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# Total Synthesis of the Tropoloisoquinoline Alkaloid Pareitropone via Alkynyliodonium Salt Chemistry and Related Studies

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The first chemical synthesis of pareitropone, by a route featuring application of alkynyliodonium salt chemistry, is described. The key transform initiates with addition of an alkylidenecarbene, derived by intramolecular nucleophile addition to the alkynyliodonium moiety, to a proximal aromatic ring. This addition delivers a highly strained norcaradiene substructure that rapidly reorganizes to furnish the pareitropone skeleton.

The tropoloisoquinoline alkaloids comprise a rather small family of secondary metabolites from the *Menispermaceae* that have elicited some interest as a consequence of both their novel architecture and their potency in select cytotoxicity assays.[1] They differ among themselves principally by the extent and position of oxygenation along the molecular periphery, ranging from the simplest trioxygenated species pareitropone (**1**) to the hexoxygenated analogue pareirubrine A (**4**), Figure 1. The structural resemblance of these compounds to colchicine has prompted speculation that the tropoloisoquinolines' cytotoxicity might stem from tubulin binding activity, but direct assay with **3** and **5** did not provide support for this hypothesis.[2] The curious observation that cytotoxic potency roughly scales inversely with the extent of oxygenation defies explanation at present. Nevertheless, the remarkable cytotoxicity in the leukemia P388 screen exhibited by pareitropone elevates this particular tropoloisoquinoline to a position of prominence in the search for chemotherapeutic leads.[1a] The scarcity of the natural isolate (0.0004 wt % from *Cissampelos pareira*)[1a] and the relatively uncomplicated structure argue for the premise that useful quantities of this material to support further biological testing can be accessed by total chemical synthesis.[3]

The history of synthesis studies in the tropoloisoquinoline series suggests that whereas these structures are simple, they are not simply made. Successful efforts from the laboratories of Banwell,[2,4] Boger,[5] and Cha,[6] along with uncompleted attempts by Evans[7] and Molina,[8] all highlight the cycloheptatrienone ring as the focal point of the synthesis strategies. The Banwell and Evans approaches pass through quinone ketal-derived cyclopropanes en route to the seven-membered ring, Scheme 1. Boger and, independently, Cha exploit cycloaddition chemistry to furnish a tropolone precursor. None of these approaches, however, are capable of directly delivering

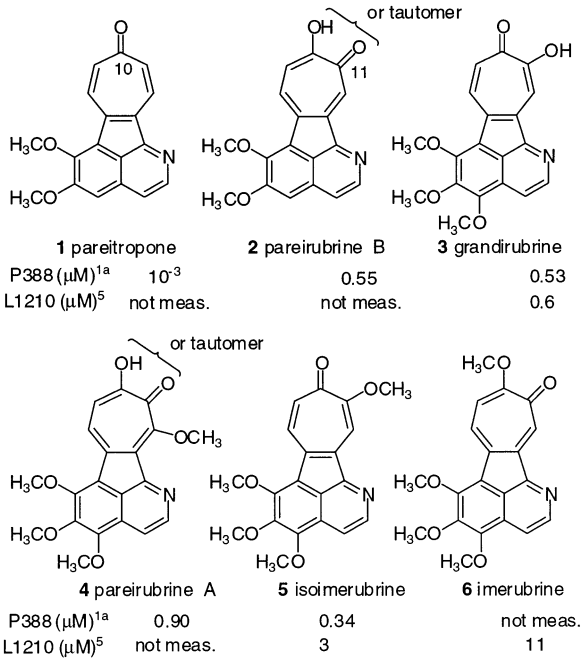


**FIGURE 1.** Structurally characterized tropoloisoquinoline alkaloids.

(1) (a) Morita, H.; Takeya, K.; Itokawa, H. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 597−598. (b) Silverton, J. V.; Kabuto, C.; Buck, K. T.; Cava, M. P. *J. Am. Chem. Soc.* **1977**, *99*, 6708−6712. (c) Morita, H.; Matsumoto, K.; Takeya, K.; Itokawa, H.; Iitaka, Y. *Chem. Pharm. Bull.* **1993**, *41*, 1418−1422. (d) Menachery, M. D.; Cava, M. P. *Heterocycles* **1980**, *14*, 943−945.

(2) Banwell, M. G.; Hamel, E.; Ireland, N. K.; Mackay, M. F. *Heterocycles* **1994**, *39*, 205−217.

(3) A preliminary account of this work can be found in Feldman, K. S.; Curatelli, T. D. *J. Am. Chem. Soc.* **2002**, *124*, 11600−11601.

(4) (a) Banwell, M. G.; Bonadio, A.; Turner, K. A.; Ireland, N. K.; Mackay, M. F. *Aust. J. Chem.* **1993**, *46*, 325−351. (b) Banwell, M. G.; Hamel, E.; Ireland, N. K.; Mackay, M. F.; Serelis, A. K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1905−1911. (c) Banwell, M. G. *Pure Appl. Chem.* **1996**, *68*, 539−542.

(5) Boger, D. L.; Takahashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12452−12459.

(6) Lee, J. C.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 3243−3246.

(7) Evans, D. A.; Hart, D. J.; Koelsch, P. M.; Cain, P. A. *Pure Appl. Chem.* **1979**, *51*, 1285−1300.

(8) Molina, P.; Garcia-Zafra, S.; Fresneda, P. M. *Synlett* **1995**, 43−45.

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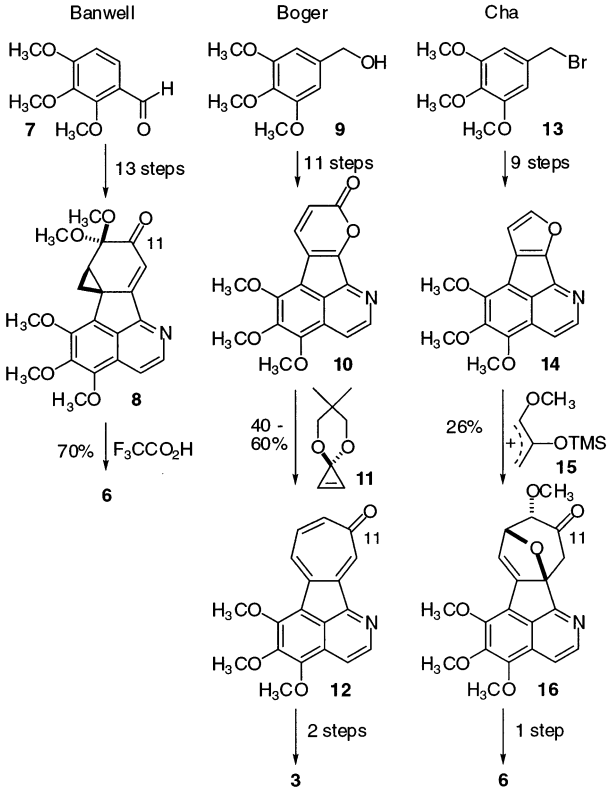
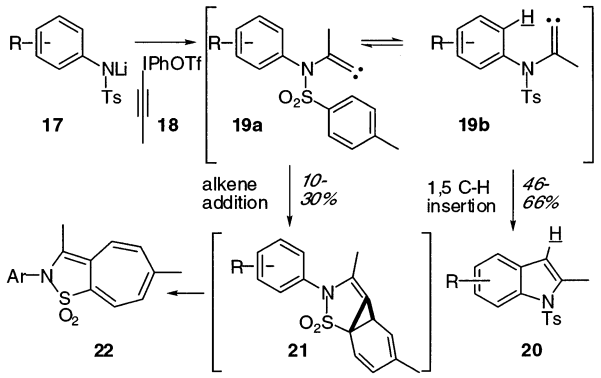
**SCHEME 1**



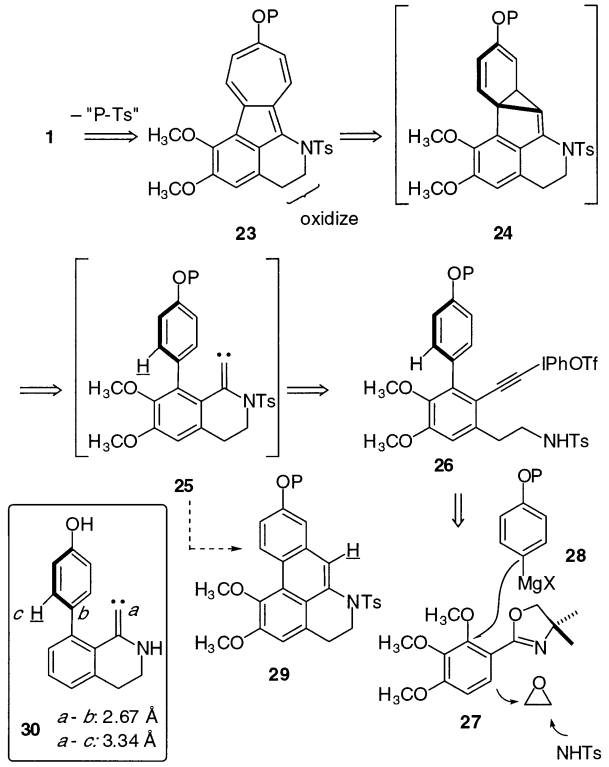

**SCHEME 2**




the 10-ketotropone unit of pareitropone. Rather, in each case, an 11-keto product results. Therefore, the development of a new strategy to target specifically the 10-keto cycloheptatriene ring of **1** was indicated.

