrolidine (131 µL, 1.59 mmol), CSA (185 mg, 0.797 mmol), and excess 4 Å molecular sieves. The mixture was stirred at rt for 2 h (monitored by TLC for starting material consumption) and then filtered to remove the molecular sieves. The filtrate was diluted with Et₂O (30 mL) and washed sequentially with saturated NH₄Cl solution (45 mL), H₂O (3 X 45 mL) and brine (3 X 45 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (20% EtOAc/hexanes) to provide 215 mg (70%) of the title compound as a colorless oil: IR (neat): 1708 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.51 (dd, J = 5.8, 2.9 Hz, 1H), 7.31 – 7.29 (m, 2H), 7.26 – 7.14 (m, 18H), 6.04 (dd, J = 5.8, 1.1 Hz, 1H), 4.84 (d, J = 10.8 Hz, 1H), 4.74 (dd, J = 11.5, 2.9 Hz, 1H), 4.67 (d, J = 10.8 Hz, 1H), 4.58 – 4.53 (m, 3H), 4.49 (d, J = 11.5 Hz, 1H), 4.02 – 4.00 (m, 2H), 3.29 – 3.19 (m, 2H), 2.82 (dd, J = 6.3, 4.8 Hz, 1H), 1.12 (s, 3H); ¹³C NMR (90 MHz, CDCl₃) δ 207.7, 165.6, 139.4, 138.7, 138.4, 138.3, 132.5, 132.4, 128.5, 128.3(X2), 128.1, 127.89, 127.86, 127.8, 127.7, 127.5, 127.04, 127.00, 84.9, 83.6, 81.5, 77.9, 75.4, 74.4, 73.2, 64.4, 49.9, 46.0, 16.1 ESI+ m/z (relative intensity) 575.3 (M + H, 30%), 597.3 (M + Na, 100%); HRMS (ES+) Calcd for C₃₈H₃₉O₅: 575.2797, Found: 575.2802; [α]D²² = -162° (c = 0.01, CHCl₃)
**2-BenzylOxy-N,N-diethylbenzamide (4-21).** To a 0 °C stirring solution of amide 4-20 (1.00 g, 5.17 mmol) in 50 mL of DMF was added NaH (60% dispersion in mineral oil, 238 mg, 6.21 mmol) followed by BnBr (743 µL, 6.21 mmol). The mixture was warmed to rt and stirred for 16 h. The reaction solution was then treated with ice chips until gas evolution ceased. The mixture was then diluted with 50 mL of brine and extracted with Et₂O (3 x 100 mL). The combined organic layers were washed with brine (300 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by passage through a plug of silica, eluting with 75% Et₂O/hexanes → Et₂O to provide 1.39 g (95%) of the title compound as a white solid: mp 66 – 67 °C; IR (neat): 1629 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.25 (m, 7H), 7.01 – 6.94 (m, 2H), 5.09 (m, 2H), 3.79 (m, 1H), 3.31 (m, 1H), 3.20 – 3.10 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H), 1.00 (t, J = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.0, 154.7, 137.2, 130.3, 128.8, 128.2, 128.02, 127.99, 127.5, 121.6, 113.0, 70.6, 43.1, 39.2, 14.4, 13.2; ESI⁺ m/z (relative intensity) 284.2 (M + H, 100%), 306.1 (M + Na, 30%); HRMS (ES+) Calcd for C₁₈H₂₂O₂N: 284.1651, Found: 284.1656.
2-Benzxyloxy-N,N-diethyl-6-formylbenzamide (4-22). To a -78 °C stirring solution of sec-BuLi (1.4 M in cyclohexane, 240 µL, 0.34 mmol) was added TMEDA (51 µL, 0.34 mmol) followed by a solution of amide 4-21 (69 mg, 0.24 mmol) in 3 mL of THF. Stirring was continued at that temperature for 20 min. DMF (38 µL, 0.49 mmol) was then added and stirring was continued for 1 h at -78 °C. Ice-cold saturated NH₄Cl solution (5 mL) was added and the reaction mixture was extracted with Et₂O (3 X 15 mL). The combined organic layers were washed with saturated NH₄Cl solution (45 mL), H₂O (2 X 45 mL) and brine (2 X 45 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash chromatography (75% Et₂O/hexanes → Et₂O) to provide 53 mg (70%) of the title compound as a yellow solid: mp 75 – 76 °C; IR (neat): 1695, 1627 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 10.01 (s, 1H), 7.54 (dd, J = 7.7, 0.8 Hz, 1H), 7.43 – 7.33 (m, 6H), 7.21 (dd, J = 8.1, 0.6 Hz, 1H), 5.15 (d, J = 11.9 Hz, 1H), 5.11 (d, J = 11.8 Hz, 1H), 3.73 (m, 1H), 3.49 (m, 1H), 3.17 – 3.08 (m, 2H), 1.21 (t, J = 7.1 Hz, 3H), 0.99 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 191.0, 166.1, 155.2, 136.5, 134.2, 130.3, 130.1, 128.9, 128.5, 127.5, 122.0, 118.5, 71.2, 43.2, 39.4, 14.2, 12.9; ESI+ m/z (relative intensity) 312.2 (M + H, 100%), 334.2 (M + Na, 30%); HRMS (ES+) Calcd for C₁₉H₂₂O₃N: 312.1600, Found: 312.1601.
1,2,3,4,9-Pentakisbenzyloxy-2-methyl-1,2,3,4,4a,11a-hexahydrobenzo[b]fluorene-5,10,11-trione (4-24). To a -78 °C stirring solution of lactone 4-25 (190 mg, 0.33 mmol) in 3.3 mL of THF was added dropwise LHMDS (1.0 M in THF, 330 µL, 0.33 mmol) and the solution was stirred for 10 min at that temperature. A solution of enone 4-19 (88 mg, 0.33 mmol) in 3.3 mL of THF was added dropwise via cannula and the solution was stirred for an additional 10 min and then allowed to warm to rt during which time the solution turned dark red. Ice-cold saturated NH₄Cl solution (5 mL) was added and the mixture was diluted with Et₂O (25 mL). The organic layer was washed with H₂O (3 X 25 mL) and brine (3 X 25 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc/1% MeOH/hexanes →20% EtOAc/1% MeOH/hexanes) to provide 243 mg (90%) of the title compound as a bright orange solid: mp 63 °C (dec.); IR (neat): 3341, 1706, 1631 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 10.12 (s, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.57 (s, 1H), 7.38 – 7.09 (m, 26H), 6.79 (d, J = 7.6 Hz, 1H), 5.09 (s, 2H), 4.96 (d, J = 11.0 Hz, 1H), 4.91 (d, J = 10.6 Hz, 1H), 4.73 (d, J = 11.4 Hz, 1H), 4.63 (d, J = 11.0 Hz, 1H), 4.58 – 4.51 (m, 3H), 4.34 (d, J = 10.6 Hz, 1H), 4.26 (d, J = 3.1 Hz, 1H), 4.15 (d, J = 8.7 Hz, 1H), 3.74 (app t, J = 9.4 Hz, 1H), 3.44 (app t, J = 9.4 Hz, 1H), 3.21 (dd, J = 8.7, 3.1 Hz, 1H), 1.19 (s, 3H); ¹³C NMR (90 MHz, CDCl₃) δ 201.7, 157.7, 149.6, 140.7, 139.2, 138.5, 138.2, 136.6, 134.8, 131.7, 129.1, 128.9, 128.8, 128.7, 128.5, 128.4, 128.3, 128.22, 128.16, 128.1, 128.0, 127.8, 127.54, 127.49, 127.3, 127.1, 127.0, 116.3, 115.1, 115.0, 106.3, 85.0, 84.4, 81.8, 75.1, 74.9, 72.6, 71.5, 65.8, 64.1, 52.8, 39.6, 15.9; ES+ m/z (relative intensity) 813.4 (M + H, 100%), 835.4 (M + Na, 45%); HRMS (ES+) Calcd for C₅₃H₄₀O₈: 813.3427, Found: 813.3453; [α]D²² = -75° (c = 0.01, CHCl₃)
4-Benzyl oxy-3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile (4-25). To a 0 °C stirring solution of aldehyde 4-22 (1.50 g, 4.82 mmol) in 25 mL of CH$_2$Cl$_2$ was added KCN (63 mg, 0.96 mmol) followed by 18-crown-6 (254 mg, 0.963 mmol). After 10 min of stirring at that temperature, TMSCN (844 µL, 6.75 mmol) was added and stirring was continued for 3 h at 0 °C. The solvent was removed under reduced pressure and the residue was taken up in 13.3 mL of AcOH. The resulting mixture was stirred at rt for 12 h. Saturated NH$_4$Cl solution (30 mL) was added and then the mixture was extracted with CH$_2$Cl$_2$ (3 X 50 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (35% EtOAc/hexanes) to provide 808 mg (63%) of the title compound as a yellow solid: mp 121 – 122 °C; IR (neat): 1780 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) δ 7.54 (t, $J$ = 8.1 Hz, 1H), 7.37 – 7.34 (m, 2H), 7.28 – 7.20 (m, 2H), 7.17 (m, 1H), 7.07 (d, $J$ = 6.8 Hz, 1H), 6.95 (d, $J$ = 8.3 Hz, 1H), 5.88 (s, 1H), 5.18 (s, 2H); $^{13}$C NMR (90 MHz, CDCl$_3$) δ 165.1, 157.8, 144.0, 137.6, 135.3, 128.6, 128.0, 126.6, 114.5, 114.3, 114.0, 111.8, 70.4, 64.7; ESI+ m/z (relative intensity) 266.1 (M + H, 10%), 283.1 (M + NH$_4$, 100%), 288.1 (M + Na, 60%); HRMS (ES+) Calcd for C$_{16}$H$_{11}$O$_3$Na: 288.0637, Found: 288.0629.
1,2,3,4,9-Pentakisbenzyloxy-5,10-dihydroxy-2-methyl-1,2,3,4-tetrahydrobenzo[b]fluoren-11-one (4-27). To a stirring solution of tetracycle 4-24 (78 mg, 0.096 mmol) in 10 mL of CH$_2$Cl$_2$ was added activated MnO$_2$ (167 mg, 1.92 mmol) and the mixture was stirred at rt for 1 h and then filtered through Celite and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc/1% MeOH/hexanes $\rightarrow$ 20% EtOAc/1% MeOH/hexanes) to provide 43 mg (55%) of the title compound as a red semi-solid: IR (neat): 3342, 1683, 1606 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 9.18 (s, 1H), 7.72 (d, $J$ = 7.9 Hz, 1H), 7.41 – 7.05 (m, 28H), 6.96 (d, $J$ = 7.9 Hz, 1H), 5.17 (s, 2H), 5.00 (d, $J$ = 11.5 Hz, 1H), 4.83 (d, $J$ = 7.9 Hz, 1H), 4.72 (d, $J$ = 7.6 Hz, 1H), 4.65 – 4.63 (m, 2H), 4.59 (d, $J$ = 5.4 Hz, 1H), 4.55 (s, 1H), 4.51 – 4.49 (m, 2H), 4.46 – 4.43 (m, 2H), 1.19 (s, 3H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 192.0, 158.3, 152.7, 150.5, 141.7, 139.2, 138.9, 138.6, 136.7, 136.0, 134.7, 133.4, 130.0, 129.0, 128.9, 128.5, 128.3, 128.2, 128.10 (X3), 128.06, 128.0, 127.41, 127.39, 127.3, 127.1, 126.1, 126.1, 118.5, 118.1, 115.2, 110.53, 110.45, 81.7, 78.2, 78.1, 74.9, 72.0, 71.2, 69.3, 68.3, 63.1, 15.1; ESI+ $m/z$ (relative intensity) 811.6 (M + H, 80%); HRMS (ES+) Calcd for C$_{53}$H$_{47}$O$_8$: 811.3271, Found: 811.3255. [$\alpha$]$_D^{22}$ = 56° ($c$ = 0.0025, CHCl$_3$)
6-Bromo-2-methyl-cyclohex-5-ene-1,2,3,4-tetra-4-methoxybenzyl Ether (4-29). To an ice-cold stirred solution of tetraol 4-11 (50 mg, 0.21 mmol) in 3 mL of DMF was added NaH (60% dispersion in mineral oil, 134 mg, 3.35 mmol) and PMBBr (483 µL, 3.35 mmol) sequentially. The mixture was warmed to room temperature and stirred for 16 h. The reaction solution was treated with ice chips until gas evolution ceased. Upon consumption of the excess NaH, aqueous saturated NH₄Cl (10 mL) was added, and the mixture was diluted with Et₂O (15 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 x 15 mL). The combined organic extracts were washed with H₂O (3 x 60 mL) and brine (3 x 60 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash chromatography (10% Et₂O/hexanes → 15% Et₂O/hexanes → 30% Et₂O/hexanes) to provide 64 mg (43%) of the title compound as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.31 – 7.24 (m, 8H), 6.89 – 6.83 (m, 8H), 6.21 (d, J = 2.9 Hz, 1H), 4.86 (d, J = 10.8 Hz, 1H), 4.81 (d, J = 10.5 Hz, 1H), 4.78 – 4.75 (m, 2H), 4.69 (d, J = 10.8 Hz, 1H), 4.61 (s, 2H), 4.56 (d, J = 10.8 Hz, 1H), 4.17 (d, J = 7.3 Hz, 1H), 4.14 (s, 1H), 3.94 (dd, J = 7.3, 2.9 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H + 3H), 3.81 (s, 3H), 1.37 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 159.2, 159.1, 159.0, 158.7, 131.8, 131.5, 131.2, 130.5, 130.3, 129.6, 129.5, 129.3, 128.5, 122.8, 113.8, 113.6 (X2), 113.5, 84.2, 81.1, 80.0, 77.3, 74.8, 73.5, 71.7, 64.1, 55.21 (X3), 55.18,
16.0; ESI+ m/z (relative intensity) 736.4 (M + NH4, 100%); HRMS (ES+) Calcd for C39H47O8N79Br: 736.2485, Found: 736.2518.

