Synthesis B. J. Reinus, S. M. Kerwin Paper

N-Alkynyl Pyrrole Based Total Synthesis of Shensongine A

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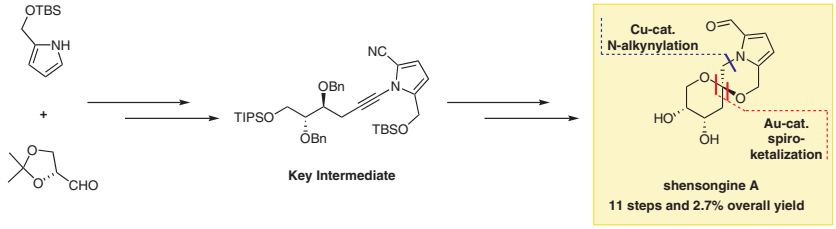

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Abstract A copper-catalyzed N-alkynylation of pyrrole and a gold-catalyzed spiroketalization were key steps in the total synthesis of the pyrrole spiroketal alkaloid shensongine A. The preparation of this alkaloid is concise and amenable to the rapid synthesis of a diverse library of compounds.

Key words cross-coupling, alkynes, nitrogen heterocycles, spiroketalization, shensongine A, pyrrole spiroketal alkaloids, total synthesis

The pyrrole spiroketal alkaloids (PSAs) are a group of spirocyclic natural products that were recently isolated from several different natural sources.[1–3] The PSA natural products consist of both the alpha and beta anomeric forms of pyranose and furanose ketals derived from a common parent ketone (Figure 1).

It has been postulated that the underlying parent ketone could itself be derived from two equivalents of the Maillard reaction product 3-deoxy-D-glucosone,[4] providing an explanation for the seemingly large number of natural sources for the compounds.[1–5] In 2010, three separate research groups reported the isolation of members of the PSAs, resulting in several naming systems for the alkaloids. In addition, the initial misassignment of the absolute stereochemistry for capparasines A and B contributed to some early confusion surrounding the natural products.[6]

Over the past decade, because of their association with traditional Chinese medicine, the PSAs have maintained the interest of the scientific community; and since their discovery, several of the alkaloids have been shown to have promising biological activities.[2,7] Notably, the furanose PSAs acortatarin A (**1**) and acortatarin B (**4**) have displayed encouraging antioxidant activity in diabetic renal cell models.[2] Unfortunately, only small amounts of the pyrrole spiroketal alkaloids can be isolated from their natural sources; for example, Cheng and co-workers isolated only 7.3 mg of acortatarin A (**1**) from 50 kg of *Acori tatarinowii* rhizome.[1] Consequently, there has been significant interest in establishing synthetic routes to these compounds.[2]

Our research group has been interested in the synthesis and study of *N*-alkynyl azoles for more than 15 years, and our most recent work focused on the synthesis of *N*-alkynyl pyrroles.[8,9] Currently established strategies for synthesizing the PSAs rely heavily on acid-catalyzed spiroketalizations; however, we believe a single synthetic strategy utilizing an *N*-alkynyl pyrrole could allow access to both the furanose and pyranose members of the PSAs (Scheme 1). This approach harnesses the use of alkynes as carbonyl equivalents,[10] and by avoiding the thermodynamic penalty of conversion of carbonyls into their nucleophilic, enol form, provides more flexibility than alternative approaches. By

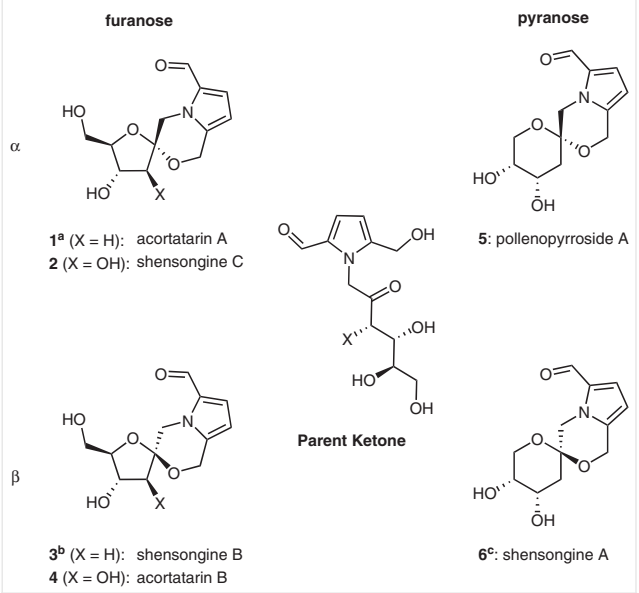

Figure 1 The pyrrole spiroketal alkaloids. [a] Alternative names for acortatarin A: pollenopyrroside B and capparisine A. [b] Alternative name for shensongine B: xylapyrroside B. [c] Alternative names for shensongine A: xylapyrroside A and *ent*-capparisine B.

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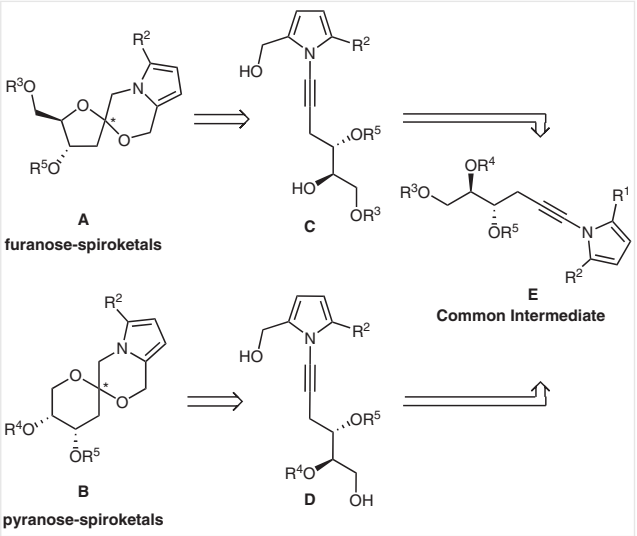
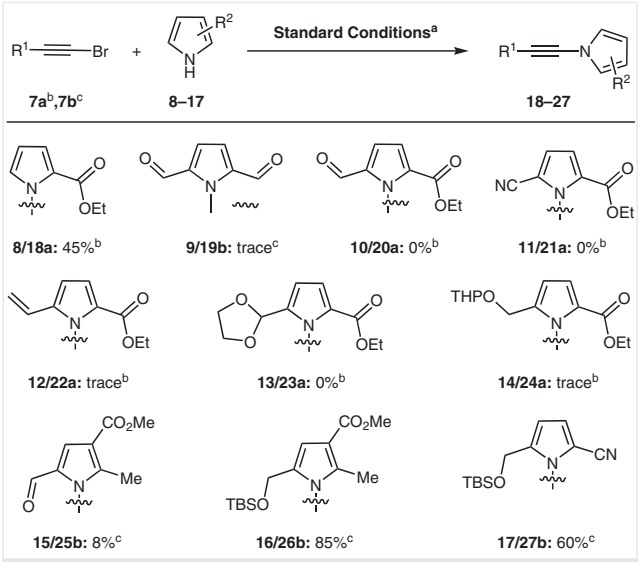
exploiting orthogonal deprotections of a common intermediate (**E**), such a strategy could be used to rapidly generate a large library of PSA derivatives. Since embarking on this project, Pale and co-workers completed the synthesis of the furanose PSA acortatarin A (**1**) by using an *N*-alkynyl pyrrole strategy.[11] In combination with our route to the pyranose PSA shensongine A (**6**) described here, the two methods uphold the legitimacy of a single divergent synthesis of both the pyranose and furanose PSAs from an aptly substituted *N*-alkynyl pyrrole intermediate (Scheme 1, **E**).



Scheme 1 Proposed divergent synthesis of the pyranose and furanose PSAs

At the start of the project, we were uncertain how much substitution we would be able to incorporate on the pyrrole and still achieve an efficient cross-coupling; thus, our initial objective was to identify a suitable pyrrole coupling partner. Within the PSA family of natural products, the substitution on pyrrole is consistent and includes a hydroxymethyl in the 5-position and an aldehyde in the 2-position.[12] With this in mind, we began looking at various pyrroles that would only require a limited number of transformations to access this substitution pattern following N-alkynylation (Scheme 2).

From our previous work[9] we knew that 1*H*-pyrrole-2-carboxylate ester (**8**) gave moderate yields of *N*-alkynyl pyrrole **18a** and that 1*H*-pyrrole-2,5-dicarbaldehyde (**9**) was unreactive (**19b**, Scheme 2). Additionally, we were aware that alkyl-alkynyl bromides and pyrroles containing α-substituted aldehydes are incompatible coupling partners.[13] Thus, our search began by looking into additional pyrroles containing two electron-withdrawing groups (EWGs), pyrroles **10** and **11**, neither of which gave the corresponding *N*-alkynylated products **20a** and **21a**. Pyrroles substituted with a vinyl group (**12**), an acetal (**13**), and a THP-protected



Scheme 2 Screening for a pyrrole coupling partner. [a] Reactions were run with pyrrole (0.2 mmol), alkynyl bromide (0.24 mmol), $CuSO_4 \cdot 5H_2O$ (0.02 mmol), 1,10-phenanthroline (0.04 mmol), K_2CO_3 (0.4 mmol), toluene (0.4 mL), 135 °C, 14 h; [b] Used **7a**: R^1 = -$(CH_2)_4$-OTBS; [c] Used **7b** R^1 = TIPS.

hydroxy-methyl (**14**) also generated essentially none of the alkynylated products (**22a**, **23a**, **24a**).

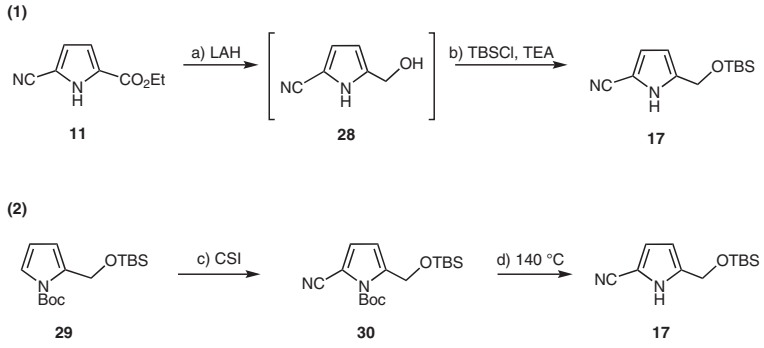
We considered a pyrrole containing an α-hydroxymethyl as part of a lactone as a promising candidate, predicting the steric and coordinative encumbrance of the hydroxy-methyl would be mitigated in such a substrate. In testing the more easily synthesized pyrrole **15**, we confirmed our earlier inference[9] that, in order to couple effectively, the pyrrole partners electronics and pK_a must be balanced to avoid unproductive copper complexation (if the p*K*a is too low) or inefficient deprotonation (if the p*K*a is too high). Pyrrole **15**, with a predicted low pK_a (14.3), proved to be a rather poor substrate, generating only 8% of the desired product. Subsequently, we found that reducing the aldehyde **15** to a protected hydroxy-methyl afforded a much improved coupling partner **16** that affords coupling product **26b** in 85% yield (Scheme 2). From these results, it appears a single EWG produces an electronic environment and pK_a that is optimal for *N*-alkynylation of pyrroles.

Continuing our search for a suitable pyrrole coupling partner, the exceptional reactivity of pyrrole **16** led us to implement the TBS silyl ether as our hydroxy-methyl protecting group of choice. Thus, determining how we would introduce the α-carboxaldehyde was the last step towards establishing a pyrrole coupling partner. The easy conversion of nitriles into aldehydes in conjunction with the compact nature of the functional group made it a reasonable choice. We were pleased to find that *N*-alkynyl pyrrole **27b** was formed in a 60% yield (Scheme 2). The ease with which

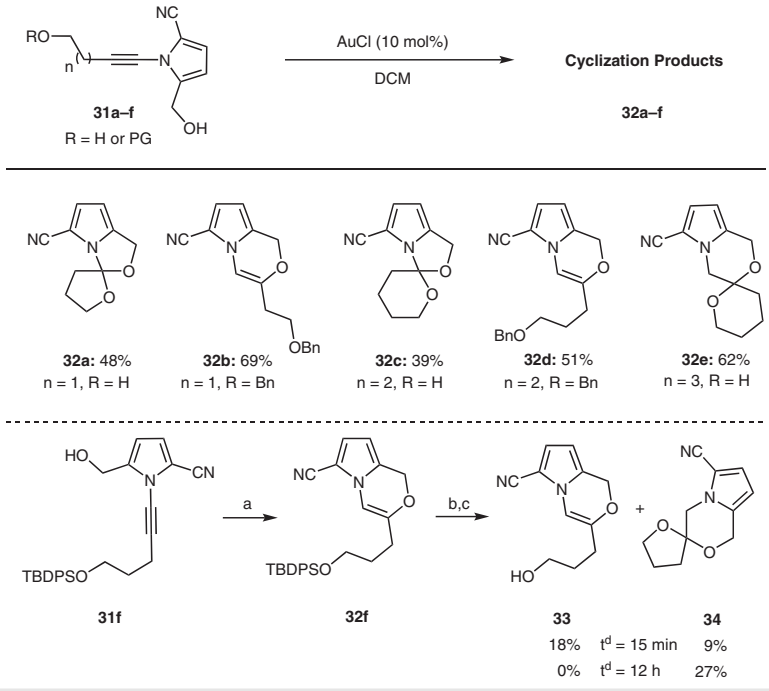
pyrrole **17** could be used towards the synthesis of the PSAs led us to conclude our investigations into pyrroles and move forward with the remainder of the project.

Investigating the reactivity of *N*-alkynyl pyrroles under cycloisomerization conditions became our next objective. However, before carrying out a series of model cyclizations, we set out to develop an efficient synthesis of pyrrole **17** (Scheme 3). Our initial synthesis of **17** was easily executed, but suffered from low overall yields (Scheme 3, eq. 1). We devised an alternative synthesis in which a Boc-protected pyrrole was used to temper the reactivity of the hydroxymethyl group as part of an effort to improve the yield of silylation (Scheme 3, eq. 2). We started with known pyrrole **29**, which could be synthesized without silylation issues and in excellent yields. Introducing the nitrile group using CSI proceeded smoothly to give **30** in 95% yield. Finally, the thermolytic cleavage of the Boc protecting group proceeded without incident, providing gram quantities of pyrrole **17** in superb overall yield.

For our model spirocyclizations, we chose to investigate the reactivity of *N*-alkynyl pyrroles with increasing chain lengths (Scheme 4; n = 1–3). Starting with n = 1, **31a**, we anticipated only a partial cycloisomerization, due to the unlikely formation of an oxetane spirocycle;[14] thus, formation



Scheme 3 Synthesis of key pyrrole intermediate **17**. *Reagents and conditions*: (a) LAH, THF, 0 °C; (b) TBSCl, imidazole, DCM, 0 °C to r.t., 29% (two steps); (c) CSI, THF, –78 °C, then TEA and DMF, 95%; (d) 140 °C, neat, 91%. CSI = chlorosulfonyl isocyanate.



Scheme 4 Model cyclization reactions. *Reagents and conditions*: (a) AuCl (10 mol%), DCM, r.t., 15 min, 62%; (b) TBAF, THF, r.t., 15 min, 27%; (c) $CDCl_3$; (d) time in $CDCl_3$.

the pyrrole[1,2-*c*]oxazole ketal derivative **32a** was unexpected. To further understand this result, we tested the reactivity of the *n* = 1 mono-benzylated diol **31b**. In this case, the 6-*endo*-*dig* product **32b** was the only observed product. Analogous reactivity was observed with the *n* = 2 substrate **31c**, which generated the pyrrole[1,2-*c*]oxazole ketal derivative **32c**, while the mono-benzylated diol displayed opposite carbon selectivity. Interestingly, the reactivity changed when testing the *n* = 3 substrate, **31e**, generating the desired cycloisomerization product, spiroketal **32e**, in a 62% yield.