This alternative approach to the pareitropone nucleus evolved from a series of chance observations made during methodology development studies directed toward indole synthesis, Scheme 2. An ongoing interest in expanding alkynyliodonium salt chemistry to encompass broad aspects of heterocycle synthesis led to the investigation of the transformation **17** → **20**.[9] Along with the desired indole product **20**, minor amounts of highly colored materials whose spectral data supported the assignment of the azulenylsulfonamide structure **22** were isolated for any "R" substrate examined. This surprising result suggested that the intermediate alkylidenecarbene **19**

**SCHEME 3**




was capable of breaching an electron-deficient arene ring to provide a highly strained norcaradiene intermediate, **21**, that apparently reorganizes to the observed product **22**. Examples of alkylidenecarbene−arene additions are scarce, and even in the cases reported, extreme conditions (≥600 °C pyrolysis)[10] or substrate-specific conformational preferences[11] (s-trans rotamer for an *N*-aryl,*N*-methyl amide)[12] can be invoked to rationalize the results. From this perspective, the ready addition of an alkylidenecarbene to the aryl ring in **19** remains puzzling, but may be no more than an expression of the indiscriminate reactivity of an exceedingly energetic reactive intermediate.[13] In any event, the vulnerability of proximal aryl rings to alkylidenecarbene addition, even if a highly strained product results, can serve as the basis for developing a strategy for accessing pareitropone.

A retrosynthetic analysis of **1** is detailed in Scheme 3.[14] The final product can, in principle, be formed from the cycloheptatrienylidene **23** via formal loss of the elements of "P-Ts" and dehydrogenation of the resulting dihydroisoquinoline. This late-stage oxidation finds some

(9) Feldman, K. S.; Bruendl, M. M.; Schildknegt, K.; Bohnstedt, A. C. *J. Org. Chem.* **1996**, *61*, 5440−5452.

(10) (a) Brown, R. F. C.; Eastwood, F. W.; Harrington, K. J.; McMullen, G. L. *Aust. J. Chem.* **1974**, *27*, 2393−2402. (b) Sonoda, M.; Itahashi, K.; Tobe, Y. *Tetrahedron Lett.* **2002**, *43*, 5269−5272.

(11) (a) Gilbert, J. C.; Blackburn, B. K. *Tetrahedron Lett.* **1990**, *31*, 4727−4730. (b) Gilbert, J. C.; Blackburn, B. K. *J. Org. Chem.* **1986**, *51*, 4089−4090.

(12) Curran, D. P.; Yu, H.; Liu, H. *Tetrahedron* **1994**, *50*, 7343−7366.

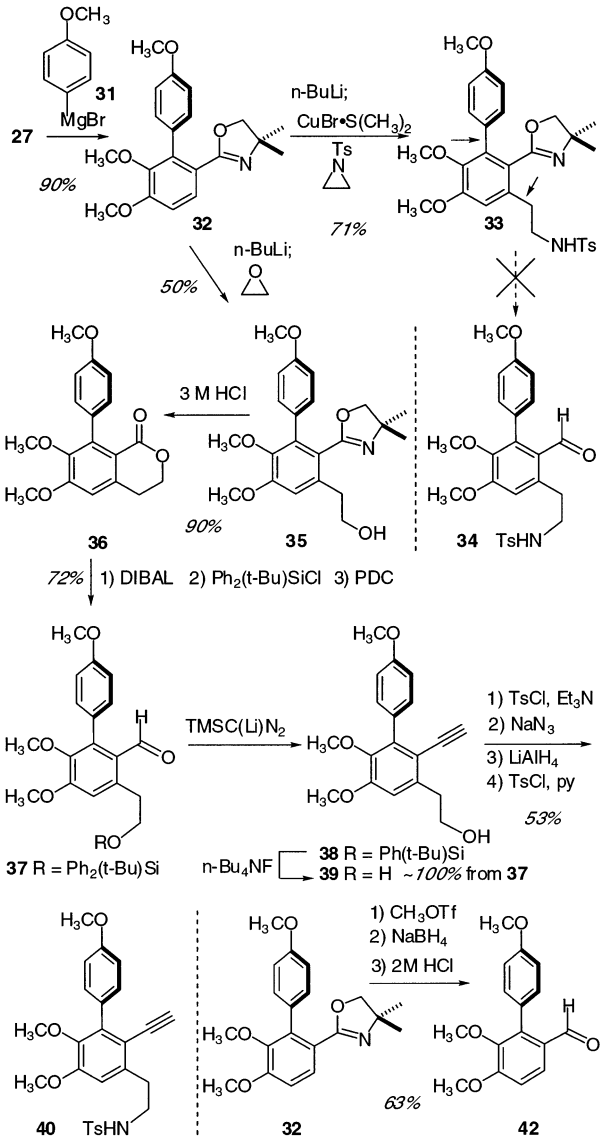
(13) The heat of formation of the parent compound vinylidene ($H_2C$=C:) can be estimated through a combination of spectroscopy and calculation to be ~100 kcal/mol. See: Hayes, R. L.; Fattal, E.; Govind, N.; Carter, E. A.*J. Am. Chem. Soc.* **2001**, *123*, 641−657 and references therein.

(14) A conceptually related approach to the tropone-fused polycyclic natural product hainanolidol can be found in Frey, B.; Wells, A. P.; Rogers, D. H.; Mander, L. N. *J. Am. Chem. Soc.* **1998**, *120*, 1914−1915.

precedent in the work of Banwell,[4b] who posited that aerobic oxidation was responsible for the aromatization of a related azafluoranthrene precursor. Whether this facile oxidation procedure can be exported to the tropone-annelated dihydroisoquinoline of interest here remains a matter of conjecture. The key step in the sequence links the alkynyliodonium salt **26** with the pareitropone framework **23** via the intermediacy of the series of putative high-energy structures **24** and **25**. Initial intramolecular addition of the sulfonamide anion derived from **26** to the alkynyliodonium salt should deliver alkylidenecarbene **25**, whose fate will determine the success of the entire scheme. Consideration of the decomposition pathways normally expressed in alkylidenecarbene chemistry leads to concerns about 1,2 shift to reformulate an alkyne, 1,6 C−H insertion to provide a stable phenanthrene product **29**, and addition to the tosyl ring (as per **19a** → **21**), in competition with the desired reaction course. The facility by which aryl-substituted alkylidenecarbenes participate in alkyne-regenerating 1,2 shifts raises a cautionary note with **25**, but the strain inherent in forming an incipient cycloheptyne product might militate against this reaction path. There exists only a limited basis for evaluating the likelihood of carbene addition to the electron-poor tosyl ring in **25** rather than the proximal electron-rich aryl ring as desired. Data on alkylidenecarbene−alkene cycloadditions provide support for a model in which an electron-deficient carbene reacts faster with electron-rich alkenes ($\rho = -0.5$).[15] Extrapolation from the alkene addition case to the arene addition case would suggest that the desired addition path will be followed. Finally, the question of aryl ring addition vs 1,6 C−H insertion arises. This alternative reaction channel is not so easy to dismiss, given the precedent of Harrington[10a] and earlier in-house studies on this process.[16] To the extent that proximity effects influence this choice of reaction site, density functional calculations[17] on the simpler model system **30** allow the tentative conclusion that addition to the buttressing aryl ring in **25** will be geometrically favored over C−H insertion. This point, however, remains to be determined by experiment. The alkynyliodonium salt can be assembled from the known oxazoline **27**[18] using reliable arene functionalization chemistry that borrows heavily from the seminal contributions of Meyers and colleagues.[19]

The synthesis work on pareitropone commenced with the selection of trimethyl ether **40** as a first-generation substrate adequate for testing the pivotal alkynyliodonium salt chemistry, Scheme 4. Close precedent from the arene functionalization literature suggested that the two key carbon−carbon bonds in **33** (arrows) could be fashioned in a straightforward manner. Toward that end, condensation of the commercially available *p*-anisole-derived Grignard reagent **31** with oxazoline **27**, itself prepared in two operations from 2,3,4-trimethoxybenzoic

**SCHEME 4**




acid,[18] led cleanly to the biaryl system **32**. The arene activation capabilities of the oxazoline ring were again exploited, in this instance to facilitate lateral metalation in anticipation of nucleophilic addition to tosylaziridine. The reaction proceeded poorly in the absence of copper mediation, but upon incorporation of $CuBr{\cdot}S(CH_3)_2$ as described by Hoye,[20] good yields of the ethyltosylamide product **33** were obtained. Reductive cleavage of the oxazoline moiety was required next, a reaction for which there is much precedent.[21] However, the first roadblock of the route was encountered in this step, as exhaustive exploration of the various oxazoline reductive cleavage protocols proved fruitless. In every case, either complete destruction or complete recovery of the starting material was observed. Steric hindrance at the oxazoline moiety might well be the culprit, as reductive cleavage of the

(15) Gilbert, J. C.; Giamalva, D. H. *J. Org. Chem.* **1992**, *57*, 4185−4188.

(16) Feldman, K. S.; Perkins, A. L. *Tetrahedron Lett.* **2001**, *42*, 6031−6033.

(17) The energy-minimized geometry of **30** was derived through a density functional calculation using a perturbative Becke−Perdew model and the DN* basis set in Spartan 5.0.

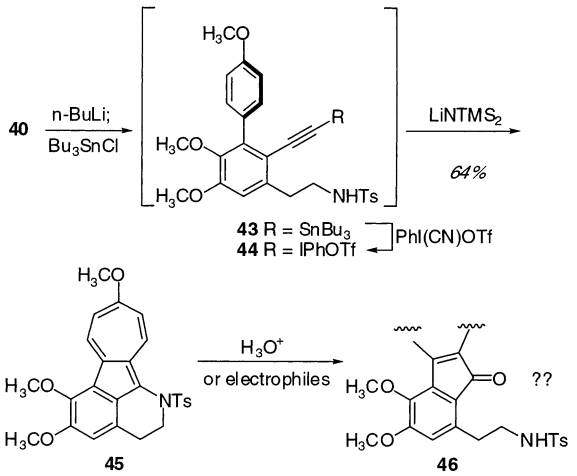
(18) Ladd, D. L.; Weinstock, J.; Wise, M.; Gessner, G. W.; Sawyer, J. L.; Flaim, K. E. *J. Med. Chem.* **1986**, *29*, 1904−1912.