6-Bromo-2-methycyclohex-5-ene-1,2,3,4-tetra(2-naphthylmethyl) Ether (4-30). To a sitrring solution of tetraol 4-11 (19 mg, 0.079 mmol) in 4 mL of DMF was added NaH (60% dispersion in mineral oil, 51 mg, 1.27 mmol), Bu4NI (22 mg, 0.059 mmol), and 2-(bromomethyl)naphthalene (281 mg, 1.27 mmol). The reaction mixture was stirred at rt for 16 h. The reaction solution was treated with ice chips until gas evolution ceased. Upon consumption of the excess NaH, aqueous saturated NH4Cl solution (15 mL) was added, and the mixture was diluted with EtOAc (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with H2O (3 X 50 mL) and brine (3 X 50 mL), dried over Na2SO4, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes → 5% Et2O/hexanes → 10% Et2O/hexanes) to provide 35 mg (55%) of the title compound as a white solid: 1H NMR (360 MHz, CDCl3) δ 7.83 – 7.60 (m, 16H), 7.56 – 7.53 (m, 2H), 7.48 – 7.40 (m, 10H), 6.34 (d, J = 2.9 Hz, 1H), 5.17 – 5.02 (m, 4H), 4.96 (d, J = 11.9 Hz, 1H), 4.86 – 4.78 (m, 3H), 4.41 (d, J = 7.4 Hz, 1H), 4.29 (s, 1H), 4.12 (dd, J = 7.3, 3.0 Hz, 1H), 1.48 (s, 3H); 13C NMR (90 MHz, CDCl3) δ 136.7, 136.4, 135.7, 135.5, 133.3, 133.21, 133.19, 133.16, 133.0, 132.9, 132.8, 132.7, 131.8, 128.2, 128.0, 127.9, 127.8, 127.6, 127.6, 126.7, 126.4, 126.2, 126.1, 126.0, 125.9,
125.8, 125.7, 125.62, 125.57, 125.4, 122.9, 84.6, 81.4, 80.3, 80.2, 75.2, 74.2, 72.0, 64.8, 16.0; ESI+ m/z (relative intensity) 816.3 (M + NH₄, 100%); HRMS (ES+) Calcd for C₅₁H₄₇O₄N₇Br: 816.2688, Found: 816.2662.

