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A Selective Intramolecular 5-*exo*-dig or 6-*endo*-dig Cyclization en Route to 2-Furanone or 2-Pyrone Containing Tricyclic Scaffolds

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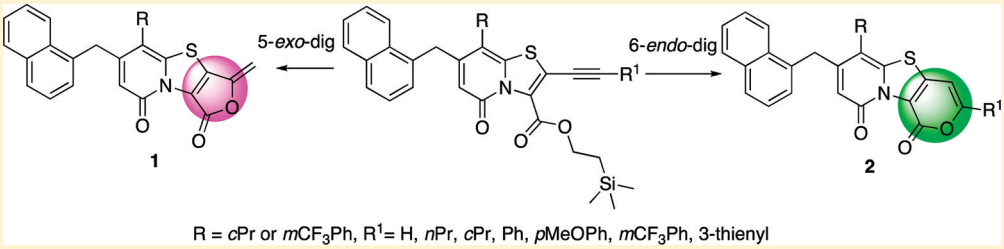
Supporting Information



ABSTRACT: Ringfused bicyclic 2-pyridones exhibit interesting biological properties against pili assembly in uropathogenic *Escherichia coli* (Pinkner, J. S. et al. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 17897−17902; Åberg, V. et al. *Org. Biomol. Chem.* **2007**, *5*, 1827−1834) as well as curli formation (Cegelski, L. et al. *Nat. Chem. Biol.* **2009**, *5*, 913−919). In the search for new ring-fused central fragments, highly selective synthetic routes to the 2-furanone or 2-pyrone containing tricyclic scaffolds **1** and **2** have been developed.

INTRODUCTION

2-Pyridones are commonly found in biologically active natural products[1] (e.g., champtothecin), and they have also attracted researchers for the design and synthesis of peptide backbone mimetics.[2] We have earlier described the synthesis of highly substituted bicyclic dihydro thiazolo ring-fused 2-pyridones **3**−**6** shown in Figure 1.[3−6] These compounds, as their corresponding carboxylic acids, were originally designed to inhibit the formation of pili in uropathogenic *Escherichia coli* by interfering with the chaperone usher pathway.[7] Interestingly, by varying the substitution pattern on these central fragments, compounds with amyloid inhibiting properties could also be synthesized. From this collection, compounds named curlicides were identified that inhibit the formation of bacterial fibers, curli, which are functional amyloid structures.[8]

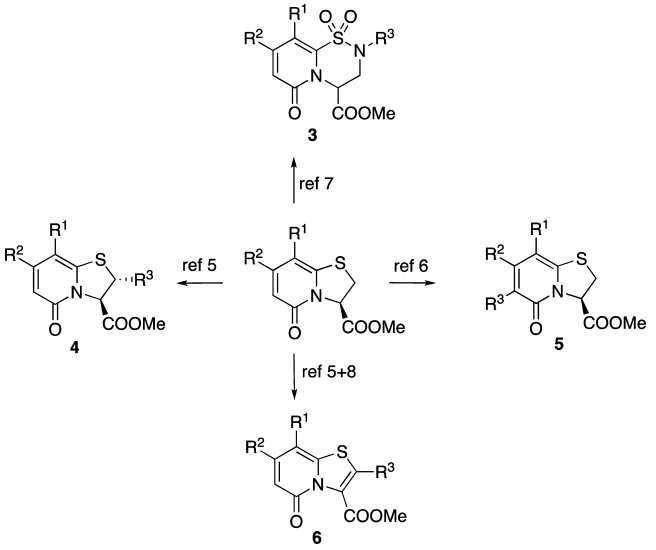


Figure 1. Several methods to selectively introduce substituents onto dihydro thiazolo ring-fused 2-pyridones.

Since there is a tremendous need for new central fragments in drug discovery,[9] we have, in parallel with the development of antibacterial compounds, taken a more general approach to synthesize different rigidified tricyclic peptidomimetic scaffolds based on the 2-pyridone core[10,11] (e.g., **7** and **8**, Figure 2).

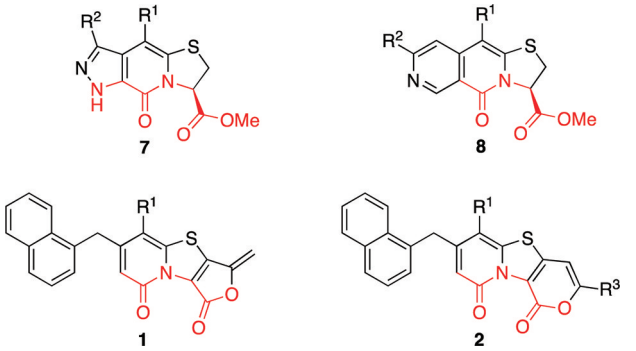


Figure 2. Previously developed tricyclic peptidomimetic scaffolds **7** and **8**, together with the new 2-furanone (**1**) and 2-pyrone (**2**) containing tricyclic scaffolds described in this article. The peptide backbone connectivity is highlighted in red.