(19) (a) Meyers, A. I.; Gant, T. G. *Tetrahedron* **1994**, *50*, 2297−2360. (b) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837−860.

(20) Hoye, T. R.; Chen, M.; Hoang, B.; Mi, L.; Priest, O. P. *J. Org. Chem.* **1999**, *64*, 7184−7201.

(21) (a) Nordin, I. C. *J. Heterocycl. Chem.* **1966**, *3*, 531−532. (b) Wilson, S. R.; Mao, D. T.; Khatri, H. N. *Synth. Commun.* **1980**, *10*, 17−23. (c) Meyers, A. I.; Himmelsbach, R. J.; Reuman, M. *J. Org. Chem.* **1983**, *48*, 4053−4058.

**SCHEME 5**




oxazoline in the less congested model substrate **41** occurred without event. The discovery by Patel and McLean in a related system that oxazoline hydrolysis is facilitated by participation of a proximal hydroxyethyl fragment provided the necessary impetus to design a workaround.[22] Substitution of ethylene oxide for tosylaziridine in the condensation with the aryl anion derived from **32** led to formation of the arylethanol product **35** in moderate yield. As anticipated, treatment of **35** with relatively mild acid effects oxazoline hydrolysis with concomitant formation of the derived lactone product **36**. Partial reduction of this lactone to a hemiacetal, as a means of differentiating the oxygenated termini, could not be accomplished, and so complete reduction to a diol followed by selective monosilylation of the more accessible alcohol was employed to distinguish between the carbon chains. Pyridinium dichromate-mediated oxidation of the benzylic alcohol in this species then delivered the aldehyde **37**. Attempts to chain-extend this hindered aldehyde via the Corey−Fuchs procedure ($CBr_4$, $PPh_3$; *n*-BuLi) afforded highly variable yields of the desired alkyne **38**, a problem compounded by the frequent loss of the silyl ether upon initial treatment of **37** with the dibromomethylene reagent. The alternative of using lithiotrimethylsilyldiazomethane became increasingly appealing, and reproducibly high yields of the alkyne product **38** were available by this procedure. Interestingly, this transformation likely passes through an alkylidenecarbene intermediate similar to **25**. However, in this instance, the proton-substituted carbene suffers very rapid 1,2 H shift to regenerate the alkyne rather than undergoing a presumably much slower arene addition as proposed for the conversion of **25** to **24**. Standard functional group manipulations were sufficient to process the alcohol unit of **39** into the desired tosylamide fragment of **40**. Thus, the inability to reductively cleave the oxazoline ring of **33** was a costly failure, as six additional steps were required to access **40** from **32**.

The acquisition of tosylamide alkyne **40** sets the stage for testing the key premise of the synthesis strategy, Scheme 5. Conversion of the terminal alkyne function within **40** to the alkynylstannane **43** occurred smoothly under typical basic conditions, but the product's tendency to suffer partial destannylation upon attempted chromatographic purification or even upon standing necessitated some modification of the initial plan. Rather than risk entering the key step with a substrate of variable and unknown purity, a procedure was adopted whereby the crude alkynylstannane was flushed rapidly through silica to remove tin residues and then used immediately in the iodination sequence. Treatment of the freshly prepared alkynylstannane **43** with PhI(CN)OTf (Stang's reagent)[23] at −42 °C in $CH_2Cl_2$ presumably furnishes the alkynyliodonium salt **44**, which was isolated as an oily solid by solvent removal and rinsing with prechilled (−78 °C) hexane, all while maintaining the flask in a −42 °C bath. Prechilled DME was added to this salt at −42 °C followed by base to trigger the cascade of reactions detailed in Scheme 3 and deliver the dark purple cycloheptatrienylidene product **45** in good yield. No evidence for an alternative phenanthrene-type product (cf. **29**) could be discerned in the $^1$H NMR spectrum of the crude reaction products. In addition, the tosyl residue survived intact, ruling out any significant diversion of the alkylidenecarbene through toluene ring addition. Subsequent runs demonstrated that the low-temperature hexane wash of **44** could be omitted with no decrease in yield of the tetracyclic product **45**. The transformation was quite clean, although material loss upon chromatographic purification may be responsible for an incomplete mass balance.

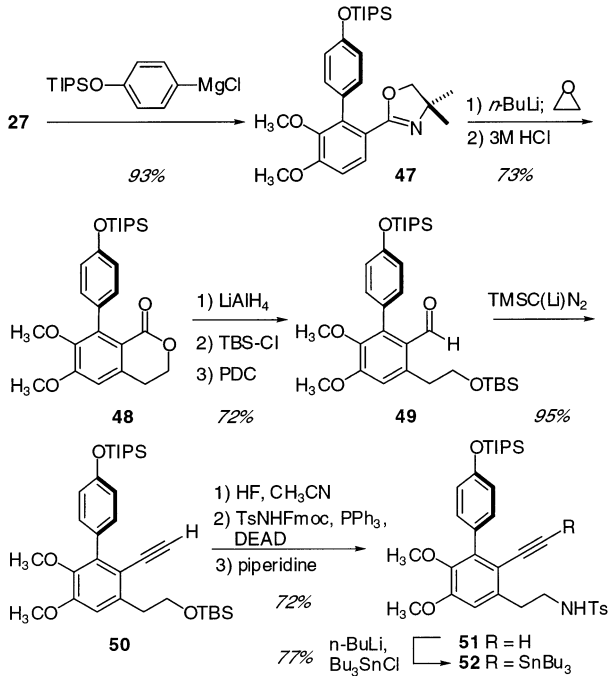
The structural assignment of **45** rests on a combination of $^1$H and $^{13}$C NMR techniques, as well as the confirmatory IR and MS analyses. Signal positions and coupling constants exhibited by the alkenyl protons were entirely consistent with the cycloheptatriene assignment. The DEPT-135 and DEPT-90 spectra, in conjunction with HMQC and HMBC NMR experiments, allowed the complete and unambiguous assignment of all of the alkenyl carbons and protons. The realization that this methoxy-substituted cycloheptatrienylidene species would only serve as a model system and not play a role in the synthesis of pareitropone became apparent as numerous attempts to hydrolyze the enol ether unit of **45** failed to deliver tropone product. Exposure of **45** to a range of aqueous acids as well as assorted electrophiles ($BBr_3$, NBS, $Br_2$, $Hg(OAc)_2$) generally led to consumption of starting material without formation of any completely characterizable products. Partial characterization of crude hydrolysis reaction mixtures suggested that fluorenone-type products **46** were being formed, at least to some extent. This observation appears consistent with the notion that the tosylenamide unit is more susceptible to hydrolysis than the enol ether fragment. Perhaps ring strain resulting from confining the enamide alkene to the juncture between three rings contributes to this unexpected lability. Whatever the reason, these results, taken together, provide encouragement to continue pursuit of pareitropone via an alkynyliodonium salt-based strategy with the added proviso that suitable protection of the cycloheptatrienylidene hydroxyl must be built in from the beginning (cf. "P", Scheme 3).

Replacement of the troublesome methyl ether with the presumably more labile triisopropylsilyl (TIPS) ether

(22) Patel, H. A.; MacLean, D. B. *Can. J. Chem.* **1983**, *61*, 7−13.

(23) Stang, P. J.; Zhdankin, V. V. *J. Am. Chem. Soc.* **1991**, *113*, 4571−4756.

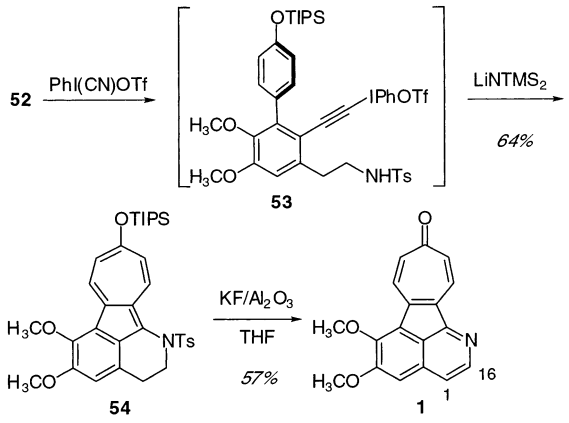
**SCHEME 6**




marked the beginning of the second-generation approach to pareitropone, Scheme 6. The chemistry followed lines similar to those described earlier, and proceeded without event to deliver the silyl ether **50**. It is noteworthy that the rather refractory oxazoline ring in the ethylene oxide addition product of **47** could be hydrolyzed under acidic conditions which were mild enough to preserve the TIPS ether. Selective monosilylation of the diol derived from lactone **48** was achieved with *tert*-butyldimethylsilyl chloride, as resorting to the more hindered diphenyl analogue did not prove necessary in this series. A departure from the previous tosylamide introduction sequence shaved three steps from the earlier route. Thus, treatment of the alcohol derived from desilylation of the primary silyl ether in **50** (again, note that the TIPS ether survives unscathed) with 3 equiv of TsNHFmoc under Mitsunobu-type reaction conditions not only effects C−O to C−N conversion, but also cleaves the Fmoc group in situ to furnish the tosylamide function directly. Presumably, the base generated in this transformation is sufficient to fragment the Fmoc unit as per the precedent of Bach and Kather.[24] In a separate series of experiments, use of only 1.1 equiv of TsNHFmoc under similar Mitsunobu conditions led to isolation of the Fmoc-protected tosylimide in 80% yield. Subsequent treatment of this imide with piperidine furnished the desired tosylamide **51** in better overall yield than with the one-pot procedure (74% vs 64%). Conversion of the terminal alkyne in **51** into the alkynylstannane **52** led, in this case, to a product which was marginally more stable to purification than the methyl ether analogue **43**.