1-(3,4,5,6-Tetrakis-(2-naphthylmethyl)oxy-5-methyl-cyclohex-1-enyl)-ethanone (4-32). To a -100 °C stirring solution of bromide 4-30 (35 mg, 0.044 mmol) in 1 mL of Et₂O was added tert-BuLi (1.7 M in pentane, 51 µL, 0.088 mmol) and stirring was continued at that temperature for 25 min. At that time, N-methoxy-N-methylacetamide (12 µL, 0.11 mmol) was added dropwise and then the solution was allowed to warm to 0 °C over 2 h. Ice-cold saturated NH₄Cl solution (4 mL) was then added and the reaction mixture was diluted with 10 mL of Et₂O. The aqueous layer was extracted with Et₂O (2 X 10 mL) and the combined organic layers were washed with water (3 X 30 mL) and brine (3 X 30 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography (20% Et₂O/hexanes → 40% Et₂O/hexanes) to provide 12 mg (36%) of the title compound as tacky off-white solid: IR (neat): 1674 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.82 – 7.33 (m, 28H), 6.73 (d, J = 2.7 Hz, 1H), 5.24 (d, J = 11.5 Hz, 1H), 5.09 (d, J = 11.5 Hz, 1H), 5.00 – 4.95 (m, 3H), 4.92 - 4.88 (m, 2H), 4.85 (s, 1H), 4.80 (d, J = 11.6 Hz, 1H), 4.62 (d, J = 7.7 Hz, 1H), 4.31 (dd, J = 7.7, 2.9 Hz, 1H), 2.28 (s, 3H), 1.31 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 198.3, 139.8 (X2), 133.2 (X2), 127.92, 127.89, 127.85, 127.80, 127.76,
127.65, 127.60, 127.56, 126.2(X2), 126.1, 125.9, 125.84, 125.79, 125.6, 125.5, 81.9, 80.3, 79.6, 75.3, 74.3, 73.9, 72.8, 64.3, 25.6, 15.3; ESI+ m/z (relative intensity) 780.5 (M + NH₄, 100%), 785.4 (M + Na, 30%); HRMS (ES+) Calcd for C₅₃H₅₀O₅N: 780.3689, Found: 780.3678.