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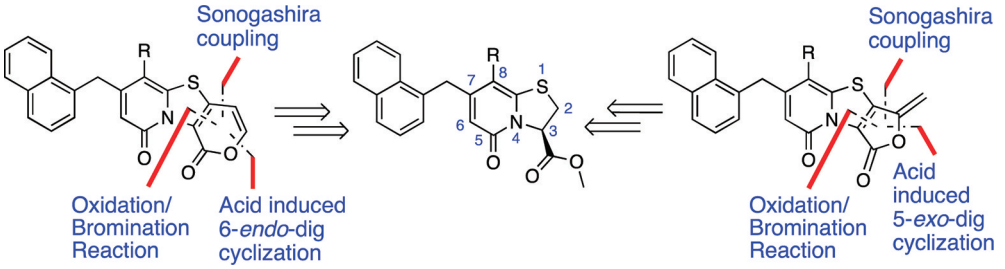
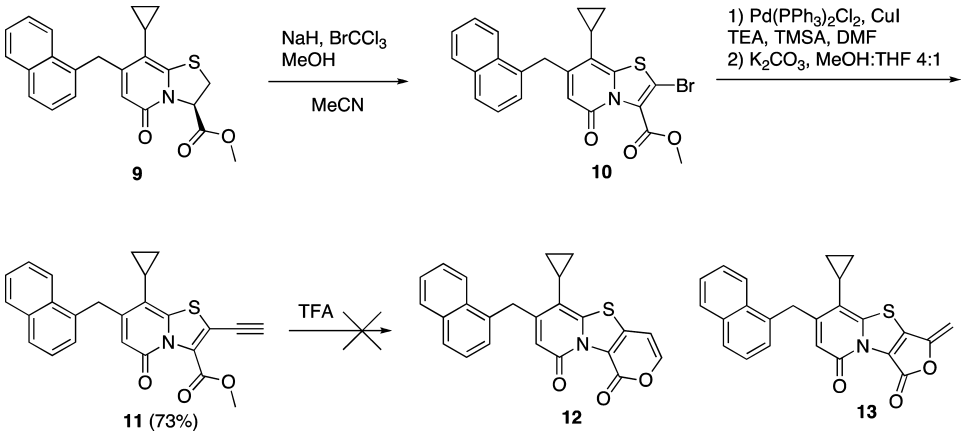
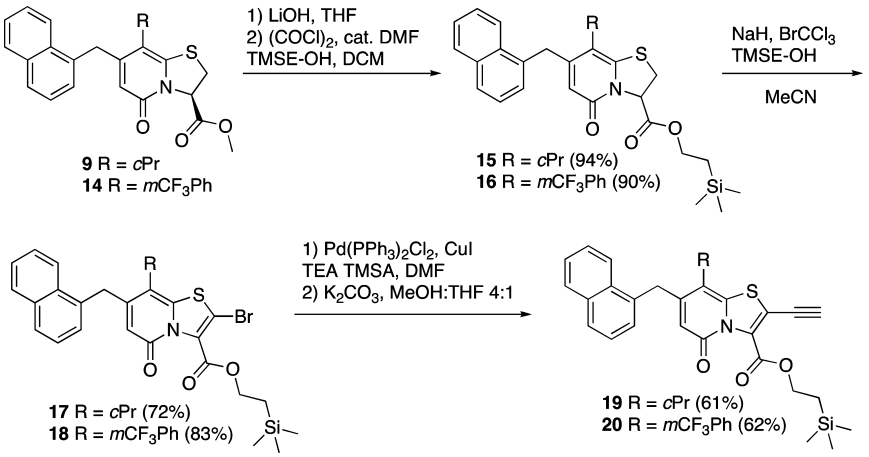


Figure 3. Reterosynthetic strategy to the 2-pyrone or 2-furanone containing tricyclic scaffolds.

Scheme 1. Synthesis of the Acetylene Functionalized Ring-Fused Bicyclic 2-Pyridone and Attempted Cyclization



Scheme 2. Synthesis of the TMSE Protected Key Intermediates



2-Pyrones and 2-furanones are interesting compounds with widespread biological characteristics and are common in many natural products, for instance Terreulactone A[12] and (−)-Tetrodecamycin.[13] In all ring-fused 2-pyridone derived peptidomimetics previously developed in the group, the C-terminal carboxylic ester was positioned in the ring system as a substituent with freedom to rotate (see Figure 1). However, introducing a ring-fused 2-pyrone or 2-furanone to the central fragment would result in a more rigidified scaffold but still with a peptide backbone connectivity. Herein, we present the development of methods to regioselectively synthesize either 2-furanone or 2-pyrone fused tricyclic scaffolds (**1** and **2**, Figure 2). These are two new central fragments, which can be substituted with a variety of substituents, thus having great potential in the future design and synthesis of peptidomimetic compounds.