Exposure of pure alkynylstannane **52** to Stang's reagent and then base as described previously again led to clean conversion into a deep blue-green cycloheptatrienylidene product, **54**, Scheme 7. Structural assignment for this species rests on a comparison of select NMR data

**SCHEME 7**




with those generated for the rigorously characterized methyl ether analogue **45**, and on its eventual conversion into the target **1**. Attempts to improve this yield by performing the iodonium salt synthesis with a prechilled hexane wash had little effect. Treatment of silyl ether **54** with KF on alumina, uniquely among all fluoride sources tested, led to formation of a troponoid product in which loss of "TIPS-Ts" was evident. In fact, the lack of aliphatic signals in the $^1$H NMR spectrum of the crude reaction mixture was puzzling at first, but subsequent purification of this material afforded a red-brown solid, whose spectral data exactly matched those reported for the natural product pareitropone,[1a] as the major component. Apparently, a first-formed C(1)−C(16) dihydro precursor of pareitropone is oxidized upon exposure to air, providing the fully aromatic isoquinoline-containing product. Initial screening of many other fluoride sources (*n*-BuNF ± acidic additives, CsF, HF in various solvents) led to the observation that consumption of starting material **54**, while rapid at −78 °C, was not matched by the formation of any characterizable products. Indecipherable mixtures of materials inevitably resulted. The singular success of KF/$Al_2O_3$ in THF may be due to trapping by absorption of the initial, sensitive dihydropareitropone species (or pareitropone itself) before it can participate in unidentified but destructive processes. Control experiments showed that $Al_2O_3$ alone did not induce any observable reaction with **54**, whereas KF suspended in THF led to destruction of **54** without isolation of any characterizable material. As a final control, treatment of pareitropone itself with *n*-$Bu_4NF$ at −78 °C rapidly led to consumption of the natural product and formation of a complex mixture of unidentified materials, a result reminiscent of the outcomes observed during the initial desilylation studies with **54**. In a few runs, evidence supporting the presence of small amounts of a chromatographically inseparable material tentatively identified as the C(1)−C(16) dihydro derivative could be seen in the $^1$H NMR spectrum of the crude reaction mixture. Further exposure of this mixture to air led to complete conversion into pareitropone. The pareitropone so formed exhibited spectral data that matched exactly those values reported for the natural material.

Pareitropone (**1**) has been synthesized from 2,3,4-trimethoxybenzoic acid in 14 steps (7% overall yield). The central thesis of the plan was validated by successful addition of a reactive alkylidenecarbene intermediate to

(24) Bach, T.; Kather, K. *J. Org. Chem.* **1996**, *61*, 7642−7643.

a proximal arene ring in preference to other potentially interfering reaction pathways. This work demonstrates that if selectivity can be enforced by judicious design of the substrate, then these highly energetic alkynyliodonium salt-derived carbenoid species show much promise for contributing to strategy-level advances in target-directed synthesis. Further studies are ongoing.

## Experimental Section

Moisture- and oxygen-sensitive reactions were carried out in flame-dried glassware under an argon atmosphere. Tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), and diethyl ether ($Et_2O$) were distilled from sodium benzophenone ketyl under an argon atmosphere immediately before use. Toluene, benzene, and dichloromethane ($CH_2Cl_2$) were distilled from calcium hydride ($CaH_2$) under an argon atmosphere immediately before use. All organic reagents were used as purchased. Purification of products via flash chromatography[25] was performed with 32−63 $\mu$m silica gel and the solvent systems indicated. Hexanes, $CH_2Cl_2$, and $Et_2O$ used in flash chromatography were distilled from $CaH_2$ prior to use. Melting points are uncorrected. Low- and high-resolution mass spectra were obtained according to the specified technique and were performed at The Pennsylvania State University, University Park, PA. Combustion analyses were performed by Midwest Microlabs, Indianapolis, IN. Copies of $^1$H and $^{13}$C NMR spectra are supplied in the Supporting Information.

***N*-{2-[2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-5,6,4′-trimethoxybiphenyl- 3-yl]ethyl}-4-methylbenzenesulfonamide (33).** *n*-Butyllithium (*n*-BuLi) (588 $\mu$L of a 2.24 M solution in hexanes, 1.31 mmol) was added dropwise to a solution of oxazoline **32** (300 mg, 0.88 mmol) in THF (3.6 mL) at −5 °C. The reaction mixture was allowed to stir for 10 min, after which was added $CuBr{\cdot}S(CH_3)_2$ (181 mg, 0.88 mmol). Stirring was continued for 12 min, and then tosylaziridine[26] (260 mg, 1.32 mmol) was added in one portion. The reaction mixture was maintained at −5 °C for an additional 10 min and then warmed to room temperature overnight. Saturated, aq $NaHCO_3$ and $Et_2O$ were added, and the phases were separated. The aqueous phase was extracted further with $Et_2O$, and the combined organic fractions were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by flash chromatography (60% ethyl acetate in hexanes as eluent) to afford tosylamide **33** (334 mg, 71%) as a white solid: mp 108−110 °C; IR ($CCl_4$) 1649 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.07 (t, $J$ = 4.0 Hz, 1H), 7.52 (d, $J$ = 8.3 Hz, 2H), 7.25 (d, $J$ = 6.6 Hz, 2H), 7.08 (d, $J$ = 8.5 Hz, 2H), 6.93 (d, $J$ = 6.7 Hz, 2H), 6.40 (s, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.61 (s, 2H), 3.57 (s, 3H), 3.24 (m, 2H), 2.75 (t, $J$ = 5.7 Hz, 2H), 1.23 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 162.8, 159.0, 154.2, 145.5, 142.6, 137.2, 135.6, 134.1, 130.6, 129.1, 128.9, 127.0, 121.7, 113.4, 111.7, 79.7, 67.7, 60.8, 55.6, 55.5, 44.7, 32.1, 28.3, 21.5; APCIMS *m*/*z* (relative intensity) 539 ($MH^+$, 100); HRMS calcd for $C_{29}H_{35}N_2O_6S$ [$MH^+$] 539.2216, found 539.2181.

**2-[2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-5,6,4′-trimethoxybiphenyl-3-yl]ethanol (35).** *n*-BuLi (9.6 mL of a 2.5 M solution in hexanes, 24.0 mmol) was added dropwise to a solution of oxazoline **32** (5.46 g, 16.0 mmol) in dry THF (30 mL) at −10 °C. The reaction mixture was allowed to stir for 10 min, after which was added an excess of liquid ethylene oxide (20 mL, 400 mmol) via cannula. The reaction mixture was warmed to room temperature, and stirring was continued for 1 h. Water and $Et_2O$ were added, and the phases were separated. The aqueous phase was extracted further with $Et_2O$, and the combined organic fractions were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by flash chromatography (ethyl acetate as eluent) to afford alcohol **35** (2.98 g, 50%) as a white solid: mp 113−114 °C; IR (KBr) 3280, 1665 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.30 (d, $J$ = 8.0 Hz, 2H), 6.91 (d, $J$ = 8.4 Hz, 2H), 6.81 (s, 1H), 4.0−3.9 (m, 5H), 3.85 (s, 3H), 3.63 (s, 2H), 3.47 (s, 3H), 2.92 (t, $J$ = 6.0 Hz, 2H),1.26 (s, 6H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 163.4, 159.1, 154.6, 145.4, 136.1, 136.0, 131.0, 129.3, 122.2, 113.4, 112.7, 79.8, 67.7, 64.1, 60.8, 56.2, 55.6, 36.9, 28.4; ESIMS *m*/*z* (relative intensity) 386 ($MH^+$, 100). Anal. Calcd: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.22; H, 6.91; N, 3.67.

**6,7-Dimethoxy-8-(4-methoxyphenyl)isochroman-1-one (36).** A solution of oxazoline alcohol **35** (2.98 g, 7.75 mmol) in 3 M HCl (65 mL) was refluxed for 20 min, in which time a white solid precipitated from the clear solution. The mixture was cooled to room temperature, and the solid was filtered off, rinsed with water, and dried under vacuum overnight to yield the lactone **36** (2.18 g, 90%) as white needles: mp 183−185 °C; IR (KBr)1717 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.17 (d, $J$ = 8.6 Hz, 2H), 6.92 (d, $J$ = 8.6 Hz, 2H), 6.76 (s, 1H), 4.42 (t, $J$ = 5.4 Hz, 2H), 3.92 (s, 3H), 3.82 (s, 3H), 3.46 (s, 3H), 2.97 (t, $J$ = 5.4 Hz, 2H); $^{13}$C NMR (90 MHz, $CHCl_3$) $\delta$ 163.5, 159.0, 157.0, 147.1, 140.0, 138.7, 130.5, 129.1, 117.5, 113.5, 109.9, 66.8, 60.9, 56.4, 55.5, 29.7; APCIMS *m*/*z* (relative intensity) 315 ($MH^+$, 100); HRMS calcd for $C_{18}H_{19}O_5$ [$MH^+$] 315.1232, found 315.1221.