2-[3-Bromo-2,5,6-tris-(tert-butyldimethylsilanyloxy)-1-methylcyclohex-3-enyloxy]methyl]napthalene (4-34). To a -30 °C stirring solution of ketone 4-8 (410 mg, 0.725 mmol) in 15 mL of Et₂O was added MeLi (1.6 M in Et₂O, 910 µL, 1.5 mmol). After 30 min of stirring at that temperature, ice-cold saturated NH₄Cl solution (15 mL) was added and the reaction mixture was diluted with Et₂O (15 mL). The organic layer was washed with H₂O (3 X 30 mL) and brine (3 X 30 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was dissolved in 3 mL of DMF and NAPBr (321 mg, 1.45 mmol), Bu₄NI (27 mg, 0.073 mmol), and NaH (60% dispersion in mineral oil, 58 mg, 1.45 mmol) were added sequentially. The reaction mixture was stirred at rt for 16 h. At that time, ice-cold saturated NH₄Cl solution (15 mL) was added and the reaction mixture was diluted with Et₂O (25 mL). The aqueous layer was extracted with Et₂O (2 X 25 mL) and the combined organic layers were washed with H₂O (3 X 75 mL) and brine (3 X 75 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes → 1% Et₂O/hexanes) to provide 322 mg (62%) of the title compound as a colorless oil: ¹H NMR
(360 MHz, CDCl$_3$) $\delta$ 7.89 (s, 1H), 7.84 – 7.82 (m, 3H), 7.62 (dd, $J =$ 8.3, 1.4 Hz, 1H), 7.49 – 7.46 (m, 2H), 6.04 (m, 1H), 5.18 (d, $J =$ 11.2 Hz, 1H), 4.71 (d, $J =$ 11.2 Hz, 1H), 4.00 (m, 1H), 3.97 (m, 1H), 3.57 (s, 1H), 1.27 (s, 3H), 0.91 (s, 9H), 0.87 (s, 9H), 0.85 (s, 9H), 0.13 (s, 6H), 0.11 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 135.3, 133.2, 133.0, 130.3, 128.0, 127.8, 127.7, 127.1, 126.7, 126.1, 125.9, 125.8, 79.3 (X2), 76.3, 75.9, 74.6, 26.4, 26.2, 25.9, 25.7, 18.5, 18.4, 17.9, -1.7, -2.0, -3.0, -3.4, -3.8, -4.8; ESI$^+$ m/z (relative intensity) 738.4 ($M + NH_4^+$, 80%), 743.3 ($M + Na$, 100%); HRMS (ES$^+$) Calcd for C$_{36}$H$_{65}$O$_4$NSi$_3$Br: 738.3405, Found: 738.3383.

1-[3,4,6-Tris-(tert-butyldimethylsilanyloxy)-5-methyl-5-(naphthalen-2-ylmethoxy)-cyclohex-1-enyl]-ethanone (4-35). To a -100 °C stirring solution of bromide 4-34 (320 mg, 0.443 mmol) in 4 mL of Et$_2$O was added tert-BuLi (1.7 M in pentane, 521 µL, 0.881 mmol) and stirring was continued at that temperature for 30 min. At that time, N-methoxy-N-methylacetamide (118 µL, 1.11 mmol) was added dropwise and then the solution was allowed to warm to 0 °C over 2 h. Ice-cold saturated NH$_4$Cl solution (4 mL) was then added and the reaction mixture was diluted with 15 mL of Et$_2$O. The aqueous layer was extracted with Et$_2$O (2 X 15 mL) and the combined organic layers were washed with water (3 X 50 mL) and brine (3 X 50 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography (hexanes $\to$ 5% Et$_2$O/hexanes) to yield 28 mg (9%) of the title
compound as a colorless oil: IR (neat): 1678 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.78 – 7.72 (m, 4H), 7.46 – 7.38 (m, 3H), 6.46 (d, \(J = 3.6\) Hz, 1H), 4.75 (d, \(J = 11.5\) Hz, 1H), 4.69 (d, \(J = 11.9\) Hz, 1H), 4.49 (s, 1H), 4.15 (app t, \(J = 3.6\) Hz, 1H), 4.01 (d, \(J = 2.9\) Hz, 1H), 2.24 (s, 3H), 1.19 (s, 3H), 0.91 (s, 9H + 9H), 0.82 (s, 9H), 0.154 (s, 3H), 0.149 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H); \(^{13}\)C NMR (90 MHz, CDCl\(_3\)) \(\delta\) 199.5, 140.6, 136.5, 133.2, 132.7, 127.8, 127.6, 127.5, 125.9 (X2), 125.8, 125.7, 125.5, 78.7, 77.5, 76.2, 75.1, 73.3, 26.48, 26.46, 26.3, 26.2, 26.1, 18.5, 18.4, 18.1, -1.56, -1.60, -3.0, -3.6, -3.7, -4.2; ESI+ m/z (relative intensity) 685.4 (M + H, 100%), 707.4 (M + Na, 95%); HRMS (ES+) Calcd for C\(_{38}\)H\(_{64}\)O\(_5\)Si\(_3\)Na: 707.3959, Found: 707.3967.