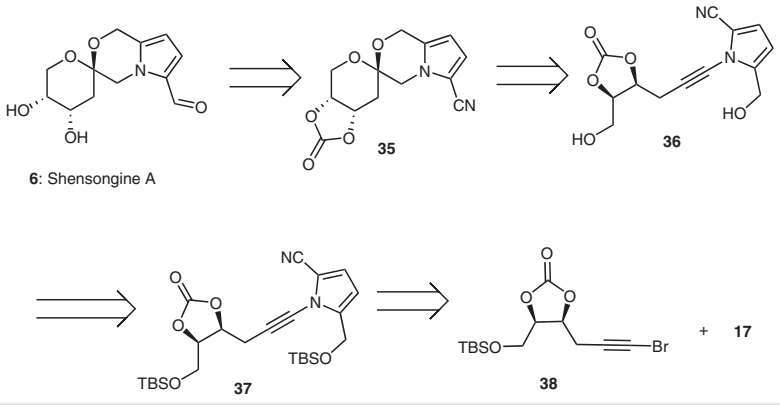
The model studies of Scheme 4 were a success in terms of advancing our understanding of the reactivity of *N*-alkynyl pyrrole-diols towards cycloisomerizations. It appears that cyclization proceeds preferentially from the alkyne-tethered alcohol, and that the favored modes of cyclizations are 5-*endo*-*dig*, 6-*endo*-*dig*, and 6-*exo*-*dig* in this series, with subsequent cyclization involving the pyrrole 2-hydroxymethyl group to form the ketals. Thus, accessing [6,6]-spiroketals (the pyranose PSA derivatives) from a suitable diol using this strategy should be straightforward. However, as the 5-*exo*-*dig* cyclization mode from the more facile alkyne-tethered alcohol is not observed, accessing the [6,5]-spiroketals (the furanose PSA derivatives) is unlikely to be successful in the case of a single-step spiroketalization under these conditions, although a multistep process appears viable.

In an effort to establish a multistep synthesis of a [6,5]-spiroketal and to conclude our model studies, we synthesized *N*-alkynyl pyrrole **31f** (Scheme 4). Cyclization of this mono-protected diol, gave the corresponding 1*H*-pyrrolo[2,1-*c*][1,4]oxazine **32f** in 62% yield. Subsequently, subjecting **32f** to a standard tetrabutylammonium fluoride (TBAF) deprotection resulted not only in the isolation of the expected alcohol, **33**, but pyrrole spiroketal **34** as well. While sitting in chloroform overnight, compound **33** fully cyclized to spiroketal **34**.[15] Overall, the results of the model study support the probable success of a diligently planned divergent synthesis of both the [6,5] and [6,6] PSAs from a common intermediate.

The fewer steps involved in constructing [6,6] versus [6,5] spirocycles using our strategy and the more favorable formation of the [6,6] β-anomer led us to choose shensongine A (**6**) as our first synthetic target. For our retrosynthesis of **6** we decided to use a cyclic carbonate as our protecting group for the *cis*-diol; organic carbonates are easily installed and deprotected, making it an attractive choice (Scheme 5). Through routine functional group manipulations we felt that advanced intermediate **35** could provide an easy path to shensongine A (**6**). A spiroketalization could give intermediate **35** from diol **36**, and **36** could come from the corresponding silylated *N*-alkynyl pyrrole **37**. Thus, we were left to synthesize alkynyl bromide **38**.

We began our synthesis of **38** with the known addition of propargyl zinc to glyceraldehyde derivative **39** (Scheme 6). By utilizing routine chemistry, compound **40**, the major diastereomer of propargyl zinc addition to **39** was smoothly transformed into silyl-ether **41** in 57% overall yield. Subsequent installation of the carbonate followed by bromination of the alkyne gave **38** in 39% two-step yield. Suitably positioned to explore the key *N*-alkynylation step, we were unable to isolate the desired *N*-alkynyl pyrrole **37**; rather, we only isolated small amounts of the undesired elimination product **42**.

In planning our second effort towards synthesizing **6**, we chose to protect the *cis*-diol as an acetonide. Our initial strategy failed because of the carbonate serving as a leaving group and we believed the acetonide would not suffer the same fate. In addition, acetonides have found use in other groups' strategies for synthesizing the pyrrole spiroketal alkaloids.[16] We began the synthesis with the olefination of deoxyribopyranose **43**, followed by TBS protection to give the *cis*-diol (Scheme 7). Reaction with 2,2-dimethoxypropane and PPTS gave **44** in 69% overall yield. Subsequently,

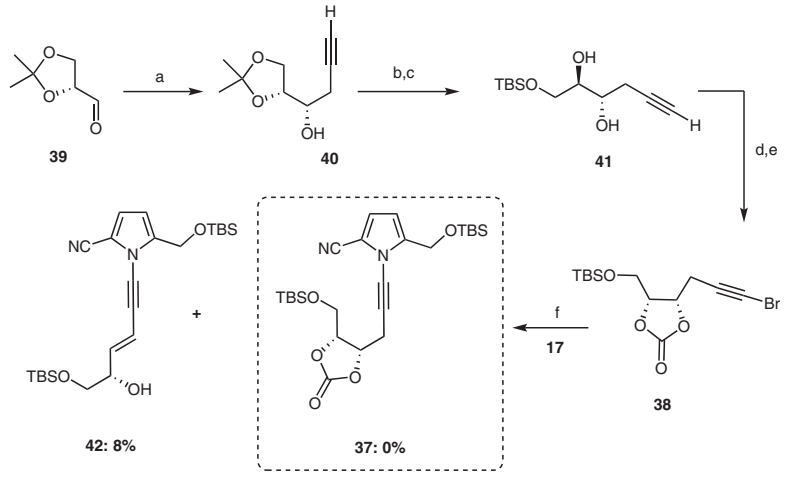


Scheme 5 Retrosynthetic analysis of shensongine A

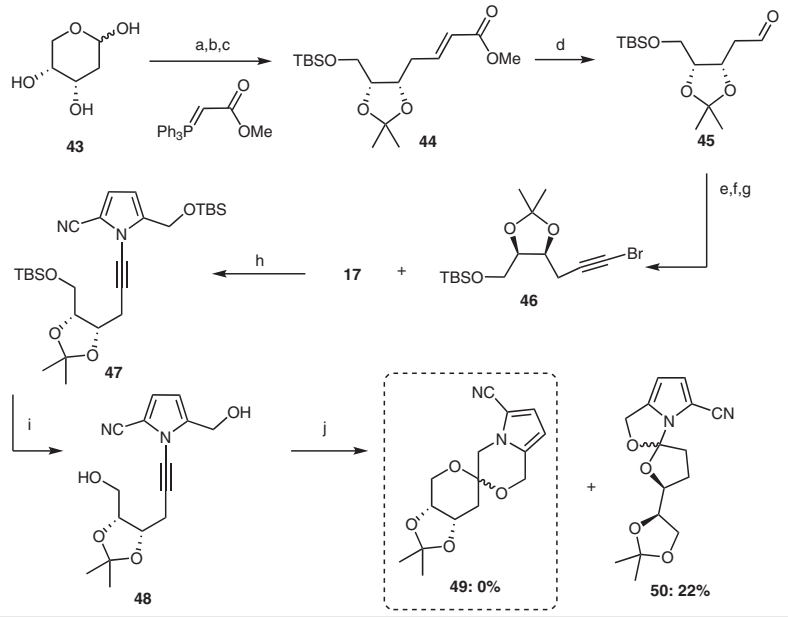
ozonolysis gave aldehyde **45** in an excellent 93% yield; finally, a Corey–Fuchs alkyne synthesis followed by bromination of the resultant alkyne gave **46** in 74% yield.

Alkynyl bromide **46** reacted smoothly to form *N*-alkynyl pyrrole **47** in 37% yield. Although the alkynylation did not suffer from issues with elimination, following the removal of the silyl ethers, diol **48** did not give the desired spiroketal **49**. Instead we isolated small amounts of **50** from what appears to be the result of an initial migration of the acetonide followed by an undesired cyclization to the pyrrole[1,2-*c*]oxazole ketal. We anticipated this as a potential issue and abandoned the strategy.

For our third attempt at synthesizing shensongine A (**6**), we looked to benzyl ethers for protecting the *cis*-diol (Scheme 8). Benzyl ethers should not suffer from elimination nor from rearrangement, thus they seemed aptly



Scheme 6 Unsuccessful carbonate strategy. *Reagents and conditions*: (a) propargyl bromide, Zn, 0 °C, THF, (dropwise addition to glyceraldehyde derivative), –78 °C to r.t., 31%; (b) TFA, THF, H_2O, r.t.; (c) TBSCl, TEA, DMAP, DCM, 0 °C to r.t., 52% for steps b and c; (d) triphosgene, pyridine, DMAP, 0 °C to r.t., 59%; (e) NBS, cat. $AgNO_3$, acetone, 66%; (f) $CuSO_4{\cdot}5H_2O$ (10 mol%), 1,10-phen (20 mol%), K_2CO_3 (200 mol%), toluene (0.5 M), 135 °C, 8%.

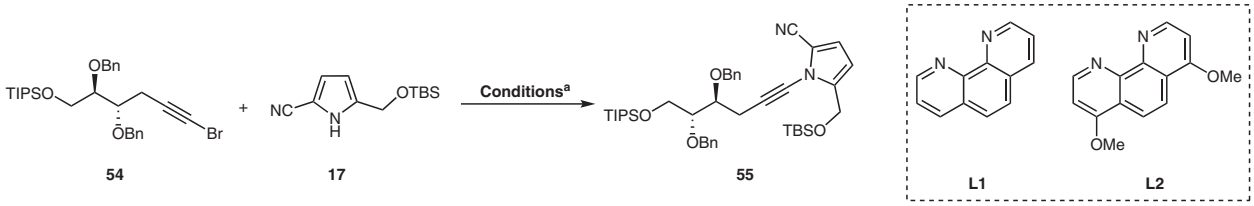


Scheme 7 Unsuccessful acetonide strategy. *Reagents and conditions*: (a) (methoxycarbonylmethylene)triphenylphosphorane, THF, 55 °C; (b) TBSCl, TEA, DMAP, DCM, 0 °C to r.t., 80% (two steps); (c) 2,2-dimethoxypropane, PPTS, acetone, r.t., 86%; (d) ozone, DCM, –78 °C, then PPh_3, 93%; (e) CBr_4, PPh_3, DCM, 0 °C, 88%; (f) *n*-BuLi, THF, –78 °C, 92%; (g) NBS, cat. $AgNO_3$, acetone, 91%; (h) $CuSO_4{\cdot}5H_2O$ (10 mol%), 1,10-phen (20 mol%), K_2CO_3 (200 mol%), toluene (0.5 M), 135 °C, 37%; (i) TFA, THF, H_2O, 0 °C to r.t.; 98%; (j) Ph_3PAuCl (10 mol%), AgOTf (10 mol%), DCM, r.t., 22%.

suited for the task. Starting from **39**, which we could synthesize from D-manitol in 40 gram lots, we were able to perform a propargyl zinc addition at a scale large enough to provide 35 grams of **40** in a dr of 4.4 to 1. Carrying this mixture of diastereomers forward by installing the first benzyl ether aided by TBAI gave alkyne **51** essentially as a pure diastereomer (dr >20:1) after chromatography in 68% yield. Subsequently, the acid-catalyzed removal of the acetonide followed by installation of a TIPS protecting group proceeded without incident, giving alkyne **52** in a 92% overall yield. The second benzyl ether could be introduced in 70% yield to give alkyne **53**, but some care was necessary to avoid silyl migration. Finally, a standard bromination gave alkynyl bromide **54** in 89% yield.

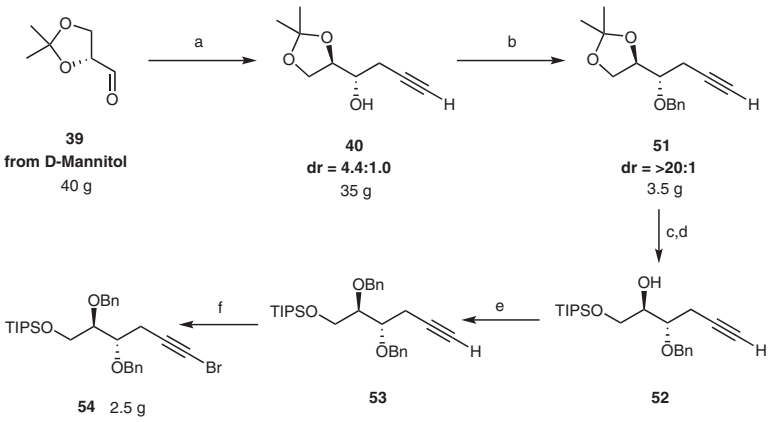
By using the sequence established in Scheme 8 we were able to synthesize up to 2.5 grams of alkynyl bromide **54**, enabling us to optimize the subsequent N-alkynylation step (Table 1). After significant screening, we were pleased to

Table 1 Screening the Cross-Coupling of **54** and **17**



Entry	Precat.	Ligand	Base	Solvent	*T* (°C)	**54** (mol%)	**17** (mol%)	Yield (%)[b]
1	$CuSO_4$	L2	K_2CO_3	toluene	115	120	100	<5
2	$CuSO_4$	L2	K_3PO_4	toluene	115	120	100	**59 (51)**[c]
3	$CuSO_4$	L1	K_2CO_3	toluene	115	120	100	30
4	$CuSO_4$	L1	K_3PO_4	toluene	115	120	100	<5
5	$CuSO_4$	L2	K_2CO_3	toluene	135	120	100	<5
6[d]	$CuSO_4$	L2	K_3PO_4	toluene	135	120	100	14
7	$CuSO_4$	L1	K_2CO_3	toluene	135	120	100	32
8	$CuSO_4$	L1	K_3PO_4	toluene	135	120	100	<5
9	$CuSO_4$	L1	K_2CO_3	toluene	115	120	100	36
10	$CuSO_4$	L1	K_2CO_3	toluene	135	100	100	28
11	$CuSO_4$	L2	K_3PO_4	toluene	115	100	100	16[c]
12[e]	$CuSO_4$	L2	K_3PO_4	toluene	115	100	100	33[c]
13[f]	$CuSO_4$	L2	K_3PO_4	toluene	115	100	120	25[c]
14[g]	$CuSO_4$	L2	K_3PO_4	toluene	115	120	100	42
15[h]	$CuSO_4$	L2	K_3PO_4	toluene	115	120	100	49
16[i]	$CuSO_4$	L2	K_3PO_4	toluene	115	120	100	41
17[j]	$CuSO_4$	L2	K_3PO_4	toluene	115	120	100	46
18	$CuSO_4$	L2	K_3PO_4	DMSO	115	120	100	22
19	$CuSO_4$	L2	K_3PO_4	C_6F_6	115	120	100	36
20[k]	$CuSO_4$	L2	K_3PO_4	toluene	115	120	100	<5
21[l]	$CuSO_4$	L2	K_3PO_4	toluene	115	120	100	<5

[a] Reaction conditions: pyrrole **17** (0.2 mmol), alkynyl bromide **54** (0.24 mmol), $CuSO_4 \cdot 5H_2O$ (0.02 mmol), ligand (0.04 mmol), base (0.4 mmol), solvent (0.4 mL), at the indicated temperature for 14 h.
[b] Yields were calculated by NMR using TCE (1,1,2,2-tetrachloroethane) as internal standard.
[c] Isolated yield.
[d] Reaction was run for 36 h.
[e] Slow addition of alkynyl bromide over 5 h.
[f] Slow addition of pyrrole over 5 h.
[g] 5 mol% catalyst.
[h] 20 mol% catalyst.
[i] 0.8 mL toluene.
[j] 0.2 mL toluene.
[k] Used alkynyl chloride.
[l] Used alkynyl iodide.

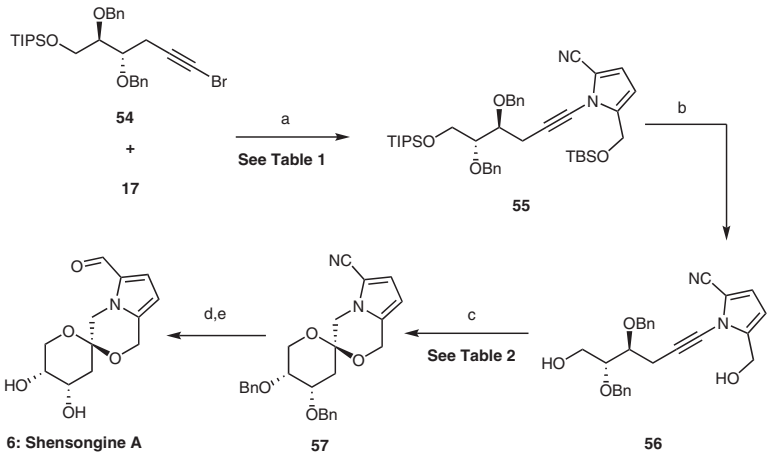


Scheme 8 Multigram synthesis of alkynyl bromide **54**. *Reagents and conditions*: (a) Propargyl bromide, Zn, 0 °C, THF, (dropwise addition to glyceraldehyde derivative), –78 °C to r.t., 56%; (b) NaH, 0 °C, then BnBr, TBAI, 0 to 55 °C, THF, 68%; (c) 1N HCl, MeOH, r.t.; (d) TIPSCl, DMF, imidazole, 92% (two steps); (e) NaH, 0 °C, BnBr, 0 °C to r.t., 70%; (f) NBS, cat. $AgNO_3$, acetone, r.t., 89%.

find that we could synthesize *N*-alkynyl pyrrole **55** in 51% isolated yield (entry 2). Our screens covered many parameters, including base combinations with ligands (entries 1–4), elevated temperatures (entries 5–8), extended reaction times (entry 9), mole ratios (entries 10–13), both the slow addition of **54** to **17** and the slow addition of **17** to **54** (entries 12 and 13), catalyst loading (entries 14 and 15), concentration (entries 16 and 17), solvents (entries 18 and 19), and we even looked at other alkynyl halides (entries 20 and 21).