**3-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-5,6,4′-trimethoxybiphenyl-2-carbaldehyde (37).** Diisobutylaluminum hydride (10.4 mL of a 1 M solution in toluene, 10.4 mmol) was added to a stirring solution of lactone **36** (2.18 g, 6.93 mmol) in dry $CH_2Cl_2$ (20 mL) at −78 °C. After the solution was stirred for an additional 40 min, the excess reductant was quenched by the addition of $Et_2O$ and a solution of 10% potassium sodium tartrate. The biphasic solution was stirred until two clear layers resulted (about 1 h), the layers were separated, and the aqueous phase was extracted further with $Et_2O$. The combined organic phases were washed with brine, dried with $Na_2SO_4$, and concentrated in vacuo to afford the crude diol product as a yellow oil (2.21 g, 100%). A small amount of this diol was purified by preparatory chromatography (100% ethyl acetate) for characterization purposes: IR (neat) 3360 (OH) cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.25 (d, $J$ = 8.8 Hz, 2H), 6.95 (d, $J$ = 8.8 Hz, 2H), 6.80 (s, 1H), 4.33 (s, 2H), 3.91 (t, $J$ = 5.6 Hz, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 3.48 (s, 3H), 2.98 (t, $J$ = 5.6 Hz, 2H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 157.8, 151.6, 144.5, 136.4, 134.1, 130.1 (2 unresolved signals), 128.0, 112.4, 112.0, 62.7, 59.5, 57.8, 54.9, 54.3, 34.9; APCIMS *m*/*z* (relative intensity) 301 ($M + H - H_2O^+$, 100); HRMS (APCI) calcd for $C_{18}H_{23}O_6$ [$MH - H_2O^+$] 310.1440, found 310.1446.

The crude diol (2.21 g, 11.7 mmol) was dissolved in dry DMF (10 mL), and imidazole (520 mg, 7.64 mmol) and *tert*-butyldiphenylsilyl chloride (1.81 mL, 6.94 mmol) were added sequentially. After the solution was stirred for 20 min at room temperature, TLC indicated complete consumption of starting material, and the reaction was poured into water and ethyl acetate. The aqueous phase was extracted with ethyl acetate (3×), and the combined organic fractions were washed with water and brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. Purification of the residue by flash chromatography (20−30% ethyl acetate in hexanes as eluent) afforded a monosilyl ether product (2.89 g, 75%) as a yellow oil which crystallized upon standing: mp 115−118 °C; IR (KBr) 3457 (OH) cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.6−7.4 (m, 4H), 7.4−7.3 (m, 2H), 7.3−7.1 (m, 4H), 7.18 (d, $J$ = 8.6 Hz, 2H), 6.89 (d, $J$ = 8.6 Hz, 2H), 6.62 (s, 1H), 4.26 (s, 2H), 3.82 (t, $J$ = 6.1 Hz), 3.84 (s, 3H), 3.74 (s, 3H), 3.45 (s, 3H), 2.96 (t, $J$ = 6.1 Hz, 2H), 0.94 (s, 9H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 157.4, 150.9, 144.0, 135.8, 134.2, 133.5, 132.1, 131.7, 131.3, 130.7, 129.9, 129.7, 128.4, 127.7, 126.3, 111.9, 64.3, 59.2, 57.7, 54.4, 53.9, 34.2, 25.4, 17.7; APCMS *m*/*z* (relative intensity) 539 ($MH - H_2O^+$, 100); HRMS calcd for $C_{34}H_{39}O_4Si$ [$MH - H_2O^+$] 539.2618, found 539.2620.

(25) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923−2925.

(26) Martin, A. E.; Ford, T. M.; Bulkowski, J. E. *J. Org. Chem*. **1982**, *47*, 412−415.

The alcohol from above (4.66 g, 8.37 mmol) in dry $CH_2Cl_2$ (30 mL) was treated with powdered 4 Å molecular sieves (2.93 g) and pyridinium dichromate (15.7 g, 41.9 mmol). The brown suspension was allowed to stir at room temperature overnight, diluted with $Et_2O$, and filtered through Celite. The filtrate was concentrated, and the residue was purified by flash chromatography (20% ethyl acetate in hexanes as eluent) to yield aldehyde **37** (4.46 g, 96%) as an orange oil: IR (neat) 1681 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.59 (s, 1H), 7.58 (dd, $J$ = 8.1, 1.5 Hz, 4H), 7.5−7.3 (m, 6H), 7.23 (d, $J$ = 8.4 Hz, 2H), 6.98 (d, $J$ = 8.8 Hz, 2H), 6.86 (s, 1H), 3.98 (t, $J$ = 6.0 Hz, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.52 (s, 3H), 3.30 (t, $J$ = 6.0 Hz, 2H), 1.05 (s, 9H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 192.7, 158.8, 155.1, 144.4, 140.8, 135.3, 133.4, 131.5, 129.2, 128.9, 127.3, 126.2, 125.8, 114.8, 113.0, 64.3, 60.1, 55.4, 55.2, 36.9, 26.4; APCIMS $m/z$ (relative intensity) 555 ($MH^+$, 100); HRMS calcd for $C_{34}H_{39}O_5Si$ [$MH^+$] 555.2567, found 555.2560.

**2-(2-Ethynyl-5,6,4′-trimethoxybiphenyl-3-yl)ethanol (39).** *n*-BuLi (579 $\mu$L of a 2.18 M solution in hexanes, 1.26 mmol) was added to a solution of diisopropylamine (120 $\mu$L, 1.35 mmol) in THF (13 mL) at −78 °C, and stirring was continued for 12 min. At this time, trimethylsilyldiazomethane (721 $\mu$L of a 2.0 M solution in hexanes, 1.44 mmol) was added, and after the resulting solution was stirred for a further 30 min at −78 °C, a solution of the aldehyde **37** (500 mg, 0.90 mmol) in THF (7 mL) prechilled to −78 °C was added via cannula. After 10 min, the reaction was warmed to room temperature, during which time the solution changed from yellow to deep red accompanied by gas evolution. Ethyl acetate and water were added, and the phases were separated. The aqueous phase was extracted with ethyl acetate (3×), and the combined organic fractions were washed with brine, dried over $Na_2SO_4$, and concentrated to provide 500 mg of alkyne **39**, which was used without purification in the next step.

This alkyne silyl ether (600 mg, 1.09 mmol) in dry THF (9 mL) was treated with tetrabutylammonium fluoride (1.20 mL of a 1.0 M solution in THF, 1.2 mmol) at 0 °C, and after the solution was warmed to room temperature and stirred for 30 min, ethyl acetate and water were added to the reaction mixture. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with water and then brine, dried over $Na_2SO_4$, and concentrated. The light yellow solid was purified by flash chromatography (50% ethyl acetate in hexanes as eluent) to furnish alcohol **39** (340 mg, ∼100% from **37**): mp 81−82 °C; IR (KBr) 3520, 3370, 2094 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.36 (d, $J$ = 8.4 Hz, 2H), 6.97 (d, $J$ = 8.8 Hz, 2H), 6.83 (s, 1H), 3.96 (t, $J$ = 6.4 Hz, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 3.49 (s, 3H), 3.11 (t, $J$ = 6.4 Hz, 2H), 3.01 (s, 1H),1.63 (br s, 1H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 157.2, 151.6, 143.6, 137.7, 136.5, 129.6, 126.9, 112.8, 111.4, 81.3, 79.6, 61.2, 58.8, 54.2, 53.5, 36.7; APCIMS $m/z$ (relative intensity) 313 ($MH^+$, 100); HRMS calcd for $C_{19}H_{21}O_4$ [$MH^+$] 313.1440, found 313.1445.

***N*-[2-(2-Ethynyl-5,6,4′-trimethoxybiphenyl-3-yl)ethyl]-4-methylbezenesulfonamide (40).** Dry triethylamine (43 $\mu$L, 0.31 mmol) and *p*-toluenesulfonyl chloride (53 mg, 0.28 mmol) were added to a solution of alcohol **39** (87 mg, 0.28 mmol) in $CH_2Cl_2$ (1.5 mL). The reaction mixture was allowed to stir at room temperature overnight and then poured into ethyl acetate and satd aq $CuSO_4$. The aqueous phase was extracted with ethyl acetate (3×), and the combined ethyl acetate fractions were washed with satd aq $CuSO_4$ and then brine, dried over $Na_2SO_4$, and concentrated. The residue was purified by flash chromatography (20−30% ethyl acetate in hexanes as eluent) to afford the tosylate product (121 mg, 93%) as a light gray solid: mp 140−142 °C; IR (KBr) 3277, 2100, 1034 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.71 (d, $J$ = 8.3 Hz, 2H), 7.3−7.2 (m, 4H), 6.93 (d, $J$ = 8.6 Hz, 2H), 6.73 (s, 1H), 4.32 (t, $J$ = 6.8 Hz, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.47 (s, 3H), 3.16 (t, $J$ = 6.8 Hz, 2H), 2.96 (s, 1H), 2.42 (s, 3H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 159.3, 153.7, 146.0, 145.1, 139.6, 135.8, 131.6, 130.2, 129.3, 128.7, 128.2, 114.7, 113.5, 83.9, 81.0, 70.1, 60.8, 56.3, 55.5, 35.1, 22.0; APCIMS $m/z$ (relative intensity) 467 ($MH^+$, 100); HRMS calcd for $C_{26}H_{27}O_6S$ [$MH^+$] 467.1528, found 467.1504.

A solution of this tosylate (2.25 g, 4.82 mmol) in dry DMF (10 mL) was treated with sodium azide (941 mg, 14.5 mmol) at room temperature overnight. Water and ethyl acetate were added, and the phases were separated. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with brine, dried over $Na_2SO_4$, and concentrated. The resulting azide was immediately dissolved in THF (10 mL) and added to a suspension of lithium aluminum hydride (220 mg, 5.97 mmol) in THF (15 mL) via cannula. After the solution was stirred at room temperature for 30 min, TLC analysis indicated consumption of the starting azide. Ethyl acetate and water were carefully added to the reaction mixture, and the phases were separated. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with water and then brine and dried over $Na_2SO_4$. The solvent was removed to give the crude amine intermediate, which was dissolved in dry $CH_2Cl_2$ (15 mL). Dry pyridine (585 $\mu$L, 7.23 mmol) and *p*-toluenesulfonyl chloride (1.38 g, 7.23 mmol) were added to the amine solution, and after the reaction was allowed to stir at room temperature overnight, water and ethyl acetate were added. After the phases were separated and the aqueous phase was extracted with ethyl acetate, the combined organic fractions were washed with brine, dried with $Na_2SO_4$ , and concentrated. The residue was purified by flash chromatography (40% ethyl acetate in hexanes as eluent) to give sulfonamide **40** (1.29 g, 57%) as a light brown solid: mp 150−153 °C; IR (neat) 3316, 3270, 2095 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.70 (d, $J$ = 8.3 Hz, 2H), 7.28 (m, 4H), 6.94 (d, $J$ = 8.6 Hz, 2H), 6.67 (s, 1H), 4.64 t, $J$ = 5.3 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.46 (s, 3H), 3.30 (apparent q, $J$ = 6.4 Hz, 2H), 3.00 (s, 1H), 2.98 (t, $J$ = 6.8 Hz, 2H), 2.41 (s, 3H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 159.3, 153.8, 145.8, 143.7, 139.6, 138.0, 137.5, 131.6, 130.0, 128.8, 127.5, 114.6, 113.5, 112.9, 83.9, 81.3, 60.8, 56.3, 55.5, 43.8, 35.6, 21.9; ESIMS $m/z$ (relative intensity) 466 (M + $H^+$, 100); HRMS calcd for $C_{26}H_{28}NO_5S$ [$MH^+$] 466.1688, found 466.1682.