![OTBS](OTBS)

1-[3,4,6-Tris-(\textit{tert}-butyldimethylsilanyloxy)-5-hydroxy-5-methylcyclohex-1-enyl]-ethanone (4-36). To a stirring biphasic mixture of enone 4-35 (28 mg, 0.041 mmol) in CH\(_2\)Cl\(_2\) (1 mL) and H\(_2\)O (1 mL) was added DDQ (28 mg, 0.12 mmol) and stirring was continued for 2 h. At that time, saturated Na\(_2\)S\(_2\)O\(_3\) solution (5 mL) and saturated NaHCO\(_3\) solution (10 mL) were added sequentially. The reaction mixture was diluted with EtOAc (25 mL), washed with NaHCO\(_3\) solution (3 X 25 mL), H\(_2\)O (3 X 25 mL) and brine (3 X 25 mL), dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The residue was purified by flash chromatography (2% Et\(_2\)O/hexanes \(\rightarrow\) 5% Et\(_2\)O/hexanes) to provide 20 mg (90%) of the title compound as a colorless oil: IR (neat): 3425, 1662 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.58 (d, \(J = 3.3\) Hz, 1H), 4.43 (d, \(J = 2.7\) Hz, 1H), 3.87 (app t, \(J = 3.6\) Hz, 2H), 3.18 (dd, \(J = 11.5, 4.2\) Hz, 1H), 2.24 (s, 3H), 2.18 (app t, \(J = 6.0\) Hz, 1H), 1.20 (s, 9H), 0.89 (s, 9H), 0.154 (s, 3H), 0.149 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H); \(^{13}\)C NMR (90 MHz, CDCl\(_3\)) \(\delta\) 199.5, 140.6, 136.5, 133.2, 132.7, 127.8, 127.6, 127.5, 125.9 (X2), 125.8, 125.7, 125.5, 78.7, 77.5, 76.2, 75.1, 73.3, 26.48, 26.46, 26.3, 26.2, 26.1, 18.5, 18.4, 18.1, -1.56, -1.60, -3.0, -3.6, -3.7, -4.2; ESI+ m/z (relative intensity) 685.4 (M + H, 100%), 707.4 (M + Na, 95%); HRMS (ES+) Calcd for C\(_{38}\)H\(_{64}\)O\(_5\)Si\(_3\)Na: 707.3959, Found: 707.3967.

![OTBS](OTBS)
Hz, 1H), 4.12 (m, 1H), 3.75 (d, \( J = 2.9 \) Hz, 1H), 3.55 (d, \( J = 2.9 \) Hz, 1H), 2.35 (s, 3H), 1.28 (s, 3H), 0.92 (s, 9H), 0.87 (s, 9H + 9H), 0.16 – 0.14 (m, 9H), 0.14 – 0.12 (s, 6H), 0.11 (s, 3H); \(^{13}\)C NMR (90 MHz, CDCl\(_3\)) \( \delta 200.7, 139.5, 138.3, 77.9, 76.4, 73.9, 69.4, 26.5, 26.3, 26.2, 26.0, 21.7, 18.6, 18.5, 18.0, -1.6, -1.7, -3.4, -3.6, -3.9, -4.3; ESI+ \( m/z \) (relative intensity) 545.4 (M + H, 100%), 567.4 (M + Na, 50%); HRMS (ES+) Calcd for C\(_{27}\)H\(_{57}\)O\(_3\)Si\(_3\): 545.3514, Found: 545.3531.

6.4 Internally Hydrogen-Bonded Naphthoquinones.

\( \text{(6,7-Dimethyl-5,8-dioxo-5,8-dihydronaphthalen-1-yl)-carbamic Acid tert-Butyl Ester (5-11a).} \) To a stirring solution of 2,3-dimethylhydroquinone (5-9) (110 mg, 0.77 mmol) in 4 mL of Et\(_2\)O was added activated MnO\(_2\) (630 mg, 7.2 mmol) and the suspension was stirred at rt for 1 h. Buta-1,3-dienyl-carbamic Acid tert-butyl Ester (5-8) (118 mg, 0.697 mmol) was added and the reaction solution was refluxed for 20 h. The crude product was filtered through Celite/neutral alumina (5:1) and concentrated under reduced pressure. The residue was purified by flash chromatography (25% EtOAc/hexanes) to provide 154 mg (73%) of the title compound as a yellow solid: mp 174 - 175 °C; IR (CCl\(_4\)): 3263, 1735 cm\(^{-1}\); \(^1\)H NMR (300 MHz, C\(_6\)D\(_6\)) \( \delta 11.77 \) (br s, 1H),
9.02 (dd, $J = 8.6$, 1.2 Hz, 1H), 7.72 (dd, $J = 7.5$, 1.2 Hz, 1H), 7.08 (td, $J = 8.0$, 0.4 Hz, 1H), 1.73 (q, $J = 1.0$ Hz, 3H), 1.67 (q, $J = 1.0$ Hz, 3H), 1.44 (s, 9H); $^{13}$C NMR (90 MHz, CD$_2$Cl$_2$) $\delta$ 189.2, 185.1, 153.6, 145.1, 143.7, 142.6, 135.3, 133.6, 124.4, 121.1, 116.6, 81.7, 28.8, 13.4, 13.2; APCI m/z (relative intensity) 202.1 (M + 2H – CO$_2$C(CH$_3$)$_3$, 100%); HRMS calcd for C$_{12}$H$_{12}$NO$_2$ (M + 2H – CO$_2$C(CH$_3$)$_3$) 202.08625, found 202.08545.

\[
\begin{align*}
\text{NH}_2 & \\
\text{O} & \\
\text{C} & \\
\text{O} & \\
\text{O} & \\
\end{align*}
\]