Despite the scope of our efforts, we were unable to improve the yield of the coupling beyond the results detailed in Table 1, entry 2, which we decided must represent an optimal balance of the various side reactions that we observed, such as homocoupling of the bromoalkyne and decomposition of *N*-alkynyl pyrrole **55**, and we moved forward to pursue finishing the synthesis.

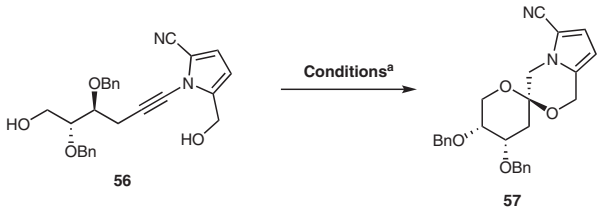
The TBAF deprotection of **55** proceeded without incident (93%; Scheme 9) enabling us to investigate the synthesis of the [6,6]-spiroketal **57** (Table 2). We were satisfied to find AuCl with PPTS, standard cycloisomerization conditions,[17,18] gave the desired spiroketal in 27% yield (entry 1).[19] While investigating alternative conditions, we found simply mixing AuCl with diol **56** in DCM gave **57** in a much greater yield (66%; entry 2). Under similar conditions, $AuCl_3$ gave a comparably good result, producing **57** in 59% yield (entry 3). We found gold(I) phosphine precatalyst and AgOTf to be poor catalysts, giving none of the desired spiroketal (entries 4–6). Additionally, neither mercury nor palladium catalysts, both known to catalyze alcohol



Scheme 9 Synthesis of shensongine A. *Reagents and conditions*: (a) $CuSO_4{\cdot}5H_2O$ (10 mol%), 4,7-dimethoxy-1,10-phenanthroline (20 mol%), K_3PO_4 (200 mol%), toluene (0.5 M), 115 °C, 51%; (b) TBAF, THF, 0 °C, 93%; (c) AuCl (10 mol%), DCM, r.t., 120 h, 60%; (d) DIBAL-H, DCM, 0 °C to r.t., 61%; (e) $TiCl_4$ (1 M in DCM), DCM, –78 to 0 °C, 70%.

additions to alkynes, performed well (entries 7 and 8).[20] Thus, by using the AuCl conditions detailed in entry 2, we were able to isolate spiroketal **57** in 60% yield, allowing us to complete the final steps of our shensongine A (**6**) synthesis (Scheme 9). The reduction of nitrile **57** with DIBAL-H gave moderate yields of aldehyde **57-1** (61%; Scheme 9). To complete the total synthesis we employed the same conditions previously reported[6b] for deprotection of the two benzyl ethers with $TiCl_4$ and obtained shensongine A (**6**) in 70% yield.

Table 2 Screening Conditions for the Metal-Catalyzed Cycloisomerization of **56**



Entry	Precatalyst	Additive	Solvent	*T* (°C)	Yield (%)[b]
1	AuCl	PPTS	THF	RT	27
2	AuCl	–	DCM	RT	66 (60)[c]
3	$AuCl_3$	–	DCM	RT	59
4	$Au(Ph_3P)Cl$	–	DCM	RT	0
5	$Au(Ph_3P)Cl$	AgOTf	DCM	RT	0
6	AgOTf	–	DCM	RT	0
7	$Hg(OTf)_2$	–	MeCN	RT	0
8	$Pd(PhCN)_2Cl_2$	–	MeCN	reflux (82)	13

[a] Reaction conditions: **56** (0.02 mmol), cat. (0.002 mmol), solvent (0.1 mL), at the indicated temperature for 48 h.
[b] Yields were calculated by NMR using TCE (1,1,2,2-tetrachloroethane) as internal standard.
[c] Isolated in 60% yield at 0.3 mmol scale and run for 120 h.

In summary, we have developed a strategy for synthesizing the pyrrole spiroketal alkaloids and demonstrated the potential of the strategy through its application to the synthesis of the [6,6]-spiroketal alkaloid shensongine A (**6**) in 11 steps and 2.7% overall yield. Our route utilizes two key steps: (1) a cross-coupling of an alkynyl bromide with a pyrrole and (2) a gold-catalyzed cycloisomerization of an *N*-alkynyl pyrrole. In conjuction with Pale and co-worker's synthesis of acortatarin A (**1**), this synthesis supports the hypothesis that an *N*-alkynyl pyrrole strategy can be used to access all the PSA natural products. Future work from our lab will look to identify an appropriately protected *N*-alkynyl pyrrole that can be used in the divergent synthesis of the PSA natural products and to implement its use in the rapid synthesis of a library of derivatives.

All reactions were run under argon in round-bottom flasks or in sealed vials using PTFE caps unless otherwise stated. All solvents and reagents were reagent grade and used as received unless otherwise stated. Column chromatography was carried out on SiliaFlash P60 silica gel (230–400 mesh). Reactions were monitored by TLC on Merck silica gel 60 W F245 aluminum-backed plates. Optical rotations were measured with a PerkinElmer 241 MC polarimeter. Melting points were recorded with a Büchi B-540 melting point apparatus and are uncorrected. IR spectra were obtained with a PerkinElmer Spectrum 100 FT-IR spectrophotometer using a diamond anvil ATR accessory. High-resolution mass spectra (HRMS) were obtained with an Agilent 6530 Q-TOF spectrometer. Accurate masses are reported for the molecular ion $[M + Na]^+$ or $[M + H]^+$. NMR spectra were recorded at 400 MHz (^1H) and 100 MHz (^{13}C) with an Agilent MR spectrometer. NMR spectra were recorded as parts per million (ppm) using residual solvent signals as internal standards ($CHCl_3$, δ = 7.26 ppm for ^1H NMR, δ = 77.00 ppm for ^{13}C NMR). The following abbreviations are used to describe the multiplicities: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, quin. = quintet, m = multiplet, br s = broad singlet. NMR yields were calculated using 1,1,2,2-tetrachloroethane as an internal standard. Data for ^1H NMR are presented as follows: chemical shifts (δ, ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR were presented as the chemical shifts of peaks found.

Preparation of Pyrroles

All pyrroles were commercially available or synthesized by using standard chemistry. Pyrroles purchased from suppliers were purified by column chromatography or distillation prior to use. See the following section for details regarding the synthesis of pyrroles that were not commercially available.

Preparation of Alkynyl Bromides; General Procedure A

To a solution of alkyne (1.0 equiv) in acetone (0.2 M) was added NBS (1.2 equiv) and $AgNO_3$ (0.1 equiv). The mixture was stirred open to the air for 4 h. Upon completion, the acetone was removed and the residue was taken up in hexanes, the organic solution was washed with sat. NH_4Cl, H_2O (2×), and brine, and dried over Na_2SO_4. Removal of the solvent under vacuum gave the pure alkynyl bromide.

Preparation of *N*-Alkynyl Pyrroles; General Procedure B

An 8 mL vial was charged with K_2CO_3 (55 mg, 0.4 mmol) and flame-dried and allowed to cool under vacuum. Once cooled, the vial was rapidly charged with $CuSO_4{\cdot}5H_2O$ (5 mg, 0.02 mmol), 1,10-phenanthroline (7.2 mg, 0.04 mmol), and ethyl 1*H*-pyrrole-2-carboxylate (**8**; 27.8 mg, 0.2 mmol) and an oven-dried stir bar. To the vial was then added freshly distilled toluene (0.4 mL) and argon was bubbled through the mixture for 10 min. Finally, alkynyl bromide ((6-bromohex-5-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane (**7a**; 0.24 mmol) was added and argon was bubbled through the mixture for an additional 10 min. Following this degassing, the vial was rapidly sealed with a Teflon cap and placed in an oil bath at 135 °C, unless otherwise noted. After completion of the reaction, the mixture was allowed to cool to r.t. and directly loaded onto a silica gel column and purified with hexanes/EtOAc.

TBAF Deprotections; General Procedure C

A round-bottom flask containing a stir bar was charged with the substrate to be deprotected and THF (0.2 M) and subsequently cooled to 0 °C. Subsequently, 1.25 equivalents of TBAF (per silyl group to be

come to r.t. Following completion of the reaction as determined by TLC, the reaction mixture was taken up in DCM and washed with sat. NH_4Cl, H_2O (2×), and brine, and dried over Na_2SO_4. Removal of the solvent gave the crude alcohol, which was purified by flash column chromatography.

AuCl Cyclizations; General Procedure D

A vial containing a stir bar was charged with the cyclization substrate, and DCM (0.2 M). AuCl (10 mol%) was added in one portion and the mixture was allowed to stir until the reaction reached completion (as determined by TLC). Note: these reactions can be very fast. Following completion, the reaction was filtered through a plug of silica and the solvents were removed to yield the crude cyclized product, which was subsequently purified by flash column chromatography.

Preparation of Scheme 1 Substrates: Pyrroles

1*H*-Pyrrole-2,5-dicarbaldehyde (9)

Prepared according to a reported procedure.[21]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.54 (br s, 1 H), 9.79 (s, 2 H), 7.01 (d, *J* = 2.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.4, 135.7, 119.4.

Ethyl 5-Formyl-1*H*-pyrrole-2-carboxylate (10)

Prepared according to a reported procedure.[22]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.30 (br s, 1 H), 9.65 (s, 1 H), 6.92 (m, 2 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 1.36 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.4, 160.4, 134.4, 128.5, 119.7, 115.5, 61.3, 14.2.

Ethyl 5-Cyano-1*H*-pyrrole-2-carboxylate (11)

Prepared according to a reported procedure.[23]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.22 (br s, 1 H), 6.88 (d, *J* = 4.0 Hz, 1 H), 6.81 (d, *J* = 4.0 Hz, 1 H), 4.44 (q, *J* = 7.2 Hz, 2 H), 1.40 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 126.9, 119.8, 115.0, 112.8, 105.6, 62.0, 14.1.

Ethyl 5-Vinyl-1*H*-pyrrole-2-carboxylate (12)

To a mixture/slurry of $MePPh_3Br$ (893 mg, 2.5 mmol) in THF (2.5 mL) at 0 °C was added KO^{t}Bu (280.5 mg, 2.5 mmol). The mixture was allowed to stir for 30 min at r.t. under argon. The mixture was placed back on an ice bath and pyrrole **10** (334 mg, 2.0 mmol) was added dropwise as a solution in THF (0.5 mL). The mixture was allowed to warm to r.t. then subsequently brought to reflux for 1 h. The reaction mixture was filtered, rinsed with EtOAc, residual solvents removed, and the crude compound was purified by column chromatography (0–15% EtOAc in hexanes) to give the product.

Yield: 216.5 mg (65.5%); white solid; mp 53 °C; R_f = 0.55 (hexanes/EtOAc, 2:1).

IR: 3297, 2923, 2852, 1674, 1488, 1368, 1321, 1260, 1219, 1137, 1024, 798, 763, 713 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.95 (br s, 1 H), 6.87 (dd, *J* = 4.0, 2.8 Hz, 1 H), 6.58 (dd, *J* = 17.6, 11.2 Hz, 1 H), 6.27 (dd, *J* = 3.6, 2.8 Hz, 1 H), 5.65 (d, *J* = 17.6 Hz, 1 H), 5.21 (d, *J* = 11.2 Hz, 1 H), 4.34 (q, *J* = 7.2 Hz, 2 H), 1.36 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5, 135.7, 126.4, 122.7, 116.2, 113.0, 109.2, 60.4, 14.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{11}NO_2Na$: 188.0682; found: 188.0682.

Ethyl 5-(1,3-Dioxolan-2-yl)-1*H*-pyrrole-2-carboxylate (13)

An oven-dried round-bottom flask was cooled under argon and charged with a stir bar, pyrrole **10** (167 mg, 1 mmol), freshly distilled toluene (4 mL), PPTS (25 mg, 0.1 mmol), and ethylene glycol (0.84 mL, 15 mmol). The mixture was then heated to 130 °C for 8 h and, after cooling, quenched with H_2O (5 mL) and extracted with DCM. The combined organics were rinsed with brine and then dried over Na_2SO_4. Residual solvents were removed and the crude compound was purified by column chromatography (0–15% EtOAc in hexanes) to give the product.

Yield: 83.3 mg (39%); yellow-orange oil; R_f = 0.35 (hexanes/EtOAc, 2:1).

IR: 3275, 1705, 1657, 1594, 1575, 1510, 1317, 1258, 1217, 1095, 1017, 983, 823, 777 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.58 (br s, 1 H), 6.83 (dd, *J* = 4.0, 2.8 Hz, 1 H), 6.28 (dd, *J* = 3.6, 2.8 Hz, 1 H), 5.89 (s, 1 H), 4.30 (q, *J* = 7.2 Hz, 2 H), 4.02 (m, 4 H), 1.32 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 133.1, 123.0, 115.2, 109.2, 98.0, 65.0, 60.3, 14.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{13}NO_4Na$: 234.0737; found: 234.0740.

Ethyl 5-(Hydroxymethyl)-1*H*-pyrrole-2-carboxylate (14-1)

Prepared according to a reported procedure.[24]

IR: 3293, 1669, 1488, 1316, 1214, 1133, 1020, 973, 798, 761 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.34 (br s, 1 H), 6.81 (dd, *J* = 3.6, 2.4 Hz, 1 H), 6.07 (dd, *J* = 3.6, 3.6 Hz, 1 H), 4.61 (s, 2 H), 4.27 (q, *J* = 7.2 Hz, 2 H), 3.65 (br s, 1 H), 1.32 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0, 137.1, 122.3, 115.8, 108.4, 60.4, 57.4, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_8H_{11}NO_3Na$: 192.0631; found: 192.0624.

Ethyl 5-(((Tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1*H*-pyrrole-2-carboxylate (14)

A round-bottom flask was charged with a stir bar, **14-1** (149 mg, 0.88 mmol), DCM (3.0 mL), PPTS (12.5 mg, 0.05 mmol), and dihydropyran (0.1 mL, 1.1 mmol). The solution was stirred under argon overnight. The reaction was quenched with $NaHCO_3$ solution and extracted with DCM (×2), the organics were combine and washed with brine, then dried over Na_2SO_4. The residual solvents were removed and the crude product was purified by flash column chromatography (0–50% EtOAc in hexanes) to yield the product.

Yield: 211 mg (95%); pale-yellow oil; R_f = 0.65 (hexanes/EtOAc, 1:1).

IR: 3292, 2939, 1698, 1678, 1492, 1316, 1218, 1118, 1075, 1021, 967, 903, 868, 807, 765 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.85 (br s, 1 H), 6.80 (dd, *J* = 3.6, 2.4 Hz, 1 H), 6.12 (dd, *J* = 3.6, 2.8 Hz, 1 H), 4.67 (d, *J* = 13.2 Hz, 1 H), 4.63 (dd, *J* = 4.4, 3.2 Hz, 1 H), 4.54 (d, *J* = 13.2 Hz, 1 H), 4.29 (q, *J* = 7.2 Hz, 2 H), 3.86 (m, 1 H), 3.51 (m, 1 H), 1.78 (m, 1 H), 1.68 (m, 1 H), 1.53 (m, 2 H), 1.31 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 133.8, 122.6, 115.1, 109.4, 98.0, 62.4, 61.7, 60.0, 30.3, 25.1, 19.3, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{19}NO_4Na$: 276.1206; found: 276.1209.

Methyl 5-Formyl-2-methyl-1*H*-pyrrole-3-carboxylate (15)

An oven-dried round-bottom flask containing a stir bar was allowed to cool to r.t. under argon and subsequently charged with DMF (2.71 mL, 35 mmol), and then placed on an ice bath and cooled to 0 °C. $POCl_3$ (2.83 mL, 30 mmol) was carefully added and then the mixture was allowed to come to r.t. After 20 min, methyl 2-methyl-1*H*-pyrrole-3-carboxylate (2.28 g, 20 mmol) was added in portions as a solid. Small amounts of DCE were used to wash the sides of the flask. After 3 h, the small amount of DCE was removed in vacuo and subsequently water was added to the crude mixture followed by the careful addition of NaOAc (12 g in 20 mL H_2O) and Na_2CO_3 (5 g). The product precipitated from the water and was filtered and rinsed with excess water and recrystallized from toluene.

Yield: 1.86 g (56%); white solid.