**Cycloheptatrienylidene 45.** *n*-BuLi (664 $\mu$L of a 1.94 M solution in hexanes, 1.29 mmol) was added to a solution of alkyne **40** (300 mg, 0.644 mmol) in THF (6 mL) at −78 °C. After the solution was stirred for 30 min, tributyltin chloride (210 $\mu$L, 0.773 mmol) was added. The reaction mixture was allowed to stir at −78 °C for a further 45 min and then poured into $Et_2O$ and water. The phases were separated, and the aqueous phase was extracted with $Et_2O$. The combined organic fractions were washed with brine, dried over $Na_2SO_4$, and concentrated. Purification of the crude oil by flash chromatography (20% ethyl acetate in hexanes as eluent) afforded the pure alkynylstannane product (373 mg, 77%), which was used immediately in the next step. PhI(CN)OTf[23] (196 mg, 0.592 mmol) was added to $CH_2Cl_2$ (5 mL) at −42 °C, and then the alkynylstannane (373 mg, 0.494 mmol) in prechilled $CH_2Cl_2$ (2 mL, −42 °C) was cannulated into the solution. After the resulting solution was stirred at −42 °C for 30 min, the solvent was removed under reduced pressure at −42 °C. The resulting alkynyliodonium salt was dissolved in chilled DME (10 mL at −42 °C), lithium bis(trimethylsilyl)amide (LiHMDS) (642 $\mu$L of a 1 M solution in THF, 0.643 mmol) was added dropwise, and stirring was continued at −42 °C for 10 min followed by warming to room temperature. Warming resulted in the development of a deep purple color. $Et_2O$ and water were then added and the phases separated. The aqueous phase was extracted with $Et_2O$, and the combined organic phases were washed with water and then brine and dried over $Na_2SO_4$. Removal of the solvent followed by purification of the residue by flash chromatography (using $SiO_2$ treated with 20% ethyl acetate/hexanes and 1% $NEt_3$ and eluting with the same mixture) gave the cycloheptatrienylidene **45** (147 mg, 64%) as very dark purple flakes which could be recrystallized from $Et_2O$: mp 162−163 °C; IR (KBr)1585 $cm^{-1}$; $^1H$ NMR (300 MHz, $C_6D_6$) $\delta$ 8.86 (d, $J$ = 9.9 Hz, 1H), 8.84 (d, $J$ = 12.3 Hz, 1H),

7.47 (d, $J$ = 8.1 Hz, 2H), 6.69 (dd, $J$ = 12.3, 2.7 Hz, 1H), 6.52 (s, 1H), 6.35 (d, $J$ = 8.1 Hz, 2H), 5.82 (dd, $J$ = 9.6, 2.4 Hz, 1H), 3.97 (s, 3H), 3.96 (t, $J$ = 5.7 Hz, 2H), 3.40 (s, 3H), 3.14 (s, 3H), 2.22 (t, $J$ = 5.7 Hz, 2H), 1.57 (s, 3H); $^{13}$C NMR (75.5 MHz, $CDCl_3$ treated with $Al_2O_3$) $\delta$ 165.8, 149.2, 144.0, 143.7, 137.0, 134.0, 132.8, 131.9, 129.6, 128.0, 127.4, 126.5, 122.0, 120.6, 120.2, 112.1, 102.2, 60.2, 57.4, 55.6, 48.4, 24.4, 21.7; APCIMS *m*/*z* (relative intensity) 464 ($M^+$, 52), 310 ($M - C_7H_6SO_2^+$, 100); HRMS calcd for $C_{26}H_{25}NO_5S$ [$MH^+$] 464.1532, found 464.1533.

**2-[5,6-Dimethoxy-4′-(triisopropylsilanyloxy)biphenyl-2-yl]-4,4-dimethyl-4,5-dihydrooxazole (47).** (4-Iodophenoxy)triisopropylsilane (710 mg, 1.88 mmol) was dissolved in THF (12 mL) under argon and cooled to −40 °C. Isopropylmagnesium chloride (1.22 mL of a 2 M THF solution, 2.44 mmol) was added dropwise. After 16 h, a solution of 4,4-dimethyl-2-(2,3,4-trimethoxyphenyl)-4,5-oxazoline (**27**) (249 mg, 0.94 mmol) in THF (2 mL) was added via cannula, and the clear colorless solution turned yellow upon complete addition. The cooling bath was removed, and after being stirred at room temperature overnight, the mixture was poured into an ice cold satd $NH_4Cl$ solution and stirred for 10 min. The layers were separated, and the product was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. Flash column chromatography (25% ethyl acetate in hexanes as eluent) of the residue yielded the biaryloxazoline **47** (424 mg, 93%) as a clear, colorless oil: IR ($CCl_4$) 1643 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$ 7.45 (d, $J$ = 8.5 Hz, 1H), 7.21 (d, $J$ = 8.5 Hz, 2H), 6.90 (d, $J$ = 8.6 Hz, 2H), 6.88 (d, $J$ = 8.5 Hz, 1H), 3.90 (s, 3H), 3.67 (s, 2H), 3.45 (s, 3H), 1.27 (m, 3H), 1.25 (s, 6H), 1.12 (d, $J$ = 7.2 Hz, 18H); $^{13}$C NMR ($CDCl_3$, 90 MHz) $\delta$163.7, 155.3, 154.8, 146.7, 136.2, 130.7, 130.0, 126.0, 122.4, 119.3, 110.8, 79.3, 67.2, 60.4, 56.0, 28.1, 18.0, 12.8; APCIMS *m*/*z* (relative intensity) 484 ($MH^+$, 100); HRMS calcd for $C_{28}H_{42}NO_4Si$ 484.2884 (M + H), found 484.2913.

**6,7-Dimethoxy-8-[4-(triisopropylsilanyloxy)phenyl]-isochroman-1-one (48).** The oxazoline **47** (22.6 g, 46.7 mmol) was dissolved in $Et_2O$ (465 mL) and cooled to −10 °C. *n*-BuLi (37.4 mL of 2.5 M hexane solution, 93.4 mmol) was added dropwise to the clear, colorless solution, which turned bright orange upon complete addition. After 75 min, liquid ethylene oxide (5.14 g, 117 mmol) was added via cannula. After 18 h at −10 °C, the mixture was warmed to room temperature, poured into ice cold water, and stirred for 10 min. The layers were separated, and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. Flash column chromatography (50% $Et_2O$ in hexanes to 100% $Et_2O$ as eluent) of the residue yielded the $\beta$-phenethanol product (19.7 g, 80%) as a clear, light yellow oil: IR ($CCl_4$) 3260, 1737 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$ 7.23 (d, $J$ = 8.6 Hz, 2H), 6.90 (d, $J$ = 8.6 Hz, 2H), 6.81 (s, 1H), 3.93 (t, $J$ = 5.8 Hz, 2H), 3.92 (s, 3H), 3.63 (s, 2H), 3.43 (s, 3H), 2.93 (t, $J$ = 5.8 Hz, 2H), 1.29 (m, 3H), 1.27 (s, 6H), 1.13 (d, $J$ = 7.1 Hz, 18H); $^{13}$C NMR ($CDCl_3$, 90 MHz) $\delta$ 163.3, 155.4, 154.4, 145.2, 136.1, 135.7, 130.8, 129.4, 121.9, 119.3, 112.5, 79.5, 67.5, 63.9, 60.4, 56.0, 36.7, 28.2, 18.1, 12.9; ESIMS *m*/*z* (relative intensity) 528 ($MH^+$, 100); HRMS calcd for $C_{30}H_{46}NO_5Si$ 528.3145 (M + H), found 528.3136.

This alcohol (37 mg, 0.07 mmol) was dissolved in aqueous HCl (8 mL, 3 M) and heated to reflux. After 30 min, a white precipitate was observed, and after 1 h, the mixture was cooled to room temperature. The reaction solution was extracted with $CH_2Cl_2$. Concentration of the organic extract yielded **48** as a white solid (29 mg, 91%): mp 176−177 °C; IR ($CCl_4$) 1737 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.10 (d, $J$ = 8.6 Hz, 2H), 6.91 (d, $J$ = 8.6 Hz, 2H), 6.74 (s, 1H), 4.45 (t, $J$ = 5.6 Hz, 2H), 3.95 (s, 3H), 3.41 (s, 3H), 3.00 (t, $J$ = 5.6 Hz, 2H), 1.26 (m, 3H), 1.11 (d, $J$ = 7.0 Hz, 18H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 163.2, 156.8, 155.4, 146.8, 140.3, 138.3, 130.4, 129.2, 119.6, 117.4, 109.4, 66.5, 60.5, 56.2, 29.6, 18.1, 12.8; APCIMS *m*/*z* (relative intensity) 457 ($MH^+$, 100); HRMS calcd for $C_{26}H_{37}O_5Si$ 457.2410 (M + H), found 457.2390.