5-Amino-2,3-dimethyl-[1,4]naphthoquinone (5-11b). To a stirring solution of 5-11a (535 mg, 1.78 mmol) in 2 mL of CH$_2$Cl$_2$, was added trifluoroacetic acid (1.32 mL, 17.8 mmol) and the reaction solution was stirred at rt for 24 h and then the solvent was removed under reduced pressure. The crude mixture was dissolved in EtOAc (25 mL) washed with ice-cold saturated NaHCO$_3$ solution (25 mL), water (3 X 25 mL) and brine (3 X 25 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (25% EtOAc/hexanes) to provide 358 mg (100%) of the title compound as a red solid: mp 157 - 158 °C; IR (CCl$_4$): 3503, 3339 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.40 (dd, $J = 7.4$, 1.4 Hz, 1H), 7.34 (t, $J = 7.7$ Hz, 1H), 6.87 (dd, $J = 8.1$, 1.3 Hz, 1H), 6.65 (br s, 2H), 2.12 (q, $J = 1.0$ Hz, 3H), 2.10 (q, $J = 1.0$ Hz, 3H); $^{13}$C NMR (90 MHz, C$_6$D$_6$) $\delta$ 187.0, 184.6, 149.9, 144.2, 141.9, 133.9, 133.8, 122.0, 116.5, 113.0, 12.5, 12.4; APCI m/z (relative intensity) 202.1 (M + H, 100%); HRMS calcd for C$_{12}$H$_{12}$NO$_2$ (M + H) 202.0868, found 202.0864
To a stirring solution of **5-11b** (250 mg, 1.2 mmol) in 2 mL of CH$_2$Cl$_2$ was added acetyl chloride (440 µL, 6.2 mmol) and the reaction solution was stirred at rt for 4 h. The crude mixture was added to 30 mL of ice-cold saturated NaHCO$_3$ solution, extracted with CH$_2$Cl$_2$ (3 X 25 mL), and the combined organic layers were washed with water (3 X 25 mL) and brine (3 X 25 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (25% EtOAc/hexanes) to provide 302 mg (100%) of the title compound as an orange solid. Crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of an Et$_2$O/CH$_2$Cl$_2$ solution of **5-11c** over a period of 24 h at rt. mp 176 - 177 °C; IR (CCl$_4$): 3262, 1710 cm$^{-1}$; $^1$H NMR (300 MHz, C$_6$D$_6$) $\delta$ 11.92 (br s, 1H), 9.29 (dd, $J = 8.6, 1.3$ Hz, 1H), 7.75 (dd, $J = 7.6, 1.3$ Hz, 1H), 7.08 (td, $J = 8.0, 0.4$ Hz, 1H), 1.81 (s, 3H), 1.75 (q, $J = 1.1$ Hz, 3H), 1.68 (q, $J = 1.1$Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 188.7, 184.1, 169.7, 144.0, 143.1, 140.7, 134.8, 132.4, 125.2, 121.6, 115.9, 25.6, 12.81, 12.76; APCI $m/z$ (relative intensity) 244.1 (M + H, 5%), 202.1 (M + H – CH$_3$CO, 100%); HRMS calcd for C$_{14}$H$_{14}$NO$_3$ (M + H) 244.0974, found 244.0986.

**X-Ray Analysis (5-11c).**

A yellow brick shaped crystal of **5-11c** (C$_{14}$H$_{13}$NO$_3$) with approximate
dimensions 0.10 x 0.31 x 0.37 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 98(2) K, cooled by Rigaku-MSC X-Stream 2000, on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a MoKα fine-focus sealed tube (λ = 0.71073Å) operated at 1600 watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal.

A total of 1850 frames were collected with a scan width of 0.3° in ω and an exposure time of 10 seconds/frame. The total data collection time was about 8 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm. The integration of the data using a Monoclinic unit cell yielded a total of 7141 reflections to a maximum θ angle of 28.31° (0.90 Å resolution), of which 2701 were independent, completeness = 96.2%, R_{int} = 0.0473, R_{sig} = 0.0490 and 2166 were greater than 2σ(I). The final cell constants: a = 9.115(2)Å, b = 15.989(4)Å, c = 7.931(2)Å, α = 90°, β = 102.757(5)°, γ = 90°, volume = 1127.2(5)Å³, are based upon the refinement of the XYZ-centroids of 2443 reflections above 20σ(I) with 2.547° <θ <28.181°. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The
ratio of minimum to maximum apparent transmission was 0.461253.

The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package, using the space group P2(1)/c, with Z = 4 for the formula unit, C₁₄H₁₃NO₃. The final anisotropic full-matrix least-squares refinement on F² with 170 variables converged at R1 = 5.06%, for the observed data and wR2 = 14.58% for all data. The goodness-of-fit was 1.044. The largest peak on the final difference map was 0.391 e/Å³ and the largest hole was -0.325 e/Å³. Based on the final model, the calculated density of the crystal is 1.433 g/cm³ and F(000) amounts to 512 electrons.

![Chemical Structure](image)

*N-(6,7-Dimethyl-5,8-dioxo-5,8-dihydronaphthalen-1-yl)-2,2,2-trifluoroacetamide (5-11d).* To an ice-cold solution of 5-11b (40 mg, 0.2 mmol) in 1 mL of CH₂Cl₂ was added trifluoroacetic anhydride (35 µL, 0.25 mmol). The reaction solution was warmed to room temperature and stirred for 4 h. The crude mixture was added to ice-cold saturated NaHCO₃ solution (15 mL), extracted with CH₂Cl₂ (3 X 15 mL), and the combined organic layers were washed with brine (3 X 15 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash chromatography (20% EtOAc/hexanes) to provide 59 mg (100%) of the title compound as a yellow solid: mp 123 - 124 °C; IR (CCl₄): 3109, 1741 cm⁻¹; ¹H NMR (400 MHz,
**2,3-Dimethyl-5-methylamino-[1,4]naphthoquinone (5-11e).** To a stirred solution of 5-11b (22 mg, 0.11 mmol) in 1 mL of benzene was added sequentially K$_2$CO$_3$ (15 mg, 0.11 mmol), NaOH (13 mg, 0.33 mmol), Bu$_4$NBr (7 mg, 0.02 mmol), and Me$_2$SO$_4$ (62 µL, 0.65 mmol) and the reaction mixture was stirred at rt for 24 h. The crude mixture was then diluted with Et$_2$O (10 mL), washed with 1N H$_3$PO$_4$ (10 mL), water (3 X 10 mL) and brine (3 X 10 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5% EtOAc/hexanes $\rightarrow$ 10% EtOAc/hexanes) to provide 21 mg (90%) of the title compound as a purple solid: mp 161 - 162 °C; IR (CCl$_4$) 3304 cm$^{-1}$; $^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ 9.29 (br s, 1H), 7.61 (dd, J = 7.3, 1.1 Hz, 1H), 7.03 (td, J = 7.5, 0.6 Hz, 1H), 6.40 (dd, J = 8.6, 1.0 Hz, 1H), 2.25 (d, J = 5.1 Hz, 3H), 1.83 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 186.5, 185.0, 151.0, 144.4, 141.1, 134.3, 133.1, 116.6, 114.9, 111.7, 29.3, 12.7, 12.5;
APCI m/z (relative intensity) 216.1 (M + H, 100%); HRMS calcd for C\textsubscript{13}H\textsubscript{14}NO\textsubscript{2} (M + H) 216.1025, found 216.1000.