IR: 3254, 1713, 1651, 1567, 1475, 1416, 1243, 1138, 1094, 868, 776, 684 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.43 (br s, 1 H), 9.42 (s, 1 H), 7.35 (d, *J* = 2.8 Hz, 1 H), 3.84 (s, 3 H), 2.63 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.2, 164.6, 144.0, 130.4, 124.2, 115.0, 51.1, 13.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_8H_9NO_3Na$: 190.0475; found: 190.0473.

Methyl 5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyl-1*H*-pyrrole-3-carboxylate (16)

A round-bottom flask was charged with a stir bar, **15** (168 mg, 1.0 mmol), MeOH (2.0 mL), and cooled to 0 °C. Following adequate cooling while stirring, $NaBH_4$ (2 equiv) was added in portions and allowed to warm to r.t. Following completion, as determined by TLC, the reaction was diluted with water (25 mL) and extracted with DCM (3×). The combined organics were dried with sat. NaCl and dried over Na_2SO_4 and then solvents were removed to give the crude alcohol. The crude alcohol was then added to a round-bottom flask with DCM (5.0 mL) and charged with a stir bar. To the flask was also added TEA (0.6 mL), and a catalytic amount of DMAP. Following cooling to 0 °C, TBS-Cl (200 mg, 1.33 mmol) was added in portions and the reaction was allowed to cool to r.t. and stirred overnight. The following day the reaction was diluted with DCM (20 mL) and rinsed with sat. NH_4Cl (×1), water (×2), brine (×1) and dried over Na_2SO_4. Following removal of residual solvents, the crude compound was purified by column chromatography (0–15% EtOAc in hexanes) to give the product.

Yield: 123.5 mg (43%); white solid; R_f = 0.3 (hexanes/EtOAc, 5:1); mp 55–58 °C.

IR: 3302, 2951, 2856, 1675, 1596, 1450, 1339, 1224, 1134, 1060, 1001, 834, 776 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (br s, 1 H), 6.31 (d, *J* = 2.8 Hz, 1 H), 4.58 (s, 2 H), 3.77 (s, 3 H), 2.48 (s, 3 H), 0.89 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 135.3, 129.1, 111.1, 107.1, 58.3, 50.6, 25.8, 18.3, 13.1, –5.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{26}NO_3Si$: 284.1676; found: 284.1677.

5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1*H*-pyrrole-2-carbonitrile (17)

1st Generation Route

A round-bottom flask was charged with a stir bar, **11** (322 mg, 2.15 mmol), and THF (30 mL), and subsequently cooled to 0 °C under argon. Following adequate cooling, LAH (121 mg, 3.2 mmol) was carefully added in portions. After 1 h, the reaction was carefully quenched with a small amount of *i*PrOH then MeOH and diluted with NH_4Cl solution. The aqueous layer was extracted with DCM (×3) and the combined organics were washed with brine and dried over Na_2SO_4. The organics were removed to give crude **28**, which was used in the next step without further purification. Crude **28** was diluted with DCM (10 mL) and stirred at 0 °C under argon. Imidazole (306 mg, 4.5 mmol) was added, followed by TBS-Cl (452 mg, 3.0 mmol), and the reaction was allowed to warm to r.t. and stirred overnight. The following day the reaction was diluted with DCM (20 mL) and washed with NH_4Cl, water (×2), and brine. The combined organics were dried over Na_2SO_4 and the residual solvent was removed. The resulting crude product was purified by flash column chromatography (0–25% EtOAc in hexanes) to give the product.

Yield: 147 mg (29%); blood orange oil; R_f = 0.7 (hexanes/EtOAc, 2:1).

IR: 3287, 2929, 2857, 2219, 1463, 1361, 1254, 1181, 1082, 834, 776, 666 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92 (br s, 1 H), 6.79 (m, 1 H), 6.00 (m, 1 H), 4.72 (s, 2 H), 0.92 (s, 9 H), 0.10 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5, 120.6, 114.6, 105.8, 99.6, 58.5, 25.8, 18.3, –5.4.

HRMS (CI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{22}N_2OSi$: 237.1423; found: 237.1425.

2nd Generation Route

***tert*-Butyl 2-Formyl-1*H*-pyrrole-1-carboxylate (29-1)**

Prepared according to a reported procedure.[25]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.3 (s, 1 H), 7.43 (m, 1 H), 7.17 (m, 1 H), 6.27 (m, 1 H), 1.63 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.3, 148.3, 134.6, 127.3, 121.1, 111.6, 85.7, 27.9.

***tert*-Butyl 2-(Hydroxymethyl)-1*H*-pyrrole-1-carboxylate (29-2)**

Prepared according to a reported procedure.[25]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (dd, *J* = 3.2, 2.0 Hz, 1 H), 6.15 (m, 1 H), 6.08 (t, *J* = 3.6 Hz, 1 H), 4.63 (s, 2 H), 3.44 (br s, 1 H), 1.59 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9, 134.7, 121.7, 113.4, 110.3, 84.3, 57.5, 27.8.

***tert*-Butyl 2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1*H*-pyrrole-1-carboxylate (29)**

Prepared according to a reported procedure.[25]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (m, 1 H), 6.23 (m, 1 H), 6.13 (t, *J* = 3.0 Hz, 1 H), 4.89 (s, 2 H), 1.59 (s, 9 H), 0.94 (s, 9 H), 0.09 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.2, 135.3, 120.9, 111.0, 110.2, 83.4, 60.1, 27.9, 25.8, 18.3, –5.3.

tert-Butyl 2-(((tert-Butyldimethylsilyl)oxy)methyl)-5-cyano-1H-pyrrole-1-carboxylate (30)

An oven-dried round-bottom flask was charged with a stir bar and cooled under argon. The flask was then charged with **29** (10.0 g, 32.1 mmol) and freshly distilled THF (100 mL). The mixture was then cooled to –78 °C and CSI (chlorosulfonyl isocyanate, 3.33 mL, 37 mmol) was added dropwise. Following addition of the CSI, the reaction was stirred for 1.75 h and maintained at –78 °C. After the appropriate time had passed, anhydrous TEA (19 mL) was added slowly followed by the slow addition of anhydrous DMF (8.0 mL). The reaction was then allowed to warm to 0 °C and then r.t. After 15 min at r.t., the reaction mixture was poured into a seperatory funnel with sat. NH_4Cl and extracted with EtOAc (×3). The combined organics were then washed with H_2O (×3), brine, and dried over Na_2SO_4, removal of residual solvents gave the crude product, which was then purified by flash column chromatography (0–25% EtOAc in hexanes) to give the desired product.

Yield: 10.23 g (95%); clear oil.

IR: 2955, 2931, 2858, 2224, 1752, 1410, 1306, 1253, 1166, 1105, 835, 776 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.90 (d, *J* = 4.0 Hz, 1 H), 6.33 (m, 1 H), 4.88 (d, *J* = 1.2 Hz, 2 H), 1.64 (s, 9 H), 0.93 (s, 9 H), 0.10 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.4, 142.3, 124.9, 113.4, 110.7, 104.1, 87.1, 60.3, 27.7, 25.8, 18.2, –5.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{28}N_2O_3SiNa$: 359.1761; found: 359.1763.

5-(((tert-Butyldimethylsilyl)oxy)methyl)-1H-pyrrole-2-carbonitrile (17)

An oven-dried round-bottom flask was cooled under argon and charged with a stir bar and **30** (9.08 g, 27 mmol). The compound was then heated neat to 142 °C with sufficient stirring. After 45 min, the reaction was removed from the oil bath and allowed to cool for 5 min. After briefly cooling, hexanes (100 mL) were added to the round-bottom flask and the mixture was allowed to continue to stir overnight. The following day the hexanes were removed and the crude product was purified by column chromatography (0–25% EtOAc in hexanes) to give the product.

Yield: 5.79 g (91%); while solid; mp 39 °C.

Gave matching spectral data as above.

N-Alkynyl Pyrroles

Ethyl 1-(6-((tert-Butyldimethylsilyl)oxy)hex-1-yn-1-yl)-1H-pyrrole-2-carboxylate (18a)

Prepared according to General Procedure B.

Yield: 794 mg (45%); pale oil; R_f = 0.75 (hexanes/EtOAc, 2:1).

IR: 2930, 2274, 1721, 1465, 1422, 1259, 1104, 835, 733 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.00 (dd, *J* = 2.8, 2.0 Hz, 1 H), 6.90 (dd, *J* = 3.6, 1.6 Hz, 1 H), 6.15 (dd, *J* = 4.0, 2.8 Hz, 1 H), 4.30 (q, *J* = 7.2 Hz, 2 H), 3.65 (t, *J* = 5.6 Hz, 2 H), 2.43 (m, 2 H), 1.67 (m, 4 H), 1.34 (t, *J* = 7.2 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6, 131.5, 125.5, 117.6, 109.8, 72.6, 69.2, 62.6, 60.2, 31.9, 25.9, 25.1, 18.3, 18.1, 14.3, –5.3.

HRMS (CI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{32}NO_3Si$: 350.2151; found: 350.2145.

Methyl 5-Formyl-2-methyl-1-((triisopropylsilyl)ethynyl)-1H-pyrrole-3-carboxylate (25b)

Prepared according to General Procedure B.

Yield: 5.6 mg (8%); clear oil; R_f = 0.7 (hexanes/EtOAc, 4:1).

IR: 2944, 2865, 2186, 1718, 1682, 1568, 1502, 1440, 1234, 1134, 1072, 881, 773, 676 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.77 (s, 1 H), 7.31 (s, 1 H), 3.84 (s, 3 H), 2.68 (s, 3 H), 1.14 (m, 21 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.2, 163.8, 146.5, 132.7, 120.5, 114.8, 90.0, 76.2, 51.5, 18.5, 12.1, 11.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{29}NO_3SiNa$: 370.1809; found: 370.1815.

Methyl 5-(((tert-Butyldimethylsilyl)oxy)methyl)-2-methyl-1-((triisopropylsilyl)ethynyl)-1H-pyrrole-3-carboxylate (26b)

Prepared according to General Procedure B.

Yield: 78.9 mg (85%); pale yellow oil; R_f = 0.65 (hexanes/EtOAc, 4:1).

IR: 2944, 2864, 2185, 1714, 1593, 1544, 1462, 1224, 1070, 882, 835, 774, 676 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.40 (s, 1 H), 4.66 (s, 2 H), 3.79 (s, 3 H), 2.59 (s, 3 H), 1.12 (m, 21 H), 0.88 (s, 9 H), 0.04 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 140.0, 134.1, 112.3, 109.2, 91.7, 73.6, 57.2, 51.0, 25.8, 18.6, 18.3, 12.0, 11.2, –5.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{45}NO_3Si_2Na$: 486.2830; found: 486.2827.

5-(((tert-Butyldimethylsilyl)oxy)methyl)-1-((triisopropylsilyl)ethynyl)-1H-pyrrole-2-carbonitrile (27b)

Prepared according to General Procedure B.

Yield: 29.5 mg (60%); pale oil; R_f = 0.6 (hexanes/EtOAc, 10:1).

IR: 2943, 2865, 2225, 2188, 1462, 1423, 1370, 1254, 1198, 1122, 1075, 997, 835, 779 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.76 (d, *J* = 3.6 Hz, 1 H), 6.17 (d, *J* = 3.6 Hz, 1 H), 4.73 (s, 2 H), 1.13 (s, 21 H), 0.90 (s, 9 H), 0.07 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.6, 120.7, 112.1, 109.0, 108.0, 90.0, 74.3, 57.6, 25.7, 18.5, 18.3, 11.1, –5.4.

HRMS (CI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{41}N_2OSi_2$: 417.2757; found: 417.2754.

Preparation of Scheme 4 Substrates

(But-3-yn-1-yloxy)(tert-butyl)dimethylsilane (31a-1)

Data consistent with reported data.[26]

^1H NMR (400 MHz, $CDCl_3$): δ = 3.74 (t, *J* = 7.2 Hz, 2 H), 2.40 (td, *J* = 7.2, 2.8 Hz, 2 H), 1.95 (t, *J* = 2.8 Hz, 1 H), 0.89 (s, 9 H), 0.07 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 81.5, 69.2, 61.7, 25.8, 22.8, 18.3, –5.3.

((4-Bromobut-3-yn-1-yl)oxy)(tert-butyl)dimethylsilane (31a-2)

Prepared according to General Procedure A; data consistent with reported data.[27]

^1H NMR (400 MHz, $CDCl_3$): δ = 3.72 (t, *J* = 7.2 Hz, 2 H), 2.40 (t, *J* = 7.2 Hz, 2 H), 0.89 (s, 9 H), 0.06 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 77.4, 61.4, 39.0, 25.8, 23.9, 18.2, –5.3.

1-(4-((*tert*-Butyldimethylsilyl)oxy)but-1-yn-1-yl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1*H*-pyrrole-2-carbonitrile (31a-3)

Prepared according to General Procedure B.

Yield: 68.8 mg (33%); clear oil.

IR: 2954, 2929, 2857, 2225, 1440, 1254, 1104, 835, 775 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.73 (d, *J* = 3.6 Hz, 1 H), 6.14 (d, *J* = 3.6 Hz, 1 H), 4.67 (s, 2 H), 3.80 (t, *J* = 7.2 Hz, 2 H), 2.64 (t, *J* = 7.2 Hz, 2 H), 0.90 (s, 9 H), 0.90 (s, 9 H), 0.08 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.3, 120.3, 112.3, 109.0, 107.9, 71.9, 69.4, 61.5, 57.4, 25.8, 25.7, 22.7, 18.2, –5.3, –5.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{38}N_2O_2Si_2Na$: 441.2364; found: 441.2378.

1-(4-Hydroxybut-1-yn-1-yl)-5-(hydroxymethyl)-1*H*-pyrrole-2-carbonitrile (31a)

Prepared according to General Procedure C.

Yield: 20.3 mg (65%); pale oil.

IR: 3358, 2924, 2223, 1440, 1311, 1208, 1026, 792, 753 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.72 (d, *J* = 4.0 Hz, 1 H), 6.17 (d, *J* = 4.0 Hz, 1 H), 4.62 (s, 2 H), 3.81 (t, *J* = 6.0 Hz, 2 H), 3.29 (br s, 2 H), 2.67 (t, *J* = 6.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.1, 120.2, 112.3, 110.0, 108.0, 72.8, 70.2, 60.7, 56.0, 22.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{10}N_2O_2Na$: 213.0634; found: 213.0628.

4,5-Dihydro-1′*H*,3*H*-spiro[furan-2,3′-pyrrolo[1,2-*c*]oxazole]-5′-carbonitrile (32a)

Prepared according to General Procedure D.

Yield: 13.3 mg (48%); pale-yellow oil.

IR: 3268, 3140, 2944, 2216, 1169, 1035, 989, 792 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.93 (d, *J* = 3.6 Hz, 1 H), 5.88 (dt, *J* = 4.0, 0.8 Hz, 1 H), 5.04 (dd, *J* = 12.4, 0.8 Hz, 1 H), 4.90 (dd, *J* = 12.4, 0.8 Hz, 1 H), 4.23 (dt, *J* = 8.0, 6.8 Hz, 1 H), 4.12 (dt, *J* = 5.6, 8.0 Hz, 1 H), 2.75 (m, 1 H), 2.48 (m, 1 H), 2.33 (m, 1 H), 2.24 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4, 126.5, 118.9, 112.9, 99.5, 94.8, 69.4, 65.5, 35.0, 24.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{10}N_2O_2Na$: 213.0634; found: 213.0635.

((But-3-yn-1-yloxy)methyl)benzene (31b-1)

Data consistent with reported data.[28]

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 5 H), 4.57 (s, 2 H), 3.61 (t, *J* = 6.8 Hz, 2 H), 2.52 (td, *J* = 6.8, 2.8 Hz, 2 H), 2.01 (t, *J* = 2.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 128.3, 127.6, 81.2, 72.9, 69.2, 68.1, 19.8.

(((4-Bromobut-3-yn-1-yl)oxy)methyl)benzene (31b-2)

Prepared according to General Procedure A.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.29 (m, 5 H), 4.57 (s, 2 H), 3.60 (t, *J* = 6.8 Hz, 2 H), 2.54 (t, *J* = 6.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.7, 128.2, 127.4, 127.4, 76.5, 72.7, 67.6, 39.0, 20.8.

1-(4-(Benzyloxy)but-1-yn-1-yl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1*H*-pyrrole-2-carbonitrile (31b-3)

Prepared according to General Procedure B.

Yield: 69.6 mg (35%); pale oil.

IR: 2929, 2857, 2224, 1440, 1362, 1311, 1254, 1212, 1097, 1005, 836, 778, 736, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.26 (m, 5 H), 6.74 (d, *J* = 4.4 Hz, 1 H), 6.15 (d, *J* = 4.4 Hz, 1 H), 4.68 (s, 2 H), 4.59 (s, 2 H), 3.70 (t, *J* = 6.8 Hz, 2 H), 2.75 (t, *J* = 7.2 Hz, 2 H), 0.91 (s, 9 H), 0.08 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.3, 137.8, 128.3, 127.6, 127.6, 120.3, 112.3, 109.0, 108.0, 73.0, 72.9, 69.4, 68.0, 57.3, 25.7, 20.6, 19.7, –5.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{30}N_2O_2SiNa$: 417.1969; found: 417.1977.