**3-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-5,6-dimethoxy-4′-(triisopropylsilanyloxy)biphenyl-2-carbaldehyde (49).** The lactone **48** (4.16 g, 9.12 mmol) was dissolved in $Et_2O$ (365 mL) and cooled to 0 °C. Lithium aluminum hydride (520 mg, 13.7 mmol) was added in one portion, and the mixture was stirred for 1 h. The excess reductant was quenched with ethyl acetate, and the mixture was poured into an ice cold, satd aq solution of potassium sodium tartrate and stirred for 30 min. The layers were separated, and the aqueous phase was further extracted with $Et_2O$. The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated to yield the diol product (4.17 g, 99%) as a clear, colorless oil: IR ($CCl_4$) 3613, 3319 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.18 (d, $J$ = 8.5 Hz, 2H), 6.93 (d, $J$ = 8.5 Hz, 2H), 6.77 (s, 1H), 4.32 (s, 2H), 3.87 (s, 3 H) 3.87 (t, $J$ = 5.7 Hz, 2H), 3.41 (s, 3H), 2.95 (t, $J$ = 5.7 Hz, 2H), 1.27 (m, 3H), 1.12 (d, $J$ = 7.0 Hz, 18H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 155.4, 152.6, 145.4, 137.6, 135.3, 131.3, 131.0, 129.5, 119.6, 113.0, 63.6, 60.4, 58.8, 56.0, 36.0, 18.1, 12.8; APCIMS *m*/*z* (relative intensity) 443 ([$MH - H_2O$]$^+$, 100); HRMS calcd for $C_{26}H_{39}O_4Si$ 443.2577 (M + H − $H_2O$), found 443.2610.

This diol (4.17 g, 9.06 mmol) was dissolved in DMF (181 mL), and *tert*-butyldimethylsilyl chloride (1.64 g, 10.9 mmol) and imidazole (924 mg, 13.6 mmol) were each added in one portion. After 3 h, an additional 0.3 equiv of *tert*-butyldimethylsilyl chloride and 0.5 equiv of imidazole were added. After an additional 1 h, the solvent was removed in vacuo, and the residue was taken up in $Et_2O$ and washed with water. The layers were separated, and the aqueous phase was further extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. Flash column chromatography (10% ethyl acetate in hexanes as eluent) of the residue yielded the product silyl ether (4.04 g, 78%) as a clear, colorless oil: IR ($CCl_4$) 3613, 3448 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$ 7.22 (d, $J$ = 8.6 Hz, 2H), 6.93 (d, $J$ = 8.6 Hz, 2H), 6.78 (s, 1H), 4.33 (d, $J$ = 5.7 Hz, 2H), 3.95 (t, $J$ = 5.7 Hz, 2H), 3.88 (s, 3H), 3.40 (s, 3H), 3.26 (t, $J$ = 5.7 Hz, 1H), 2.98 (t, $J$ = 5.7 Hz, 2H), 1.27 (m, 3H), 1.12 (d, $J$ = 7.1 Hz, 18H), 0.80 (s, 9H), 0.0 (s, 6H); $^{13}$C NMR ($CDCl_3$, 90 MHz) $\delta$ 155.4, 152.5, 145.6, 137.5, 135.2, 131.9, 131.3, 129.6, 119.6, 112.5, 65.2, 60.5, 59.1, 56.2, 35.8, 26.1, 18.8, 18.1, 12.9, −5.3; APCIMS *m*/*z* (relative intensity) 558 [$MH - H_2O$]$^+$, 100); HRMS calcd for $C_{32}H_{55}O_5Si_2$ 575.3588 (M + H), found 575.3588.

The benzylic alcohol from above (6.84 g, 11.9 mmol) was dissolved in $CH_2Cl_2$ (60 mL), followed by addition of powdered 4 Å molecular sieves (2.39 g) and pyridinium dichromate (22.4 g, 59.5 mmol). The mixture was stirred for 18 h, filtered through a pad of silica gel, and concentrated, and the residue was purified by flash column chromatography (10% ethyl acetate in hexanes as eluent) to yield aldehyde **49** (6.35 g, 93%) as a clear, orange oil: IR ($CCl_4$) 2943, 2872, 1684, 1608 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 9.64 (s, 1H), 7.15 (d, $J$ = 8.6 Hz, 2H), 6.94 (d, $J$ = 8.6 Hz, 2H), 6.87 (s, 1H), 3.95 (s, 3H), 3.91 (t, $J$ = 6.2 Hz, 2H), 3.44 (s, 3H), 3.21 (t, $J$ = 6.2 Hz, 2H), 1.27 (m, 3H), 1.12 (d, $J$ = 7.1 Hz, 18H), 0.85 (s, 9H), −0.05 (s, 6H); $^{13}$C NMR ($CDCl_3$, 90 MHz) $\delta$ 193.5, 156.1, 155.9, 145.0, 142.0, 139.3, 132.0, 126.9, 126.7, 119.8, 115.5, 64.2, 60.6, 56.0, 38.1, 26.1, 18.5, 18.1, 13.3, −5.2; APCIMS *m*/*z* (relative intensity) 574 ($MH^+$, 100); HRMS calcd for $C_{32}H_{53}O_5Si_2$ 573.3431 (M + H), found 573.3425.

**5-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-6-ethynyl-2,3-dimethoxy-4′-(triisopropylsilanyloxy)biphenyl (50).** *n*-BuLi (8.09 mmol, 3.24 mL from a 2.5 M hexanes solution) was added to a solution of diisopropylamine (817 mg, 8.09 mmol) in THF (27 mL) at −78 °C. After 30 min, a solution of trimethylsilyldiazomethane (8.09 mmol, 4.05 mL from a 2 M hexanes solution) was added dropwise. After 30 min, a solution of aldehyde **49** (3.09 g, 5.40 mmol) in THF (11 mL) was added. An evolution of gas was observed, and the mixture was allowed to slowly warm to room temperature overnight. The mixture was poured into ice cold water, and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered, and concen-

trated. Flash column chromatography (5% $Et_2O$ in hexanes as eluent) of the residue yielded the alkyne **50** (2.90 g, 95%) as a clear, yellow oil: IR ($CDCl_3$) 3295, 2238 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.25 (d, $J$ = 6.7 Hz, 2H), 6.92 (d, $J$ = 6.7 Hz, 2H), 6.80 (s, 1H), 3.89 (t, $J$ = 6.8 Hz, 2H), 3.89 (s, 3H), 3.41 (s, 3H), 3.03 (t, $J$ = 6.8 Hz, 2H), 2.98 (s, 1H), 1.26 (m, 3H), 1.11 (d, $J$ = 6.9 Hz, 18H), 0.87 (s, 9H), −0.01 (s, 6H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 155.5, 153.2, 145.2, 139.7, 139.0, 131.4, 129.5, 119.5, 114.5, 113.3, 82.8, 81.4, 63.5, 60.5, 56.0, 39.0, 26.2, 18.6, 18.1, 12.9, −5.1; APCIMS $m/z$ (relative intensity) 570 ($MH^+$, 94); HRMS calcd for $C_{33}H_{53}O_4Si_2$ 569.3482 (M + H), found 569.3500.

***N*-{2-[2-Ethynyl-5,6-dimethoxy-4′-(triisopropylsilanyloxy)biphenyl-3-yl]ethyl}-4-methylbenzenesulfonamide (51).** The alkynyl silyl ether **50** (1.36 g, 2.39 mmol) was dissolved in acetonitrile (48 mL) in a Nalgene bottle, and a solution of 25% HF in acetonitrile was added dropwise until consumption of the starting material was observed by TLC (50% $Et_2O$ in hexanes as eluent). At completion of the reaction, the solution was carefully poured into an ice cold aqueous solution of $NaHCO_3$. After the resulting solution was stirred for 20 min, the aqueous phase was extracted with $Et_2O$, and the combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. Flash column chromatography (50% $Et_2O$ in hexanes as eluent) of the residue yielded the product alcohol (1.05 g, 97%) as a clear, yellow oil: IR ($CCl_4$) 3624, 3307, 2097 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.25 (d, $J$ = 8.6 Hz, 2H), 6.92 (d, $J$ = 8.6 Hz, 2H), 6.79 (s, 1H), 3.93 (t, $J$ = 6.2 Hz, 2H), 3.90 (s, 3H), 3.42 (s, 3H), 3.08 (t, $J$ = 6.6 Hz, 2H), 3.01 (s, 1H), 1.29 (m, 3H), 1.12 (d, $J$ = 7.0 Hz, 18H); $^{13}C$ NMR ($CDCl_3$, 90 MHz) $\delta$ 155.6, 153.4, 145.4, 139.9, 138.3, 131.3, 129.3, 119.5, 114.7, 112.7, 83.1, 81.4, 63.1, 60.5, 56.1, 38.6, 18.1, 12.8; APCIMS $m/z$ (relative intensity) 455 (MH, 100); HRMS calcd for $C_{27}H_{39}O_4Si$ 455.2617 (M + H), found 455.2576.