![](image)

\textit{N-(6,7-Dimethyl-5,8-dioxo-5,8-dihyronaphthalen-1-yl)-N-methylacetamide} (5-12a). A solution of 5-11e (45 mg, 0.21 mmol) in 1 mL acetyl chloride was stirred at rt for 20 min. The crude mixture was added to ice-cold sat’d NaHCO\textsubscript{3} (20 mL), extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 X 20 mL), and the combined organic layers were washed with brine (3 X 20 mL), dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated under reduced pressure. The residue was purified by flash chromatography (20% hexanes/EtOAc) to provide 53 mg (98%) of the title compound as a yellow solid: mp 202 - 203 °C; IR (CCl\textsubscript{4}) 1664, 1630 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, C\textsubscript{7}D\textsubscript{8}) δ 7.92 (dd, J = 7.9, 1.5 Hz, 1H), 6.96 (s, 1H), 6.87 (s, 1H), 3.07 (s, 3H), 1.79 (s, 3H), 1.76 (s, 3H), 1.56 (s, 3H); \textsuperscript{13}C NMR (90 MHz, mixture of rotamers, CDCl\textsubscript{3}) δ 184.4, 184.1, 184.0, 183.8, 181.6, 169.6, 164.7, 144.5, 142.9, 142.5, 142.1, 141.8, 135.4, 134.9, 134.24, 134.16, 133.90, 133.86, 127.2, 127.0, 126.8, 126.2, 38.7, 35.9, 21.9, 13.0, 12.6, 12.5; APCI m/z (relative intensity) 258.1 (M + H, 100%); HRMS calcd for C\textsubscript{15}H\textsubscript{16}NO\textsubscript{3} (M + H) 258.1130, found 258.1145.
**N-(6,7-Dimethyl-5,8-dioxo-5,8-dihydronaphthalen-1-yl)-2,2,2-trifluoro-N-methylacetamide (5-12b).** To a stirring solution of 5-11e (101 mg, 0.469 mmol) in 3 mL of CH$_2$Cl$_2$ was added trifluoroacetic anhydride (263 µL, 1.86 mmol) and the reaction solution was stirred at rt for 4 h. The crude mixture was added to ice-cold saturated NaHCO$_3$ solution (50 mL), extracted with CH$_2$Cl$_2$ (3 X 35 mL), and the combined organic layers were washed with brine (100 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (25% EtOAc/hexanes) to provide 143 mg (98%) of the title compound as a yellow solid: mp 158 - 159 °C; IR (CCl$_4$) 1712, 1665, 1629 cm$^{-1}$, $^1$H NMR (300 MHz, 85 °C, C$_7$D$_8$) $\delta$ 7.94 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.08 (t, $J = 7.8$ Hz, 1H), 6.89 (d, $J = 7.9$ Hz, 1H), 3.08 (s, 3H), 1.77 (q, $J = 1.0$ Hz, 3H), 1.74 (q, $J = 1.0$ Hz, 3H); $^{13}$C NMR (90 MHz, mixture of rotamers, CDCl$_3$) $\delta$ 184.0, 183.8, 156.2 (q, $J_{CCF} = 35.6$ Hz), 144.7, 144.6, 142.6, 142.4, 140.4, 138.6, 135.2, 134.4, 134.2, 133.94, 133.89, 128.1, 127.50, 127.45, 116.2 (q, $J_{CF} = 286.7$ Hz), 38.3, 13.1, 13.0, 12.8, 12.7; ESI m/z (relative intensity) 312.1 (M + H, 20%), 334.1 (M + Na, 100%); HRMS calcd for C$_{15}$H$_{13}$NO$_3$F$_3$ (M + H) 312.0848, found 312.0863.
To a stirring solution of trans, trans-muconic acid (5-7a) (201 mg, 1.41 mmol) in 20 mL of tert-butanol was added sequentially diphenylphosphoryl azide (727 µL, 3.38 mmol) and Et$_3$N (469 µL, 3.38 mmol) and the reaction solution was refluxed for 8.5 h. The crude mixture was then concentrated under reduced pressure. The residue was recrystallized from EtOH/H$_2$O (80:20) to give the title compound as a white solid: mp 150 °C (dec.); IR (neat) 3348, 1692 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 9.10 (d, $J = 9.9$ Hz, 2H), 6.31 (t, $J = 11.0$ Hz, 2H), 5.59 (d, $J = 10.9$ Hz, 2H), 1.39 (s, 18H); $^{13}$C NMR (75 MHz, DMSO-d$_6$) δ 152.6, 123.6, 108.7, 78.9, 28.1; ESI $m/z$ (relative intensity) 307.1 (M + Na, 100%); HRMS calcld for C$_{14}$H$_{24}$N$_2$O$_4$Na (M + Na) 307.1634, found 307.1623.