1-(4-(Benzyloxy)but-1-yn-1-yl)-5-(hydroxymethyl)-1*H*-pyrrole-2-carbonitrile (31b)

Prepared according to General Procedure C.

Light orange oil that despite careful chromatographic purification contained ca. 5% of the alkyne homo-coupling side product (28.8 mg, 60%).

R_f = 0.45 (hexanes/EtOAc, 1:1).

IR: 3428, 2868, 2222, 1440, 1311, 1207, 1098, 1027, 791, 747, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 5 H), 6.72 (d, *J* = 4.0 Hz, 1 H), 6.16 (d, *J* = 4.4 Hz, 1 H), 4.59 (s, 2 H), 4.58 (s, 2 H), 3.69 (t, *J* = 6.4 Hz, 2 H), 2.78 (br s, 1 H), 2.74 (t, *J* = 6.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.4, 137.4, 128.4, 127.9, 127.8, 120.2, 112.1, 109.7, 107.9, 73.1, 72.6, 69.6, 67.9, 56.2, 19.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{16}N_2O_2Na$: 303.1104; found: 303.1105.

3-(2-(Benzyloxy)ethyl)-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-6-carbonitrile (32b)

Prepared according to General Procedure D.

Yield: 11.3 mg (69%); pale oil; R_f = 0.65 (hexanes/EtOAc, 2:1).

IR: 3386, 2899, 2862, 2216, 1678, 1450, 1359, 1314, 1188, 1096, 1069, 1028, 738, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H), 6.76 (d, *J* = 4.0 Hz, 1 H), 6.55 (q, *J* = 0.8 Hz, 1 H), 5.95 (dd, *J* = 3.6, 0.8 Hz, 1 H), 5.02 (d, *J* = 0.8 Hz, 2 H), 4.55 (s, 2 H), 3.65 (t, *J* = 6.0 Hz, 2 H), 2.49 (td, *J* = 6.4, 0.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8, 137.9, 128.4, 127.7, 125.9, 119.3, 112.8, 104.5, 102.7, 100.0, 73.0, 66.6, 63.3, 32.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{16}N_2O_2Na$: 303.1104; found: 303.1104.

***tert*-Butyldimethyl(pent-4-yn-1-yloxy)silane (31c-1)**

Data consistent with reported data.[26]

^1H NMR (400 MHz, $CDCl_3$): δ = 3.69 (t, *J* = 6.0 Hz, 2 H), 2.26 (td, *J* = 7.2, 2.8 Hz, 2 H), 1.91 (t, *J* = 2.8 Hz, 1 H), 1.71 (m, 2 H), 0.88 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 84.2, 68.2, 61.3, 31.4, 25.9, 18.2, 14.8, –5.3.

((5-Bromopent-4-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane (31c-2)

Prepared according to General Procedure A.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.67 (t, *J* = 6.0 Hz, 2 H), 2.29 (t, *J* = 7.2 Hz, 2 H), 1.70 (m, 2 H), 0.88 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 79.9, 61.3, 37.6, 31.2, 25.8, 18.2, 16.0, –5.4.

5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-(5-((*tert*-butyldimethylsilyl)oxy)pent-1-yn-1-yl)-1*H*-pyrrole-2-carbonitrile (31c-3)

Prepared according to General Procedure B.

Yield: 71.4 mg (33%); pale oil; R_f = 0.8 (hexanes/EtOAc, 4:1).

IR: 2953, 2929, 2857, 2224, 1440, 1308, 1254, 1212, 1102, 834, 775 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.72 (d, *J* = 4.0 Hz, 1 H), 6.13 (d, *J* = 4.0 Hz, 1 H), 4.67 (s, 2 H), 3.74 (t, *J* = 5.6 Hz, 2 H), 2.52 (t, *J* = 7.2 Hz, 2 H), 1.81 (quint., *J* = 6.4 Hz, 2 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.08 (s, 6 H), 0.06 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.1, 120.2, 112.4, 108.9, 108.0, 74.5, 68.6, 61.3, 57.4, 31.5, 25.8, 25.7, 18.2, 14.7, –5.3, –5.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{40}N_2O_2Si_2Na$: 455.2521; found: 455.2525.

5-(Hydroxymethyl)-1-(5-hydroxypent-1-yn-1-yl)-1*H*-pyrrole-2-carbonitrile (31c)

Prepared according to General Procedure C.

Yield: 21 mg (62%); pale-oil; R_f = 0.15 (hexanes/EtOAc, 2:1).

IR: 3370, 2936, 2223, 1440, 1309, 1209, 1024, 791 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.73 (d, *J* = 3.6 Hz, 1 H), 6.18 (d, *J* = 3.6 Hz, 1 H), 4.62 (s, 2 H), 3.80 (t, *J* = 6.0 Hz, 2 H), 2.79 (br s, 2 H), 2.57 (t, *J* = 6.8 Hz, 2 H), 1.84 (quint., *J* = 6.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.9, 120.2, 112.3, 109.7, 108.2, 74.5, 68.9, 61.1, 56.1, 30.5, 14.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{12}N_2O_2Na$: 227.0791; found: 227.0789.

3,4,5,6-Tetrahydro-1′*H*-spiro[pyran-2,3′-pyrrolo[1,2-*c*]oxazole]-5′-carbonitrile (32c)

Prepared according to General Procedure D.

Yield: 8.1 mg (39%); pale oil; R_f = 0.56 (hexanes/EtOAc, 2:1).

IR: 3284, 3181, 2956, 2219, 1654, 1547, 1493, 1329, 1185, 1055, 791 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.90 (d, *J* = 4.0 Hz, 1 H), 5.89 (d, *J* = 4.0 Hz, 1 H), 5.01 (dd, *J* = 12.8, 1.2 Hz, 1 H), 4.91 (dd, *J* = 12.8, 1.2 Hz, 1 H), 4.03–3.90 (m, 2 H), 2.54 (m, 1 H), 2.06 (m, 1 H), 1.96 (m, 2 H), 1.80 (m, 1 H), 1.62 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2, 125.8, 112.5, 109.8, 99.3, 94.9, 65.1, 64.8, 32.4, 23.7, 19.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{12}N_2O_2Na$: 227.0791; found: 227.0785.

((Pent-4-yn-1-yloxy)methyl)benzene (31d-1)

Data consistent with reported data.[28]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.28 (m, 5 H), 4.54 (s, 2 H), 3.60 (t, *J* = 6.2 Hz, 2 H), 2.35 (td, *J* = 6.8, 2.4 Hz, 2 H), 1.97 (t, *J* = 2.4 Hz, 1 H), 1.86 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 128.2, 127.5, 127.4, 83.8, 72.8, 68.5, 68.4, 28.5, 15.2.

(((5-Bromopent-4-yn-1-yl)oxy)methyl)benzene (31d-2)

Prepared according to General Procedure A.

Yield: 1.36 g (93%); clear oil.

IR: 3031, 2859, 1702, 1453, 1364, 1273, 1203, 1102, 1075, 1027, 908, 735, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.28 (m, 5 H), 4.54 (s, 2 H), 3.58 (t, *J* = 6.4 Hz, 2 H), 2.37 (t, *J* = 7.6 Hz, 2 H), 1.84 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 128.2, 127.4, 127.4, 79.6, 72.8, 68.4, 37.9, 28.3, 16.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{13}BrONa$: 275.0042; found: 275.0040.

1-(5-(Benzyloxy)pent-1-yn-1-yl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1*H*-pyrrole-2-carbonitrile (31d-3)

Prepared according to General Procedure B.

Yield: 70.1 mg (34%); pale oil; R_f = 0.45 (hexanes/EtOAc, 4:1).

IR: 2929, 2856, 2223, 1440, 1363, 1309, 1255, 1212, 1078, 836, 779, 735, 697 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.24 (m, 5 H), 6.74 (d, *J* = 4.0 Hz, 1 H), 6.15 (d, *J* = 4.0 Hz, 1 H), 4.66 (s, 2 H), 4.55 (s, 2 H), 3.65 (t, *J* = 6.0 Hz, 2 H), 2.58 (t, *J* = 7.0 Hz, 2 H), 1.93 (m, 2 H), 0.92 (s, 9 H), 0.09 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.1, 138.3, 128.2, 127.6, 127.4, 120.2, 112.4, 108.9, 108.0, 74.2, 73.0, 68.9, 68.4, 57.3, 28.6, 25.7, 18.2, 15.2, –5.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{32}N_2O_2SiNa$: 431.2125; found: 431.2135.

1-(5-(Benzyloxy)pent-1-yn-1-yl)-5-(hydroxymethyl)-1*H*-pyrrole-2-carbonitrile (31d)

Prepared according to General Procedure C.

Yield: 33.1 mg (66%); clear oil; R_f = 0.5 (hexanes/EtOAc, 1:1).

IR: 3423, 2865, 2222, 1440, 1365, 1310, 1208, 1104, 1076, 1026, 790, 740, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.24 (m, 5 H), 6.73 (d, *J* = 4.0 Hz, 1 H), 6.17 (d, *J* = 4.0 Hz, 1 H), 4.58 (s, 2 H), 4.54 (s, 2 H), 3.64 (t, *J* = 6.0 Hz, 2 H), 2.58 (t, *J* = 6.8 Hz, 2 H), 2.29 (br s, 1 H), 1.92 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.8, 138.2, 128.3, 127.7, 127.6, 120.2, 112.2, 109.5, 108.3, 74.6, 73.0, 68.7, 68.5, 56.3, 28.4, 15.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{18}N_2O_2Na$: 317.1260; found: 317.1264.

3-(3-(Benzyloxy)propyl)-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-6-carbonitrile (32d)

Prepared according to General Procedure D.

Yield: 7.0 mg (51%); pale oil; R_f = 0.8 (hexanes/EtOAc, 2:1).

IR: 3408, 2860, 2215, 1677, 1475, 1311, 1173, 1100, 739, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H), 6.76 (d, *J* = 4.0 Hz, 1 H), 6.45 (d, *J* = 0.8 Hz, 1 H), 5.94 (d, *J* = 4.0 Hz, 1 H), 5.00 (s, 2 H), 4.51 (s, 2 H), 3.51 (t, *J* = 6.0 Hz, 2 H), 2.29 (td, *J* = 7.2, 0.8 Hz, 2 H), 1.86 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.2, 138.3, 128.3, 127.7, 127.6, 125.9, 119.3, 112.8, 104.5, 101.7, 99.9, 73.0, 69.0, 63.3, 28.1, 26.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{18}N_2O_2Na$: 317.1260; found: 317.1264.

tert-Butyl(hex-5-yn-1-yloxy)dimethylsilane (31e-1)

Data consistent with reported data.[29]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.62 (t, *J* = 6.0 Hz, 2 H), 2.20 (td, *J* = 6.8, 2.8 Hz, 2 H), 1.93 (t, *J* = 2.4 Hz, 1 H), 1.60 (m, 4 H), 0.88 (s, 9 H), 0.04 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 84.5, 68.2, 62.5, 31.8, 25.9, 24.9, 18.3, 18.1, –5.3.

((6-Bromohex-5-yn-1-yl)oxy)(_tert_-butyl)dimethylsilane (31e-2)

Prepared according to General Procedure A.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.62 (t, *J* = 6.0 Hz, 2 H), 2.23 (t, *J* = 6.8 Hz, 2 H), 1.59 (m, 4 H), 0.89 (s, 9 H), 0.04 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 80.1, 62.4, 37.7, 31.7, 25.9, 24.7, 19.4, 18.2, –5.3.

1-(6-((_tert_-Butyldimethylsilyl)oxy)hex-1-yn-1-yl)-5-(((_tert_-butyldimethylsilyl)oxy) methyl)-1*H*-pyrrole-2-carbonitrile (31e-3)

Prepared according to General Procedure B.

Pale oil isolated with some dialkyne impurity (110 mg, 49%).

IR: 2952, 2929, 2857, 2225, 1471, 1439, 1386, 1310, 1253, 1213, 1089, 1005, 833, 774 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.72 (d, *J* = 4.0 Hz, 1 H), 6.14 (d, *J* = 4.0 Hz, 1 H), 4.67 (s, 2 H), 3.65 (t, *J* = 6.0 Hz, 2 H), 2.46 (t, *J* = 6.8 Hz, 2 H), 1.68 (m, 4 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.08 (s, 6 H), 0.05 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.1, 120.2, 112.5, 108.9, 108.0, 74.7, 68.8, 62.4, 57.4, 31.8, 25.9, 25.7, 25.0, 24.7, 19.4, 18.3, –5.3, –5.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{42}N_2O_2Si_2Na$: 469.2677; found: 469.2678.

1-(6-Hydroxyhex-1-yn-1-yl)-5-(hydroxymethyl)-1*H*-pyrrole-2-carbonitrile (31e)

Prepared according to General Procedure C.

Yield: 69.7 mg (32% over two steps); clear oil.

IR: 3343, 2937, 2867, 2222, 1438, 1310, 1208, 1061, 1023, 789, 752 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.72 (d, *J* = 4.0 Hz, 1 H), 6.17 (d, *J* = 4.0 Hz, 1 H), 4.61 (s, 2 H), 3.63 (t, *J* = 6.4 Hz, 2 H), 3.08 (br s, 2 H), 2.47 (t, *J* = 6.4 Hz, 2 H), 1.69 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.9, 120.2, 112.4, 109.6, 108.0, 74.8, 68.8, 61.9, 55.9, 31.3, 24.4, 17.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{14}N_2O_2Na$: 241.0947; found: 241.0954.

3,4,5,6-Tetrahydro-1′*H*,4′*H*-spiro[pyran-2,3′-pyrrolo[2,1-*c*][1,4]-oxazine]-6′-carbonitrile (32e)

Prepared according to General Procedure D.

Yield: 27.2 mg (62%); pale oil; R_f = 0.3 (hexanes/EtOAc, 10:1).

IR: 2945, 2870, 2210, 1436, 1380, 1317, 1279, 1188, 1160, 1077, 1056, 1031, 942, 758 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.78 (d, *J* = 3.6 Hz, 1 H), 5.90 (d, *J* = 3.6 Hz, 1 H), 4.77, 4.73 (ABq, *J* = 14.8 Hz, 2 H), 4.02 (d, *J* = 12.4 Hz, 1 H), 3.76 (d, *J* = 12.4 Hz, 1 H), 3.71 (m, 2 H), 2.02–1.55 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.9, 119.6, 113.5, 103.3, 101.8, 93.6, 62.0, 57.4, 51.4, 32.3, 24.5, 18.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{14}N_2O_2Na$: 241.0947; found: 241.0951.

((5-Bromopent-4-yn-1-yl)oxy)(_tert_-butyl)diphenylsilane (31f-2)

Prepared according to General Procedure A.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (m, 4 H), 7.42 (m, 6 H), 3.76 (t, *J* = 6.0 Hz, 2 H), 2.39 (t, *J* = 7.1 Hz, 2 H), 1.77 (m, 2 H), 1.07 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.5, 133.7, 129.5, 127.6, 79.9, 62.0, 37.7, 31.1, 26.8, 19.2, 16.2.

5-(((_tert_-Butyldimethylsilyl)oxy)methyl)-1-(5-((_tert_-butyldiphenylsilyl)oxy)pent-1-yn-1-yl)-1*H*-pyrrole-2-carbonitrile (31f-3)

Prepared according to General Procedure B.

Pale oil with co-eluting impurities.

IR: 3310, 3071, 2954, 2929, 2856, 2224, 1589, 1471, 1427, 1389, 1308, 1255, 1212, 1106, 1006, 982, 837, 779, 738, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (m, 4 H), 7.39 (m, 6 H), 6.73 (d, *J* = 4.0 Hz, 1 H), 6.14 (d, *J* = 4.0 Hz, 1 H), 4.63 (s, 2 H), 3.79 (t, *J* = 6.0 Hz, 2 H), 2.59 (t, *J* = 7.2 Hz, 2 H), 1.86 (m, 2 H), 1.06 (s, 9 H), 0.90 (s, 9 H), 0.07 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.1, 135.5, 133.6, 129.5, 127.6, 120.2, 112.4, 108.9, 108.0, 74.5, 68.2, 62.2, 57.4, 31.4, 26.8, 25.7, 19.2, 18.2, 14.9, –5.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{33}H_{44}N_2O_2Si_2Na$: 579.2834; found: 579.2831.