Diethylazodicarboxylate (271 mg, 1.56 mmol) was added dropwise to a 0 °C solution of triphenylphosphine (409 mg, 1.56 mmol), FmocNHTs (566 mg, 1.44 mmol), and the alcohol from above (544 mg, 1.20 mmol) in THF (17 mL). After the solution was stirred for 20 h, the residue was concentrated, followed by purification of the residue via flash column chromatography (20% ethyl acetate in hexanes as eluent) to yield the product sulfonimide (799 mg, 80%) as a clear, yellow oil: IR ($CCl_4$) 3307, 1731, 1607 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.79 (d, $J$ = 6.6 Hz, 2H), 7.73 (d, $J$ = 7.3 Hz, 2H), 7.48 (d, $J$ = 6.9 Hz, 2H), 7.38 (t, $J$ = 7.3 Hz, 2H), 7.3−7.2 (m, 6H), 6.87 (d, $J$ = 6.9 Hz, 2H), 6.75 (s, 1H), 4.29 (d, $J$ = 6.8 Hz, 2H), 4.21 (t, $J$ = 7.3 Hz, 2H), 4.08 (t, 6.8 Hz, 1H), 3.83 (s, 3H), 3.38 (s, 3H), 3.21 (t, $J$ = 7.3 Hz, 2H), 2.99 (s, 1H), 2.49 (s, 3H), 1.26 (m, 3H), 1.09 (d, $J$ = 6.9 Hz, 18H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 155.6, 153.5, 152.6, 145.6, 144.8, 143.4, 141.5, 139.8, 137.7, 136.9, 131.4, 129.6, 129.2, 128.6, 128.1, 127.4, 125.2, 120.2, 119.5, 115.0, 112.8, 83.5, 81.0, 69.3, 60.5, 56.2, 47.7, 46.9, 35.7, 21.9, 18.1, 12.8; APCIMS $m/z$ (relative intensity) 830 ($MH^+$, 100); HRMS calcd for $C_{49}H_{56}NO_7SSi$ 830.3547 (M + H), found 830.3584.

The imide from above (799 mg, 0.964 mmol) was dissolved in DMF and cooled to 0 °C under argon. Piperidine (82.1 mg, 0.964 mmol) was added dropwise. After 20 min, the solvent was removed in vacuo, the residue was washed with water, and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. Flash column chromatography (50% $Et_2O$ in hexanes as eluent) of the residue yielded the tosylamide product **51** (542 mg, 93%) as a clear yellow oil: IR ($CCl_4$) 3307, 2097, 1719, 1596 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.69 (d, $J$ = 8.2 Hz, 2H), 7.26 (d, $J$ = 8.6 Hz, 2H), 7.21 (d, $J$ = 8.7 Hz, 2H), 6.91 (d, $J$ = 8.7 Hz, 2H), 6.65 (s, 1H), 4.63 (t, $J$ = 6.0 Hz, 1H), 3.86 (s, 3H), 3.42 (s, 3H), 3.30 (apparent q, $J$ = 6.7 Hz, 2H), 2.98 (t, $J$ = 6.7 Hz, 2H), 2.95 (s, 1H), 2.41 (s, 3H), 1.26 (m, 3H), 1.11 (d, $J$ = 6.9 Hz, 18H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 155.7, 153.6, 145.6, 143.5, 139.9, 137.5, 137.2, 131.3, 129.8, 129.0, 127.2, 119.5, 114.5, 112.5, 83.5, 81.1, 60.5, 56.1, 43.5, 35.3, 21.7, 18.1, 12.8; APCIMS $m/z$ (relative intensity) 608 ($MH^+$, 95); HRMS calcd for $C_{34}H_{46}NO_5SSi$ 608.2866 (M + H), found 608.2878.

***N*-{2-[5,6-Dimethoxy-2-(tributylstannanylethynyl)-4′-(triisopropylsilanyloxy)biphenyl-3-yl]ethyl}-4-methylbenzenesulfonamide (52)**. To a solution of alkyne **51** (542 mg, 0.89 mmol) in THF (9 mL) at −78 °C was added *n*-BuLi (1.88 mmol, 0.75 mL from a 2.5 M hexanes solution). After 30 min, $Bu_3SnCl$ (580 mg, 1.79 mmol) was added, and after 45 min further, the solution was diluted with $Et_2O$ and poured into cold brine. The layers were separated, the aqueous phase was further extracted with $Et_2O$, and the combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated. Flash column chromatography (20% ethyl acetate and 3% triethylamine in hexanes as eluent) of the residue yielded the product alkynylstannane 52 (613 mg, 77%) as a clear, yellow oil: IR ($CCl_4$) 3295, 2120, 1719 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.64 (d, $J$ = 8.2 Hz, 2H), 7.3−7.2 (m, 4H), 6.87 (d, $J$ = 8.4 Hz, 2H), 6.56 (s, 1H), 4.61 (t, $J$ = 5.9 Hz, 1H), 3.82 (s, 3H), 3.38 (s, 3H), 3.30 (apparent q, $J$ = 6.0 Hz, 2H), 2.99 (t, $J$ = 6.5 Hz, 2H), 2.40 (s, 3H), 1.44 (m, 6H), 1.3−1.2 (m, 9H), 1.12 (d, $J$ = 7.2 Hz, 18H), 1.0−0.8 (m, 15H); $^{13}C$ NMR ($CDCl_3$, 90 MHz) $\delta$ 155.5, 153.0, 145.7, 143.3, 139.1, 137.3, 136.9, 131.6, 129.7, 129.2, 127.2, 116.6, 107.4, 100.5, 60.4, 56.1, 43.8, 35.2, 29.1 ($J_{C-Sn}$ = 11.6 Hz), 27.1 ($J_{C-Sn}$ = 29.4 Hz), 21.7, 18.2, 13.9, 12.9, 11.2 ($J^{13}C-^{117}Sn$ = 190.7 Hz); APCIMS $m/z$ (relative intensity) 920 ($MNa^+$, 100), 898 (M + 2, Sn isotope); HRMS calcd for $C_{46}H_{71}NO_5SSiSnNa$ 920.3744 (M + Na), found 920.3741.

**5,6-Dimethoxy-1-(toluene-4-sulfonyl)-9-(triisopropylsilanyloxy)-2,3-dihydro-1*H*-1-azacyclohepta[*a*]acenaphthylene (54).** A solution of PhI(CN)OTf[23] (32 mg, 0.083 mmol) in $CH_2Cl_2$ (0.83 mL) was cooled to −40 °C, followed by dropwise addition of a solution of stannylalkyne **52** (62 mg, 0.069 mmol) in $CH_2Cl_2$ (0.83 mL) via cannula. After 30 min, the solvent was removed in vacuo while the flask was maintained in a −40 °C bath. The residue was taken up in DME (3.45 mL) followed by treatment with LiHMDS (0.09 mmol, 0.09 mL of a 1 M THF solution), all at −40 °C. Upon addition of LiHMDS, the color of the solution changed immediately from yellow to dark green. After being stirred for an additional 75 min while gradually being warmed to room temperature, the mixture was poured into $Et_2O$ and washed with water. The aqueous phase was further extracted with $Et_2O$, and the combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. Flash column chromatography (25% $Et_2O$ in hexanes as eluent) of the residue yielded the product cycloheptatrienylidene **54** (26.8 mg, 64%) as a dark blue-green film: IR ($CCl_4$) 1725, 1584 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 8.56 (d, $J$ = 9.7 Hz, 1H), 8.32 (d, $J$ = 12.1 Hz, 1H), 7.36 (d, $J$ = 8.0 Hz, 2H), 7.00 (d, $J$ = 8.0 Hz, 2H), 6.81 (s, 1H), 6.64 (dd, $J$ = 12.1, 2.5 Hz 1H), 6.45 (dd, $J$ = 9.7, 2.5 Hz 1H), 4.06 (s, 3H), 4.03 (t, $J$ = 5.7 Hz, 2H), 3.90 (s, 3H), 2.46 (t, $J$ = 5.7 Hz, 2H), 2.28 (s, 3H), 1.34 (m, 3H), 1.17 (d, $J$ = 7.1 Hz, 18H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 163.2, 148.8, 144.2, 143.7, 137.0, 134.6, 133.1, 132.3, 129.6, 128.2, 127.5, 127.1, 122.7, 122.0, 121.1, 120.2, 112.7, 112.1, 60.4, 57.7, 48.5, 24.5, 21.7, 18.2, 13.0; APCIMS $m/z$ (relative intensity) 606 ($MH^+$, 10); HRMS calcd for $C_{34}H_{44}NO_5SSi$ 606.2709 (M + H), found 606.2741.

**Pareitropone (1)**. Cycloheptatrienylidene **54** (19 mg, 0.03 mmol), which was precooled to −78 °C in THF (5.5 mL), was added to $Al_2O_3$-supported KF (40% by wt, 3.6 mg, 0.063 mmol) at −78 °C. The mixture was then slowly allowed to warm to room temperature. After the mixture was stirred for 3 days, the starting material was no longer visible by TLC (5% MeOH in $CH_2Cl_2$ as eluent), and the reaction mixture was concentrated. Flash column chromatography (2.5% MeOH in $CH_2Cl_2$ as eluent) yielded pareitropone (**1**) (5 mg, 57%) as a brown film: IR ($CCl_4$) 1602, 1578 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz), 8.73 (d, $J$ = 5.7 Hz, 1H), 8.29 (d, $J$ = 12.0 Hz, 1H), 8.20 (d, $J$ = 12.0 Hz, 1H), 7.55 (d, $J$ = 5.7 Hz, 1H), 7.25 (dd, $J$ = 12.0, 2.8 Hz, 1H), 7.20 (dd, $J$ = 12.0, 2.8 Hz, 1H), 7.16 (s,1H), 4.20 (s, 3H), 4.08 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 75 MHz), 188.3, 159.1, 157.8, 151.8, 147.0, 142.5, 141.7, 141.6, 141.0, 133.4, 130.5,

129.7, 125.4, 120.0, 119.0, 107.7, 62.4, 56.8; APCIMS *m*/*z* (relative intensity) 292 (M + H, 100); HRMS calcd for $C_{18}H_{14}NO_3$ 292.0973 (M + H), found 292.0990.

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**Supporting Information Available:** Copies of $^1$H and $^{13}$C NMR spectra for **33**, **34**, **36**, **37**, **39**, **40**, **45**, **47**−**52**, **54**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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