To a stirring solution of 2,3-dimethylhydroquinone (5-9) (27 mg, 0.20 mmol) in 2 mL of Et$_3$O was added activated
MnO$_2$ (136 mg, 1.56 mmol) and the reaction stirred at rt for 1h. The crude mixture was filtered through Celite and the solvent was removed under reduced pressure. The crude oil was dissolved in 2 mL of toluene, and 5-8a (50 mg, 0.18 mmol) was added and the reaction solution was refluxed for 27 h. DDQ (160 mg, 0.70 mmol) was then added and the reaction solution was refluxed for an additional 24 h then filtered through Celite and concentrated under reduced pressure. The residue was purified by flash chromatography (5% EtOAc/hexanes) to provide 66 mg (90%) of the title compound as a red solid: mp 224 - 225 °C; IR (CCl$_4$): 3240, 1736 cm$^{-1}$; $^1$H NMR (300 MHz, C$_6$D$_6$) $\delta$ 12.06 (s, 2H), 9.12 (s, 2H), 1.68 (s, 6H), 1.44 (s, 18H); $^{13}$C NMR (75 MHz, C$_6$D$_6$) $\delta$ 187.6, 153.2, 143.3, 138.1, 127.0, 114.9, 80.5, 28.2, 12.5; ESI m/z (relative intensity) 439.2 (M + Na, 100%); HRMS calcd for C$_{22}$H$_{28}$N$_2$O$_6$Na (M + Na) 439.1845, found 439.186.

5,8-Diamino-2,3-dimethyl-[1,4]naphthoquinone (5-13b). To a stirring solution of 5-13a (586 mg, 1.41 mmol) in 14 mL of toluene was added trifluoroacetic acid (325 µL, 4.22 mmol) and the reaction solution was refluxed for 24 h. The reaction mixture was diluted with Et$_2$O, added to ice-cold saturated NaHCO$_3$ solution (35 mL), washed with water (3 X 35 mL) and brine (3 X 35 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (5%EtOAc/hexanes $\rightarrow$ 20% EtOAc/hexanes) to provide 292 mg (96%) of the title compound as a purple solid: mp 254 - 255 °C; IR (CCl$_4$): 3490, 3288 cm$^{-1}$; $^1$H NMR (300
MHz, CD$_3$CN) $\delta$ 6.97 (s, 2H), 2.08 (s, 6H); $^{13}$C NMR (75 MHz, CD$_3$CN) $\delta$ 185.0, 146.5, 143.4, 128.6, 109.4, 13.0; ESI m/z (relative intensity) 217.1 (M + H, 100%); HRMS calcd for C$_{12}$H$_{13}$N$_2$O$_2$ (M + H) 217.0977, found 217.0984.

![Chemical structure](image)

**N-(4-Acetylamino-6,7-dimethyl-5,8-dioxo-5,8-dihydronaphthalen-1-yl)-acetamide (5-13c).** To a stirring solution of 5-13b (17 mg, 0.079 mmol) in 800 µL of CH$_2$Cl$_2$ was added acetyl chloride (17 µL, 0.24 mmol) and pyridine (25 µL, 0.31 mmol) and the reaction solution was stirred at rt for 10 min. The crude mixture was added to ice-cold saturated NaHCO$_3$ solution (5 mL), extracted with CH$_2$Cl$_2$ (3 X 5 mL), and the combined organic layers were washed with water (3 X 15 mL) and brine (3 X 15 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (25% EtOAc/hexanes $\rightarrow$ 50% EtOAc/hexanes) to provide 24 mg (100%) of the title compound as a red solid: mp 280 - 281 °C; IR (CCl$_4$): 3201, 1712 cm$^{-1}$; $^1$H NMR (300 MHz, C$_6$D$_6$) $\delta$ 12.18 (s, 2H), 9.34 (s, 2H), 1.81 (s, 6H), 1.72 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 188.2, 169.8, 143.9, 137.4, 128.2, 115.1, 25.7, 12.9; ESI m/z (relative intensity) 301.1 (M + H, 100%); HRMS calcd for C$_{16}$H$_{16}$N$_2$O$_4$Na (M + Na) 323.1008, found 323.0996.
To a stirring solution of 5-13b (50 mg, 0.23 mmol) in 1 mL of CH₂Cl₂ was added trifluoroacetic anhydride (67 µL, 0.48 mmol) and the reaction solution was stirred at rt for 5 min. The crude mixture was added to saturated NaHCO₃ solution (30 mL), extracted with CH₂Cl₂ (3 x 30 mL), and the combined organic layers were washed with brine (3 x 30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (20% EtOAc/hexanes) to provide 94 mg (100%) of the title compound as an orange solid: mp 252 - 253 °C; IR (CCl₄) 3076, 1747 cm⁻¹; ¹H NMR (360 MHz, C₆D₆) δ 13.18 (s, 2H), 8.75 (s, 2H), 1.56 (s, 6H); ¹³C NMR (75 MHz, C₆D₆) δ 181.2, 155.8 (q, JCCF = 38.7 Hz), 144.0, 135.5, 135.4, 117.1, 116.3 (q, JCF = 292.5 Hz), 12.3; APM/z (relative intensity) 407.1 (M - H, 80%), 408.1 (M-, 100%); HRMS calcd for C₁₆H₁₀N₂O₄F₆ (M-) 408.0545, found 408.0551.
VITA

David Keith Hester II

David Keith Hester II was born in Pahokee, FL on February 15, 1981 to parents David Keith Hester and Dolly Sue Hester. He was raised in Clewiston, FL and received his B.S. degree in Chemistry from the University of Central Florida in 2003. While in college, he was a member of UCF Crew where he rowed all eight semesters and was elected captain of the team during the 2002-2003 season. Upon acceptance to the graduate program in the Department of Chemistry at Penn State in the fall of 2003, he joined the research group of Prof. Ken S. Feldman under the co-advisement of Prof. John H. Golbeck. He worked on several projects in the area of organic synthesis methodology development and total synthesis of natural products.

Keith joined the coaching staff of Penn State Crew in the fall of 2003. Along with Coach Josh Organist he coached a women’s novice 4+ to a bronze medal at the 2005 Dad Vail Regatta. Along with Coach John Biddle, he coached a women’s varsity 4+ and a men’s lightweight 4+ to silver medals at the 2007 Dad Vail Regatta. Along with Coach Jamie Francis, he coached a men’s varsity 4+ to a gold medal at the 2008 ACRA National Championship Regatta.

After receiving his Ph. D. from Penn State in 2008, Keith began his career at Albany Molecular Research, Inc. in Albany, NY.