1-(5-((_tert_-Butyldiphenylsilyl)oxy)pent-1-yn-1-yl)-5-(hydroxymethyl)-1*H*-pyrrole-2-carbonitrile (31f)

A round-bottom flask was charged with **31f-3** (with impurities from cross-coupling), a stir bar, and a mixture of THF/H_2O/TFA in a 1:1:1 ratio (3 mL). After completion, as determined by TLC, the reaction was carefully quenched with $NaHCO_3$, extracted with DCM (3×), and the combined organics were rinsed with brine and dried over Na_2SO_4. The solvents were removed to give the crude oil, which was further purified by flash column chromatography to give the title compound.

Yield: 50.5 mg (29% over two steps); clear oil.

IR: 3445, 3071, 2930, 2857, 2222, 1472, 1440, 1427, 1308, 1208, 1106, 1026, 982, 823, 789, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (m, 4 H), 7.37 (m, 6 H), 6.74 (d, *J* = 4.0 Hz, 1 H), 6.19 (d, *J* = 4.0 Hz, 1 H), 4.57 (s, 2 H), 3.81 (t, *J* = 6.0 Hz, 2 H), 2.61 (t, *J* = 7.2 Hz, 2 H), 1.86 (m, 2 H), 1.85 (br s, 1 H), 1.07 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.6, 135.5, 133.6, 129.6, 127.6, 120.2, 112.2, 109.5, 108.4, 74.8, 68.5, 62.1, 56.4, 31.2, 26.8, 19.2, 14.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{30}N_2O_2SiNa$: 465.1969; found: 465.1970.

3-(3-((_tert_-Butyldiphenylsilyl)oxy)propyl)-1*H*-pyrrolo-[2,1-*c*][1,4]oxazine-6-carbonitrile (32f)

Prepared according to General Procedure D.

Yield: 28 mg (62%); pale oil.

IR: 3071, 2928, 2856, 2218, 1680, 1472, 1448, 1428, 1363, 1315, 1191, 1110, 822, 738, 702 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (m, 4 H), 7.39 (m, 6 H), 6.77 (d, *J* = 4.0 Hz, 1 H), 6.43 (d, *J* = 0.8 Hz, 1 H), 5.94 (dd, *J* = 4.0, 0.8 Hz, 1 H), 4.97 (d, *J* = 0.8 Hz, 2 H), 3.71 (t, *J* = 6.0 Hz, 2 H), 2.31 (td, *J* = 7.6, 0.8 Hz, 2 H), 1.80 (m, 2 H), 1.07 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.3, 135.5, 134.7, 133.6, 129.6, 127.6, 127.6, 125.9, 119.2, 112.9, 104.4, 101.6, 99.8, 63.2, 62.7, 29.6, 29.4, 27.7, 26.8, 26.5, 19.1, 18.9.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{31}N_2O_2Si$: 443.2149; found: 443.2150.

3-(3-Hydroxypropyl)-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-6-carbonitrile (33)

Prepared according to General Procedure C.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.76 (d, *J* = 3.6 Hz, 1 H), 6.49 (d, *J* = 0.8 Hz, 1 H), 5.95 (dd, *J* = 3.6, 0.8 Hz, 1 H), 5.05 (s, 2 H), 3.71 (t, *J* = 6.4 Hz, 2 H), 2.31 (td, *J* = 7.2, 0.8 Hz, 2 H), 1.82 (m, 2 H), 1.59 (br s, 1 H).

4,5-Dihydro-1′*H*,3*H*,4′*H*-spiro[furan-2,3′-pyrrolo[2,1-*c*][1,4]-oxazine]-6′-carbonitrile (34)

Prepared according to General Procedure C (note: spontaneously cyclized in $CDCl_3$).

Yield: 7.6 mg (27%); oily solid.

IR: 3121, 2956, 2891, 2211, 1486, 1430, 1398, 1307, 1258, 1189, 1163, 1100, 1050, 1018, 899, 762 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.79 (d, *J* = 3.2 Hz, 1 H), 5.90 (d, *J* = 3.2 Hz, 1 H), 4.87 (d, *J* = 12 Hz, 1 H), 4.73 (d, *J* = 12 Hz, 1 H), 4.14 (d, *J* = 10 Hz, 1 H), 4.08 (d, *J* = 10 Hz, 1 H), 4.04 (m, 2 H), 2.19 (m, 2 H), 2.04 (m, 1 H), 1.93 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.2, 119.8, 113.6, 103.4, 103.0, 101.9, 68.7, 58.1, 49.2, 35.7, 23.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{13}N_2O_2$: 205.0972; found: 205.0976.

Preparation of Scheme 6 Substrates

(*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-yn-1-ol (40)

Prepared according to a reported procedure[30] using commercially available **39**.

Yield: 1.88 g (31%); clear oil; $[\alpha]_D$ +6.5 (*c* = 1.08, DCM).

IR: 3285, 2921, 1708, 1420, 1194, 1063, 1037, 860 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.07 (m, 2 H), 3.96 (m, 1 H), 3.76 (m, 1 H), 2.57–2.41 (m, 2 H), 2.23 (br s, 1 H), 2.06 (t, *J* = 2.8 Hz, 1 H), 1.40 (s, 3 H), 1.34 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.3, 79.8, 77.2, 71.2, 70.0, 65.8, 26.6, 25.1, 23.5.

HRMS (CI): *m*/*z* $[M + H]^+$ calcd for $C_9H_{15}O_3$: 171.1021; found: 171.1024.

(2*R*,3*S*)-1-((*tert*-Butyldimethylsilyl)oxy)hex-5-yne-2,3-diol (41)

A round-bottom flask was charged with a stir bar, **40** (172 mg, 1.0 mmol), THF (2.0 mL), H_2O (2.0 mL), and TFA (2.0 mL) and the reaction was stirred overnight. All solvents were then removed and the crude product was purified by column chromatography (DCM/EtOH, 10:1). To the triol was added DCM (3.6 mL), TEA (0.3 mL), and a crystal of DMAP. The mixture was stirred under argon and cooled to 0 °C, subsequently TBS-Cl (180 mg, 1.2 mmol) was added portionwise and the reaction was allowed to warm to r.t. and stirred overnight. After the reaction reached completion, the mixture was diluted with DCM (10 mL), rinsed with sat. NH_4Cl (×1), H_2O (×1), brine, and dried over $MgSO_4$. The solvents were removed and the crude oil was purified by flash chromatography (0–50% EtOAc in hexanes) to give the product.

Yield: 125 mg (52% overall from **40**); clear oil; R_f = 0.65 (hexanes/EtOAc, 1:1); $[\alpha]_D$ +6.0 (*c* = 1.0, CH_2Cl_2).

IR: 3413, 3312, 2953, 2929, 2858, 1471, 1463, 1361, 1253, 1055, 834, 776 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.78 (m, 3 H), 3.64 (dt, *J* = 6.8, 4.4 Hz, 1 H), 2.55 (m, 2 H), 2.48 (br m, 2 H), 2.05 (t, *J* = 2.8 Hz, 1 H), 0.90 (s, 9 H), 0.09 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 80.3, 72.3, 71.0, 70.6, 63.8, 25.8, 23.6, 18.2, –5.4, –5.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{24}O_3Si$: 245.1567; found: 245.1570.

(4*R*,5*S*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(prop-2-yn-1-yl)-1,3-dioxolan-2-one (38-1)

A solution of DCM (30 mL) and triphosgene (1.42 g, 4.77 mmol) was cooled to –10 °C, after which pyridine (1.6 mL, 19.1 mmol), and DMAP (one crystal) were added. Compound **41** (1.11 g, 4.54 mmol) in DCM (30 mL) was added dropwise and the resulting mixture was stirred for 2 h at r.t. The mixture was then diluted with DCM (30 mL) and washed with sat. NH_4Cl (×1), sat. $NaHCO_3$ (×1), brine (×1), and dried over Na_2SO_4. The solvent was then removed and the crude compound was purified by column chromatography (0–50% EtOAc in hexanes) to give the product.

Yield: 730 mg (59%); off-white solid; mp 52 °C; R_f = 0.45 (hexanes/EtOAc, 2:1); $[\alpha]_D$ +39.7 (*c* = 1.0, DCM).

IR: 3295, 2930, 2858, 1798, 1471, 1365, 1255, 1172, 1146, 1074, 1003, 836, 770 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.85 (m, 1 H), 4.69 (m, 1 H), 4.06 (dd, *J* = 12, 2.0 Hz, 1 H), 3.97 (dd, *J* = 12, 3.6 Hz, 1 H), 2.97 (ddd, *J* = 17, 8.4, 2.8 Hz, 1 H), 2.86 (ddd, *J* = 17, 5.6, 2.8 Hz, 1 H), 2.09 (t, *J* = 2.8 Hz, 1 H), 0.89 (s, 9 H), 0.10 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.9, 77.8, 77.5, 76.1, 71.9, 60.3, 25.6, 19.0, 17.9, –5.7, –5.7.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{22}O_4SiNa$: 293.1180; found: 293.1182.

(4*S*,5*R*)-4-(3-Bromoprop-2-yn-1-yl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,3-dioxolan-2-one (38)

Prepared according to General Procedure A.

Yield: 625 mg (66%); white solid; mp 68 °C; R_f = 0.45 (hexanes/EtOAc, 2:1); $[\alpha]_D$ +45.0 (*c* = 1.0, $CHCl_3$).

IR: 3491, 2954, 2858, 1797, 1471, 1176, 1074, 838, 770 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.83 (m, 1 H), 4.68 (m, 1 H), 4.00 (dd, *J* = 12, 2.0 Hz, 1 H), 3.94 (dd, *J* = 12, 3.6 Hz, 1 H), 2.97 (dd, *J* = 16.8, 8.4 Hz, 1 H), 2.88 (dd, *J* = 16.8, 5.6 Hz, 1 H), 0.88 (s, 9 H), 0.09 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.8, 77.7, 75.9, 73.5, 60.3, 42.3, 25.5, 20.2, 17.9, –5.7.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{21}BrO_4SiNa$: 371.0285; found: 371.0286.

(*S*,*E*)-1-(6-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxyhex-3-en-1-yn-1-yl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1*H*-pyrrole-2-carbonitrile (42)

Prepared according to General Procedure B.

Yield: 7.7 mg (8%); pale oil; R_f = 0.5 (hexanes/EtOAc, 2:1); $[\alpha]_D$ +3.0 (c = 0.08, DCM).

IR: 3499, 2929, 2857, 2225, 1811, 1438, 1255, 1109, 1005, 956, 837, 778 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.77 (d, *J* = 4.0 Hz, 1 H), 6.22 (dd, *J* = 16, 5.2 Hz, 1 H), 6.18 (d, *J* = 4.0 Hz, 1 H), 6.02 (dd, *J* = 16, 1.6 Hz, 1 H), 4.68 (s, 2 H), 4.29 (m, 1 H), 3.71 (dd, *J* = 10, 4.0 Hz, 1 H), 3.47 (dd, *J* = 10, 7.6 Hz, 1 H), 2.64 (d, *J* = 4.0 Hz, 1 H), 0.91 (s, 9 H), 0.90 (s, 9 H), 0.09 (s, 6 H), 0.08 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.6, 141.3, 120.9, 112.2, 109.5, 109.0, 108.1, 77.5, 72.6, 72.0, 66.4, 57.3, 25.8, 25.7, 18.2, –5.3, –5.3.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{40}N_2O_3Si_2Na$: 483.2470; found: 483.2468.

Preparation of Scheme 7 Substrates

Methyl (5*S*,6*R*,*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-5,6-dihydroxyhept-2-enoate (44-1)

To deoxyribopyranose (10.6 g, 80 mmol) in THF (200 mL) was added methyl (triphenylphosphoranylidene)acetate (32.5 g, 96 mmol). The reaction was heated to reflux until completion, then the mixture was cooled and the solvent was removed. The crude residue was then taken up in DCM (5 mL) and cooled in an ice bath. To the cooled solution was added TEA (16.7 mL, 120 mmol), DMAP (one scoop), and TBS-Cl (7.2 g, 48 mmol). The reaction was allowed to warm to r.t. and stirred overnight. The following day the solvents were removed and the residue was purified by column chromatography (0–50% EtOAc in hexanes) to yield the product.

Yield: 9.75 g (80%); clear oil; R_f = 0.1 (hexanes/EtOAc, 4:1); $[\alpha]_D$ –4.9 (*c* = 1.0, DCM).

IR: 3387, 2924, 1704, 1657, 1438, 1275, 1215, 1170, 1066, 1036, 985, 877, 822 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.02 (dt, *J* = 15.6, 7.6 Hz, 1 H), 5.94 (d, *J* = 15.6 Hz, 1 H), 3.81 (m, 1 H), 3.77 (d, *J* = 4.8 Hz, 2 H), 3.73 (s, 3 H), 3.55 (q, *J* = 4.8 Hz, 1 H), 2.54 (m, 1 H), 2.41 (m, 1 H), 2.22 (br s, 2 H), 0.90 (s, 9 H), 0.09 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 145.3, 123.5, 72.8, 71.7, 63.9, 51.5, 36.1, 25.8, 18.1, –5.4, –5.5.

Methyl (*E*)-4-((4*S*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate (44)

A round-bottom flask was charged with a stir bar, **44-1** (9.75 g, 32 mmol), acetone (100 mL), 2,2-dimethoxypropane (15 mL, 120 mmol), and PPTS (2.0 g). The reaction was allowed to stir until completion as determined by TLC (generally 4–6 h). Following completion, a small amount of Na_2CO_3 was added and the solvent was removed. The crude compound was then purified by flash column chromatography (0–15% EtOAc in hexanes) to give the product.

Yield: 9.45 g (86%); clear oil; R_f = 0.45 (hexanes/EtOAc, 6:1); $[\alpha]_D$ –40.9 (*c* = 0.98, DCM).

IR: 2987, 2952, 2930, 2858, 1726, 1660, 1436, 1380, 1322, 1251, 1216, 1166, 1087, 835, 775, 666 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.02 (dt, *J* = 15.6, 7.2 Hz, 1 H), 5.91 (dt, *J* = 15.6, 1.6 Hz, 1 H), 4.25 (m, 1 H), 4.12 (q, *J* = 6.0 Hz, 1 H), 3.72 (s, 3 H), 3.65 (m, 2 H), 2.50 (m, 2 H), 1.41 (s, 3 H), 1.33 (s, 3 H), 0.87 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 145.8, 122.7, 108.2, 77.3, 75.9, 61.5, 51.4, 32.3, 28.0, 25.7, 25.4, 18.1, –5.4, –5.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{33}O_5Si$: 345.2092; found: 345.2098.

2-((4*S*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde (45)

To a round-bottom flask was added a stir bar, **44** (9.45 g, 27.4 mmol), and DCM (150 mL) and the mixture was then cooled to –78 °C. Subsequently, O_3 was bubbled through the solution until the solvent turned blue (ca. 1.5 h), indicating reaction completeness. O_2 was then bubbled through until the solution returned to clear and then the mixture was charged with PPh_3 (8.26 g, 31.5 mmol). The reaction was allowed to warm to r.t. and stirred overnight. The following day the solvent was removed and the residue was purified by flash column chromatography to yield the aldehyde.

Yield: 7.38 g (93%); clear oil; $[\alpha]_D$ –10.5 (*c* = 1.11, DCM).

IR: 2859, 1731, 1223, 1095, 838, 776, 670 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.78 (t, *J* = 1.6 Hz, 1 H), 4.69 (dt, *J* = 8.0, 6.0 Hz, 1 H), 4.16 (dt, *J* = 8.0, 5.6 Hz, 1 H), 3.59 (m, 2 H), 2.85 (ddd, *J* = 17.2, 6.0, 1.2 Hz, 1 H), 2.74 (ddd, *J* = 17.2, 8.0, 2.0 Hz, 1 H), 1.40 (s, 3 H), 1.34 (s, 3 H), 0.86 (s, 9 H), 0.04 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.0, 108.2, 71.9, 61.4, 43.6, 27.8, 25.8, 25.3, 18.1, –5.4, –5.5.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{28}O_4SiNa$: 311.1649; found: 311.1650.

***tert*-Butyl(((4*R*,5*S*)-5-(3,3-dibromoallyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy) dimethylsilane (46-1)**

A round-bottom flask was charged with a stir bar, DCM (10 mL), CBr_4 (3.3 g, 10 mmol), and cooled in an ice bath. Subsequently PPh_3 (5.2 g, 20 mmol) was added and the solution was allowed to warm to r.t. Aldehyde **45** (1.43 g, 4.9 mmol) in CH_2Cl_2 (15 mL) was added dropwise and the reaction was allowed to continue to stir until complete (10 min). Following reaction completion, the reaction was diluted with petroleum ether and the solvents were removed. The crude material was again taken up in petroleum ether and filtered. Following filtration, the solvent was again removed and the residue was purified by column chromatography (short column; 0–10% EtOAc in hexanes) to give the dibromide.

Yield: 1.93 g (88%); $[\alpha]_D$ –33.2 (*c* = 0.98, CH_2Cl_2).

IR: 3463, 2953, 2929, 2857, 1471, 1380, 1251, 1217, 1068, 835, 775, 667 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.55 (dd, *J* = 7.2, 6.4 Hz, 1 H), 4.20 (m, 1 H), 4.12 (dt, *J* = 7.6, 5.6 Hz, 1 H), 3.65 (m, 2 H), 2.47 (ddd, *J* = 15.2, 7.2, 4.4 Hz, 1 H), 2.34 (ddd, *J* = 15.2, 9.2, 6.4 Hz, 1 H), 1.41 (s, 3 H), 1.33 (s, 3 H), 0.88 (s, 9 H), 0.07 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.4, 108.2, 90.0, 77.2, 75.4, 61.3, 33.6, 28.0, 25.8, 25.4, 18.1, –5.4.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{28}Br_2O_3SiNa$: 465.0067; found: 465.0072.

tert-Butyl(((4R,5S)-2,2-dimethyl-5-(prop-2-yn-1-yl)-1,3-dioxolan-4-yl)methoxy)dimethylsilane (46-2)

To an oven-dried round-bottom flask cooled under argon was added a stir bar, **46-1** (1.93 g, 4.34 mmol), THF (22 mL), and then subsequently the mixture was cooled to −78 °C. Once thoroughly cooled, *n*-BuLi (8.15 mL, 13 mmol) was added dropwise down the side of the flask and then the mixture was stirred for 3 h. After reaction completion, the mixture was quenched with sat. NH_4Cl and extracted with EtOAc. The combined organics were washed with brine and dried over Na_2SO_4. Removal of the solvent gave an oil, which was purified by column chromatography (0–15% EtOAc in hexanes) to give the alkyne.

Yield: 1.14 g (92%); clear oil; R_f = 0.55 (hexanes/EtOAc, 5:1); $[\alpha]_D$ −16.7 (c = 0.98, DCM).

IR: 3314, 2929, 2857, 1463, 1380, 1251, 1216, 1075, 833, 776 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.33 (dt, *J* = 8.0, 5.6 Hz, 1 H), 4.16 (q, *J* = 6.1 Hz, 1 H), 3.72 (m, 2 H), 2.59 (ddd, *J* = 16.8, 5.6, 2.8 Hz, 1 H), 2.48 (ddd, *J* = 16.8, 8.0, 2.8 Hz, 1 H), 2.02 (t, *J* = 2.8 Hz, 1 H), 1.46 (s, 3 H), 1.36 (s, 3 H), 0.89 (s, 9 H), 0.06 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 108.5, 81.1, 75.6, 69.6, 61.5, 27.8, 25.8, 25.3, 20.0, 18.2, −5.4, −5.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{28}O_3SiNa$: 307.1700; found: 307.1705.

(((4*R*,5*S*)-5-(3-Bromoprop-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)(*tert*-butyl)dimethylsilane (46)

Prepared according to General Procedure A.

Yield: 1.34 g (91%); pale-yellow oil; $[\alpha]_D$ −2.9 (*c* = 1.01, DCM).

IR: 2930, 2884, 2857, 1471, 1463, 1380, 1370, 1251, 1215, 1075, 1005, 836, 776, 667 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.28 (dt, *J* = 7.2, 6.0 Hz, 1 H), 4.13 (dt, *J* = 7.2, 5.6 Hz, 1 H), 3.72 (dd, *J* = 10.8, 7.2 Hz, 1 H), 3.68 (dd, *J* = 10.8, 5.6 Hz, 1 H), 2.60 (dd, *J* = 16.8, 6.0 Hz, 1 H), 2.48 (dd, *J* = 16.8, 7.2 Hz, 1 H), 1.42 (s, 3 H), 1.33 (s, 3 H), 0.87 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 108.5, 77.2, 76.8, 75.3, 61.4, 39.5, 27.7, 25.8, 25.3, 21.1, 18.1, −5.4, −5.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{27}BrO_3SiNa$: 385.0805; found: 385.0812.

5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-(3-((4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-1-yn-1-yl)-1*H*-pyrrole-2-carbonitrile (47)

Prepared according to General Procedure B.

Yield: 74.5 mg (37%); clear oil; R_f = 0.75 (hexanes/EtOAc, 2:1); $[\alpha]_D$ −6.4 (*c* = 0.67, DCM).

IR: 2953, 2930, 2857, 2224, 1471, 1440, 1379, 1253, 1214, 1077, 1005, 836, 777 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.73 (d, *J* = 4.0 Hz, 1 H), 6.14 (d, *J* = 4.0 Hz, 1 H), 4.69 (s, 2 H), 4.39 (dt, *J* = 8.4, 5.6 Hz, 1 H), 4.19 (q, *J* = 6.0 Hz, 1 H), 3.76 (d, *J* = 6.0 Hz, 2 H), 2.85 (dd, *J* = 16.8, 5.2 Hz, 1 H), 2.72 (dd, *J* = 16.8, 8.0 Hz, 1 H), 1.46 (s, 3 H), 1.36 (s, 3 H), 0.90 (s, 9 H), 0.88 (s, 9 H), 0.08 (s, 6 H), 0.07 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.4, 120.4, 112.3, 108.9, 108.5, 107.9, 77.2, 75.5, 71.8, 69.6, 61.4, 57.4, 27.8, 25.8, 25.7, 25.3, 19.9, 18.2, 18.1, −5.3, −5.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{46}N_2O_4Si_2Na$: 541.2888; found: 541.2887.

5-(Hydroxymethyl)-1-(3-((4*S*,5*R*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-1-yn-1-yl)-1*H*-pyrrole-2-carbonitrile (48)

A round-bottom flask was charged with **47** (195 mg, 0.37 mmol) a stir bar, and a mixture of THF/H_2O/TFA in a 10:1:1 ratio (1.2 mL). After completion, as determined by TLC, the reaction was carefully quenched with $NaHCO_3$ extracted with EtOAc (3×), and the combined organics were dried over $MgSO_4$. The solvents were removed to give the crude oil, which was further purified by flash column chromatography (50–100% EtOAc in hexanes) to give the title compound.

Yield: 105 mg (98%); R_f = 0.3 (EtOAc); clear oil; $[\alpha]_D$ −16.8 (*c* = 0.63, CH_2Cl_2).

IR: 3446, 2939, 2222, 1439, 1381, 1211, 1071, 793 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.73 (d, *J* = 4.0 Hz, 1 H), 6.19 (d, *J* = 4.0 Hz, 1 H), 4.67 (d, *J* = 14 Hz, 1 H), 4.62 (d, *J* = 14 Hz, 1 H), 4.45 (q, *J* = 6.7 Hz, 1 H), 4.32 (q, *J* = 5.6 Hz, 1 H), 3.88 (dd, *J* = 11.6, 4.8 Hz, 1 H), 3.83 (dd, *J* = 11.6, 5.6 Hz, 1 H), 2.83 (dd, *J* = 16.8, 7.2 Hz, 1 H), 2.74 (dd, *J* = 16.8, 6.8 Hz, 1 H), 1.81 (br s, 2 H), 1.51 (s, 3 H), 1.39 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.4, 120.3, 112.2, 110.1, 108.9, 108.1, 75.3, 71.6, 70.3, 60.9, 56.1, 27.7, 25.2, 20.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{18}N_2O_4Na$: 313.1159; found: 313.1162.

(5*S*)-5-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-4,5-dihydro-1′*H*,3*H*-spiro[furan-2,3′-pyrrolo[1,2-*c*]oxazole]-5′-carbonitrile (50)

Prepared according to General Procedure D.

Yield: 24.1 mg (22%); oily white solid; $[\alpha]_D$ +6.3 (*c* = 0.22, DCM).

IR: 3267, 2987, 2936, 2218, 1774, 1457, 1373, 1263, 1183, 1057, 998, 843, 794, 671 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.93 (d, *J* = 3.2 Hz, 1 H), 5.88 (m, 1 H), 5.03 (m, 1 H), 4.88 (m, 1 H), 4.34 (m, 0.5 H), 4.22 (m, 0.5 H), 4.18–4.05 (m, 2 H), 3.87 (m, 1 H), 2.84–2.75 (m, 1 H), 2.54–2.26 (m, 3 H), 2.22–2.12 (m, 0.5 H), 1.42 (s, 1.5 H), 1.41 (s, 1.5 H), 1.35 (s, 1.5 H), 1.35 (s, 1.5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.7, 138.3, 126.7, 126.6, 118.8, 118.6, 112.8, 112.7, 109.6, 109.5, 99.6, 99.5, 94.9, 94.9, 81.6, 80.8, 77.5, 76.5, 67.2, 65.6, 65.4, 35.1, 34.0, 27.5, 27.2, 26.7, 26.6, 25.2, 25.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{18}N_2O_4Na$: 313.1159; found: 313.1173.

Preparation of Shensongine A

(1*S*,2*S*)-1,2-Bis((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (39-1)

Prepared according to a reported procedure from D-mannitol.[31]

^1H NMR (400 MHz, $CDCl_3$): δ = 4.10 (m, 4 H), 3.96 (m, 2 H), 3.71 (m, 2 H), 2.85 (br s, 2 H), 1.39 (s, 6 H), 1.33 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.3, 76.0, 71.0, 66.6, 26.6, 25.1.

(*R*)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde (39)

Prepared according to a reported procedure.[31]

^1H NMR (400 MHz, $CDCl_3$): δ = 9.71 (d, *J* = 2.0 Hz, 1 H), 4.37 (ddd, *J* = 7.2, 4.4, 2.0 Hz, 1 H), 4.16 (dd, *J* = 8.8, 7.2 Hz, 1 H), 4.09 (dd, *J* = 8.8, 4.8 Hz, 1 H), 1.48 (d, *J* = 0.8 Hz, 3 H), 1.41 (d, *J* = 0.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.7, 111.2, 79.8, 65.5, 26.2, 25.1.

(*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-yn-1-ol (40)

Prepared according to a reported procedure, with freshly made **39**.[30]

Yield: 35.13 g (56%).

Data matches our previous samples and reported data.[30]

(*R*)-4-((*S*)-1-(Benzyloxy)but-3-yn-1-yl)-2,2-dimethyl-1,3-dioxolane (51)

An oven-dried round-bottom flask was cooled under argon and charged with a stir bar, **40** (3.4 g, 20 mmol), and freshly distilled THF (80 mL), and cooled in an ice bath. Once sufficiently cool, NaH (960 mg, 24 mmol) was added in one portion. After 30 min, BnBr (2.87 mL, 24 mmol), and TBAI (370 mg, 1.0 mmol) were added and the reaction was allowed to warm to r.t. and stirred at 50 °C overnight. The reaction was then quenched with NH_4Cl, extracted with EtOAc (×3), and the combined organics were then rinsed with brine and dried over Na_2SO_4. Removing the solvent and purification of the crude material by column chromatography (0–50% EtOAc in hexanes) gave the title compound.

Yield: 3.54 g (68%); clear oil; $[\alpha]_D$ +43.7 (*c* = 1.11, DCM).

IR: 3290, 2882, 1959, 1454, 1380, 1272, 1212, 1073, 1027, 860, 741, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 5 H), 4.79 (d, *J* = 11.2 Hz, 1 H), 4.59 (d, *J* = 11.2 Hz, 1 H), 4.20 (dd, *J* = 12.4, 6.8 Hz, 1 H), 4.07 (dd, *J* = 8.4, 6.4 Hz, 1 H), 3.90 (dd, *J* = 8.4, 5.6 Hz, 1 H), 3.56 (dt, *J* = 7.2, 4.8 Hz, 1 H), 2.64 (ddd, *J* = 17.2, 4.8, 2.8 Hz, 1 H), 2.52 (ddd, *J* = 17.2, 5.2, 2.8 Hz, 1 H), 2.04 (t, *J* = 2.8 Hz, 1 H), 1.40 (s, 3 H), 1.35 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8, 128.3, 127.9, 127.8, 109.2, 80.4, 77.4, 76.3, 72.3, 70.3, 66.6, 26.7, 25.2, 20.9.

(2*R*,3*S*)-3-(Benzyloxy)hex-5-yne-1,2-diol (52-1)

A round-bottom flask was charged with a stir bar, **51** (3.54 g, 13.6 mmol), MeOH (50 mL), and 1N HCl (10 mL) and allowed to stir until completion (TLC). Following reaction completion, K_2CO_3 (1.9 g) was added and the mixture was stirred for 10 min. Solvents were removed and then the diol was taken up in water and extracted back out with DCM (×3), the combined organics were rinsed with brine (×1), and dried over $MgSO_4$. Removing the solvents gave the desired diol, which was used without further purification.

$[\alpha]_D$ +47.5 (*c* = 1.48, DCM).

IR: 3291, 2921, 1956, 1453, 1344, 1271, 1209, 1070, 859, 739, 713, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 5 H), 4.74 (d, *J* = 11.2 Hz, 1 H), 4.53 (d, *J* = 11.2 Hz, 1 H), 3.83 (m, 1 H), 3.75 (dd, *J* = 11.6, 3.6 Hz, 1 H), 3.70 (dd, *J* = 11.6, 5.6 Hz, 1 H), 3.63 (q, *J* = 5.6 Hz, 1 H), 2.73 (br s, 2 H), 2.58 (dd, *J* = 5.6, 2.8 Hz, 2 H), 2.04 (t, *J* = 2.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5, 128.4, 127.9, 80.4, 77.9, 72.3, 721, 70.5, 63.1, 20.3.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{16}O_3Na$: 243.0992; found: 243.0984.

(2*R*,3*S*)-3-(Benzyloxy)-1-((triisopropylsilyl)oxy)hex-5-yn-2-ol (52)

A round-bottom flask was charged with a stir bar, **52-1** (crude from previous step), DMF (50 mL), imidazole (3.7 g, 54 mmol), and cooled to 0 °C. TIPS-Cl (3.1 mL, 13.6 mmol), was then added dropwise and the reaction was warmed to r.t. and stirred overnight. The reaction was then diluted with NH_4Cl (200 mL) and extracted with Et_2O (×3). The combined organics were then washed with water (×2), brine (×1), and dried over Na_2SO_4. Removal of the solvent and purification by column chromatography gave the title compound.

Yield: 4.73 g (92%; two steps); clear oil; R_f = 0.55 (hexanes/EtOAc, 6:1); $[\alpha]_D$ +32.2 (*c* = 1.04, DCM).

IR: 3469, 3312, 2942, 2866, 1462, 1384, 1366, 1247, 1207, 1090, 1064, 1013, 995, 881, 792, 735, 679 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 5 H), 4.78 (d, *J* = 11.2 Hz, 1 H), 4.54 (d, *J* = 11.2 Hz, 1 H), 3.87 (m, 1 H), 3.76 (m, 2 H), 3.58 (m, 1 H), 2.71 (ddd, *J* = 17.2, 4.4, 2.8 Hz, 1 H), 2.59 (ddd, *J* = 17.2, 5.2, 2.8 Hz, 1 H), 2.09 (br s, 1 H), 2.03 (t, *J* = 2.8 Hz, 1 H), 2.05 (m, 21 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 128.3, 127.9, 127.7, 81.1, 76.9, 72.2, 72.0, 69.9, 63.8, 20.4, 17.9, 11.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{36}O_3SiNa$: 399.2326; found: 399.2334.

(((2*R*,3*S*)-2,3-Bis(benzyloxy)hex-5-yn-1-yl)oxy)triisopropylsilane (53)

An oven-dried round-bottom flask was cooled under argon and charged with a stir bar, **52** (2.72 g, 7.2 mmol), THF (40 mL), and then cooled to 0 °C. After adequate cooling, NaH (347 mg, 8.6 mmol) was carefully added in portions and, after 5 min, the reaction was allowed to warm to r.t. and stirring was continued for an additional 30 min. Subsequently, the reaction was cooled to 0 °C and BnBr (1.2 mL, 10.1 mmol) was added. The reaction was then allowed to warm to r.t. and stirred overnight. The reaction was then quenched with sat. NH_4Cl and the mixture was extracted with EtOAc (×3). The combined organics were washed with brine and dried over Na_2SO_4, removal of the solvents and purification by column chromatography (0–25% EtOAc in hexanes) gave the title compound.

Yield: 2.36 g (70%); clear oil; $[\alpha]_D$ –2.2 (*c* = 1.0, DCM).

IR: 3310, 3031, 2944, 2866, 2130, 1495, 1457, 1386, 1270, 1205, 1095, 1069, 1029, 882, 745, 695 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.25 (m, 10 H), 4.80 (d, *J* = 11.2 Hz, 1 H), 4.73 (d, *J* = 11.6 Hz, 1 H), 4.65 (d, *J* = 11.2 Hz, 1 H), 4.58 (d, *J* = 11.6 Hz, 1 H), 3.95 (dd, *J* = 10.6, 4.0 Hz, 1 H), 3.81 (dd, *J* = 10.6, 5.6 Hz, 1 H), 3.75 (q, *J* = 5.6 Hz, 1 H), 3.70 (m, 1 H), 2.60 (m, 2 H), 1.98 (t, *J* = 2.8 Hz, 1 H), 1.05 (m, 21 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 138.2, 128.2, 128.2, 127.9, 127.9, 127.6, 127.5, 81.5, 80.5, 73.2, 72.3, 69.8, 63.2, 20.4, 18.0, 11.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{29}H_{42}O_3SiNa$: 489.2795; found: 489.2791.

(((2*R*,3*S*)-2,3-Bis(benzyloxy)-6-bromohex-5-yn-1-yl)oxy)triisopropylsilane (54)

Prepared according to General Procedure A.

Yield: 2.45 g (89%); $[\alpha]_D$ –15.5 (*c* = 1.1, DCM).

IR: 3065, 3032, 2943, 2867, 1454, 1268, 1094, 1068, 1026, 882, 782, 735, 695 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.26 (m, 10 H), 4.79 (d, *J* = 11.6 Hz, 1 H), 4.70 (d, *J* = 11.6 Hz, 1 H), 4.64 (d, *J* = 11.6 Hz, 1 H), 4.58 (d, *J* = 11.6 Hz, 1 H), 3.95 (dd, *J* = 10.8, 4.0 Hz, 1 H), 3.83 (dd, *J* = 10.8, 5.6 Hz, 1 H), 3.76 (m, 1 H), 3.68 (m, 1 H), 2.65 (dd, *J* = 17.2, 4.8 Hz, 1 H), 2.60 (dd, *J* = 17.2, 5.6, 1 H), 1.08 (m, 21 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 138.0, 128.3, 128.2, 128.0, 127.9, 127.6, 127.5, 80.3, 77.5, 76.6, 73.1, 72.3, 63.0, 39.1, 21.6, 18.0, 11.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{42}BrO_3Si$: 545.2081; found: 545.2092.

(((2*R*,3*S*)-2,3-Bis(benzyloxy)-6-chlorohex-5-yn-1-yl)oxy)triisopropylsilane (54-1)

To an oven-dried round-bottom flask was added a stir bar, **53** (233.4 mg, 0.5 mmol) and freshly distilled THF (2.0 mL). The mixture was cooled to –10 °C and *n*-BuLi (0.6 mmol) was added dropwise. The reaction was then allowed to come to 0 °C and stirred for 45 min, after which NCS (106 mg, 0.8 mmol) was added in one portion. The reaction was then allowed to come to r.t. and stirred for an additional 1.5 h. After reaction completion, the mixture was quenched with sat. NH_4Cl, extracted with EtOAc (×3), washed with brine, and dried over Na_2SO_4. The solvents were removed and the residue was purified by column chromatography (0–10% EtOAc in hexanes) to give the title compound.

Yield: 117.3 mg (47%); clear oil; R_f = 0.4 (hexanes/EtOAc, 15:1); $[\alpha]_D$ –17.3 (*c* = 0.62, DCM).

IR: 3055, 3022, 2943, 2866, 1455, 1270, 1098, 1067, 882, 784, 734, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.25 (m, 10 H), 4.79 (d, *J* = 11.6 Hz, 1 H), 4.68 (d, *J* = 11.6 Hz, 1 H), 4.63 (d, *J* = 11.6 Hz, 1 H), 4.57 (d, *J* = 11.6 Hz, 1 H), 3.94 (dd, *J* = 10.8, 4.0 Hz, 1 H), 3.83 (dd, *J* = 10.8, 5.2 Hz, 1 H), 3.74 (q, *J* = 5.6 Hz, 1 H), 3.66 (m, 1 H), 2.59 (m, 2 H), 1.07 (m, 21 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4, 138.1, 128.3, 128.2, 128.0, 127.9, 127.6, 127.5, 80.3, 73.1, 72.3, 66.9, 63.0, 58.3, 20.7, 18.0, 11.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{29}H_{41}ClO_3SiNa$: 523.2406; found: 523.2397.

(((2*R*,3*S*)-2,3-Bis(benzyloxy)-6-iodohex-5-yn-1-yl)oxy)triisopropylsilane (54-2)

By following the procedure described for **54-1** (using I_2 in place of NCS) the title compound was isolated.

Yield: 174.1 mg (59%); clear oil; R_f = 0.45 (hexanes/toluene, 1:1); $[\alpha]_D$ –19.4 (*c* = 1.08, CH_2Cl_2).

IR: 3031, 2943, 2863, 1463, 1365, 1271, 1070, 1013, 883, 808, 735, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.25 (m, 10 H), 4.77 (d, *J* = 11.2 Hz, 1 H), 4.68 (d, *J* = 11.6 Hz, 1 H), 4.62 (dd, *J* = 11.2 Hz, 1 H), 4.57 (dd, *J* = 11.6 Hz, 1 H), 3.93 (dd, *J* = 10.8, 4.4 Hz, 1 H), 3.81 (dd, *J* = 10.8, 5.6 Hz, 1 H), 3.75 (m, 1 H), 3.66 (m, 1 H), 2.79 (dd, *J* = 17.2, 4.8 Hz, 1 H), 2.74 (dd, *J* = 17.2, 6.0 Hz, 1 H), 1.06 (m, 21 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4, 138.1, 128.3, 128.2, 128.0, 127.9, 127.6, 127.5, 91.7, 80.4, 76.9, 73.1, 72.3, 63.1, 22.7, 18.0, 11.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{29}H_{41}IO_3SiNa$: 615.1762; found: 615.1761.

1-((4*S*,5*R*)-4,5-Bis(benzyloxy)-6-((triisopropylsilyl)oxy)hex-1-yn-1-yl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1*H*-pyrrole-2-carbonitrile (55)

Prepared according to General Procedure B, using 4,7-dimethoxy-1,10-phenanthroline as the ligand, K_3PO_4 as the base and 115 °C for the temperature.

Yield: 71.5 mg (51%); pale oil; $[\alpha]_D$ –10.0 (*c* = 1.0, DCM).

IR: 3032, 2929, 2864, 2224, 1496, 1460, 1441, 1362, 1321, 1255, 1212, 1091, 1004, 836, 737, 695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.21 (m, 10 H), 6.74 (d, *J* = 4.0 Hz, 1 H), 6.15 (dd, *J* = 4.0, 0.8 Hz, 1 H), 4.81 (d, *J* = 11.6 Hz, 1 H), 4.77 (d, *J* = 11.6 Hz, 1 H), 4.69 (d, *J* = 11.6 Hz, 1 H), 4.64 (s, 2 H), 4.63 (d, *J* = 11.6 Hz, 1 H), 4.00 (dd, *J* = 10.8, 4.0 Hz, 1 H), 3.87 (m, 2 H), 3.73 (m, 1 H), 2.84 (m, 2 H), 1.08 (m, 21 H), 0.89 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.5, 138.5, 138.2, 128.2, 128.2, 127.9, 127.8, 127.5, 127.5, 120.3, 112.5, 108.7, 107.8, 80.5, 76.9, 73.1, 72.5, 72.3, 69.5, 63.0, 57.6, 25.7, 20.4, 18.2, 18.0, 11.9, –5.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{41}H_{60}N_2O_4Si_2Na$: 701.4164; found: 701.4179.

1-((4*S*,5*R*)-4,5-Bis(benzyloxy)-6-hydroxyhex-1-yn-1-yl)-5-(hydroxymethyl)-1*H*-pyrrole-2-carbonitrile (56)

Prepared according to General Procedure C.

Yield: 139.8 mg (93%); clear oil; $[\alpha]_D$ +7.1 (*c* = 1.01, DCM).

IR: 3420, 3030, 2875, 2222, 1439, 1319, 1208, 1094, 1024, 791, 747, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.24 (m, 10 H), 6.72 (d, *J* = 4.0 Hz, 1 H), 6.15 (d, *J* = 4.0 Hz, 1 H), 4.72 (d, *J* = 11.2 Hz, 1 H), 4.69 (d, *J* = 11.6 Hz, 1 H), 4.64 (d, *J* = 11.6 Hz, 1 H), 4.62 (d, *J* = 11.2 Hz, 1 H), 4.50 (d, *J* = 13.6 Hz, 1 H), 4.45 (d, *J* = 13.6 Hz, 1 H), 3.93–3.78 (m, 3 H), 3.73 (m, 1 H), 2.88 (dd, *J* = 17.2, 4.8 Hz, 1 H), 2.83 (dd, *J* = 17.2, 4.0 Hz, 1 H), 2.36 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.2, 137.5, 137.2, 128.5, 128.4, 128.1, 128.0, 127.9, 120.2, 112.3, 109.8, 107.9, 79.1, 76.1, 72.5, 72.3, 71.4, 70.3, 60.5, 56.0, 20.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{26}N_2O_4$: 453.1785; found: 453.1789.

(2*S*,4*S*,5*R*)-4,5-Bis(benzyloxy)-3,4,5,6-tetrahydro-1′*H*,4′*H*-spiro[pyran-2,3′-pyrrolo[2,1-*c*][1,4]oxazine]-6′-carbonitrile (57)

Prepared according to General Procedure D.

Yield: 84.2 mg (60%); pale oil; $[\alpha]_D$ –117.5 (*c* = 0.56, DCM).

IR: 3031, 2922, 2215, 1453, 1374, 1166, 1183, 1050, 742, 695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.26 (m, 10 H), 6.79 (d, *J* = 4.0 Hz, 1 H), 5.90 (d, *J* = 4.0 Hz, 1 H), 4.85–4.59 (m, 4 H), 4.58 (d, *J* = 12 Hz, 1 H), 4.55 (d, *J* = 12 Hz, 1 H), 4.21 (d, *J* = 12.6 Hz, 1 H), 3.99 (ddd, *J* = 11.6, 4.8, 2.8 Hz, 1 H), 3.93 (dd, *J* = 12.4, 2.4 Hz, 1 H), 3.84 (d, *J* = 12.6, 1 H), 3.76 (m, 1 H), 3.56 (dd, *J* = 12.4, 0.8 Hz, 1 H), 2.27 (t, *J* = 12 Hz, 1 H), 2.06 (dd, *J* = 12.8, 4.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2, 138.0, 130.2, 128.4, 128.3, 127.7, 127.6, 127.6, 127.3, 119.7, 113.3, 103.5, 101.9, 95.7, 72.5, 71.4, 70.7, 70.2, 62.6, 57.8, 50.7, 33.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{26}N_2O_4Na$: 453.1785; found: 453.1783.

(2*S*,4*S*,5*R*)-4,5-Bis(benzyloxy)-3,4,5,6-tetrahydro-1′*H*,4′*H*-spiro[pyran-2,3′-pyrrolo[2,1-*c*][1,4]oxazine]-6′-carbaldehyde (6-1)

A flame-dried vial was allowed to cool under argon and subsequently charged with a stir bar, **57** (78.4 mg, 0.18 mmol), and anhydrous DCM (1.0 mL). The solution was cooled to 0 °C and 1 M DIBAL-H in hexanes (0.45 mmol, 2.5 equiv) was added dropwise over 5 min. Immediately following the addition of DIBAL-H, the reaction was allowed to warm and stirred for 45 min. Following completion, the reaction was quenched with EtOAc and allowed to stir for 15 min. After quenching, a Fieser workup was performed (7 μL H_2O, followed by 7 μL 15% NaOH, followed by 18 μL H_2O). The reaction was further diluted with

EtOAc and washed with sat. NH_4Cl, brine, and dried over Na_2SO_4. Removal of the solvents and purification of the residue by column chromatography (0–50% EtOAc in hexanes) gave the title compound.

Yield: 47.7 mg (61%); clear oil; $[\alpha]_D$ –134.6 (*c* = 0.43, DCM).

IR: 2869, 1655, 1453, 1317, 1188, 1051, 741, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.45 (s, 1 H), 7.41–7.26 (m, 10 H), 6.90 (d, *J* = 4.0 Hz, 1 H), 5.99 (d, *J* = 4.0 Hz, 1 H), 4.83–4.66 (m, 5 H), 4.59 (d, *J* = 12 Hz, 1 H), 4.56 (d, *J* = 12 Hz, 1 H), 4.03 (d, *J* = 14.4 Hz, 1 H), 3.99 (ddd, *J* = 11.6, 4.8, 2.4 Hz, 1 H), 3.93 (dd, *J* = 12.4, 2.4 Hz, 1 H), 3.75 (br s, 1 H), 3.57 (d, *J* = 12 Hz, 1 H), 2.30 (t, *J* = 12 Hz, 1 H), 2.05 (dd, *J* = 12.6, 4.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.5, 138.3, 138.2, 134.2, 131.1, 128.3, 128.3, 127.6, 127.5, 127.5, 127.3, 123.8, 104.6, 95.6, 72.7, 71.3, 71.0, 70.1, 62.4, 57.6, 52.3, 33.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{28}NO_5$: 434.1962; found: 434.1964.

(2*S*,4*S*,5*R*)-4,5-Dihydroxy-3,4,5,6-tetrahydro-1′*H*,4′*H*-spiro[pyran-2,3′-pyrrolo[2,1-*c*][1,4]oxazine]-6′-carbaldehyde (Shensongine A, 6)

An oven-dried round-bottom flask was charged with a stir bar and allowed to cool under argon. The flask was then charged with **6-1** (44.4 mg, 0.1 mmol) and anhydrous DCM (0.1 mL) and allowed to cool to –78 °C. After adequate cooling, 1 M $TiCl_4$ in CH_2Cl_2 (2.04 mmol) was added dropwise and the reaction was allowed to continue stirring at –78 °C for 1.5 h. Subsequently, the reaction was brought to 0 °C in an ice bath and stirring was continued for 6 h. Upon reaction completion, sat. $NaHCO_3$ was added and the mixture was extracted with EtOAc (×3). The combined organics were then washed with brine and dried over $MgSO_4$. Removal of the solvent and purification by column chromatography (10–100% EtOAc in hexanes) provided shensongine A (**6**) with spectroscopic data that was consistent with the reported data.[5,6]

Yield: 18.1 mg (70%); white solid; mp 105 °C (decomp.); $[\alpha]_D$ –186.5 (*c* = 0.37, MeOH).

IR: 3397, 1648, 1501, 1408, 1319, 1184, 1082, 1045, 975, 849, 728 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.42 (s, 1 H), 6.91 (d, *J* = 4.0 Hz, 1 H), 6.00 (d, *J* = 4.0 Hz, 1 H), 4.81 (d, *J* = 15.6 Hz, 1 H), 4.71 (m, 2 H), 4.15 (m, 1 H), 4.00 (d, *J* = 14 Hz, 1 H), 3.88 (m, 2 H), 3.79 (dd, *J* = 12.8, 1.2 Hz, 1 H), 2.19 (br s, 2 H), 2.04 (dd, *J* = 12.8, 5.4 Hz, 1 H), 1.92 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7, 134.2, 130.9, 124.2, 104.8, 95.3, 67.3, 65.0, 64.5, 57.7, 52.1, 35.6.

^1H NMR (400 MHz, CD_3OD): δ = 9.36 (s, 1 H), 7.01 (d, *J* = 4.0 Hz, 1 H), 6.06 (d, *J* = 4.0 Hz, 1 H), 4.83 (d, *J* = 15.6 Hz, 1), 4.73 (dd, *J* = 15.6, 0.8 Hz, 1 H), 4.59 (dd, *J* = 14 Hz, 1 H), 4.07 (ddd, *J* = 11.6, 5.6, 2.8 Hz, 1 H), 3.96 (d, *J* = 14 Hz, 1 H), 3.80 (dd, *J* = 11.6, 1.2 Hz, 1 H), 3.78 (m, 1 H), 3.75 (dd, *J* = 11.6, 1.6 Hz, 1 H), 1.98 (dd, *J* = 12.8, 11.6 Hz, 1 H), 1.89 (dd, *J* = 12.8, 5.2 Hz, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 180.4, 137.3, 132.7, 126.0, 106.4, 96.9, 68.9, 66.5, 66.3, 58.8, 53.7, 36.3.

^1H NMR (400 MHz, acetone-d_6): δ = 9.46 (s, 1 H), 6.96 (d, *J* = 3.2 Hz, 1 H), 6.04 (d, *J* = 3.2 Hz, 1 H), 4.85 (d, *J* = 12.8 Hz, 1 H), 4.74 (d, *J* = 12.8 Hz, 1 H), 4.55 (d, *J* = 11.2 Hz, 1 H), 4.06 (m, 1 H), 3.94 (d, *J* = 11.2 Hz, 1 H), 3.88–3.72 (m, 3 H), 1.98 (m, 1 H), 1.91 (dd, *J* = 10, 4.0 Hz, 1 H).

^{13}C NMR (100 MHz, acetone-d_6): δ = 179.0, 135.4, 132.1, 124.1, 105.3, 96.2, 68.2, 65.9, 65.5, 58.1, 53.1, 36.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{15}NO_5Na$: 276.0842; found: 276.0852.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611904.

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