RESULTS AND DISCUSSION

It is known from the literature that 2-pyrones and 2-furanones can be synthesized via a cyclization of a carboxylic acid ester onto an alkyne.[14] In some cases the selectivity between 5-*exo*-dig and 6-*endo*-dig cyclization is poor, and for the reaction to proceed well, high concentrations of acid and/or high temperatures are demanded.[15] Previously published results show that Pd-catalyzed cross couplings such as the Suzuki–Miyaura[6] and Heck[3] couplings are possible in the 2-position of the ring-fused bicyclic 2-pyridones (Figure 3). On the basis of these results, we envisioned a retrosynthetic strategy starting with an oxidation/bromination reaction, followed by a Sonogashira coupling, and finally an acid induced cyclization onto the acetylene (Figure 3).

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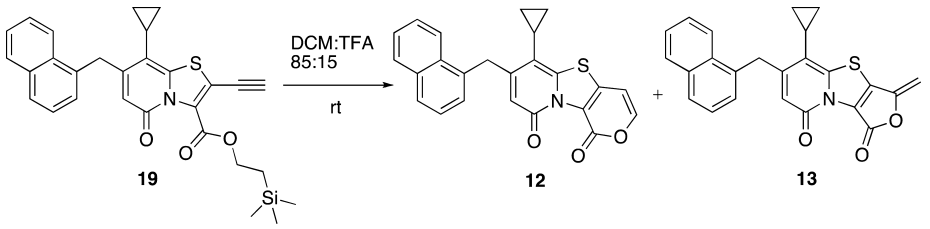
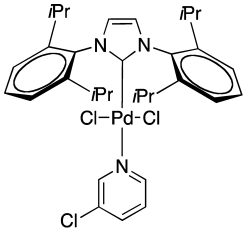
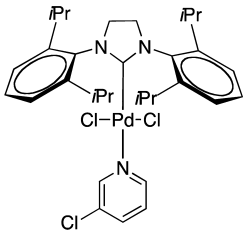
Table 1. Catalyst Screen to Obtain Selectivity in the Cyclization Reaction[a]



entry	catalyst (5 mol %)	ligand (5 mol %)	reaction time (h)	ratio **12**:**13**	conversion (isolated yield) (%)
1	$Pd(OAc)_2$		2	20:80	100[b]
2	$Pd(OAc)_2$	DPPF[c]	2	5:95	100[b]
3	$Pd(OAc)_2$	DPPP	1	>99% of **13**	100 (88)
4	Pd-IPr-NHC		2.5	90:10	100 (88)
5	Pd-SIPr-NHC		2.5	95:5	100[b]
6	$PdCl_2$		2.5	50:50	80[b]
7	$Pd(PPh_3)_2Cl_2$		2.5		complex mixture
8	$Pd(PPh_3)_4$		2		complex mixture
9	$Pd_2(dba)_3$*$CHCl_3$[d]		1.5	20:80	100[b]
10	$PPh_3AuCl/AgSbF_6$		3	5:95	100[b]
11	$AuCl_3$		3	50:50	100[b]



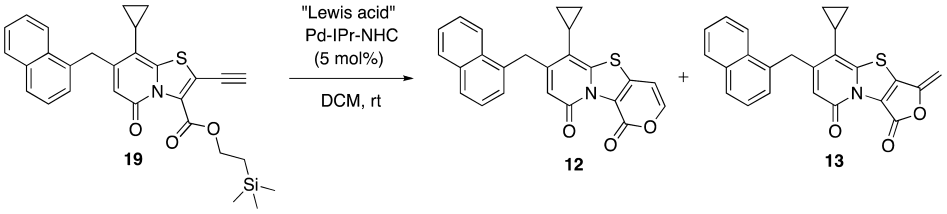
Pd-IPr-NHC



Pd-SIPr-NHC

[a]The reactions were performed in a 10 mg/mL concentration. [b]No byproducts detected by HPLC. [c]DPPF = 1,1′-Bis(diphenylphosphino)ferrocene. [d]dba = dibenzylideneacetone.

Table 2. Lewis Acid Screen[a]



entry	Lewis acid (10 eq)	ratio **12**:**13**	reaction time (h)	comment
1	$ZrCl_4$		18	complex mixture
2	$TiCl_4$		18	only ester deprotection
3	$SnCl_4$		18	complex mixture
4	$TiCl_3$		18	only ester deprotection
5	$InCl_3$	80:20	18	70% starting material
6	SbF_3		18	no reaction
7	*BF_3*Et_2O*	*100% of* ***12***	3	*100% conversion*
8	$SnCl_2$		18	no reaction

[a]The reactions were performed in a 10 mg/mL concentration.

Synthesis of the acetylene functionalized bicyclic 2-pyridone was straightforward and started from the known methylester **9**[16] (Scheme 1). The oxidation/bromination reaction previously reported[6] followed by the $Pd(PPh_3)_2Cl_2$/CuI catalyzed Sonogashira coupling with trimethylsilylacetylene (TMSA) gave **11** in 73% yield. However, the following cyclization to give compounds **12** and **13** did not proceed as expected. Even when using TFA as solvent for 18 h at room temperature, only starting material remained.

We anticipated that the corresponding carboxylic acid would ring-close under milder conditions, hence changing the methyl ester to a more acid labile ester that could withstand the conditions used in the synthetic sequence; our choice was the trimethylsilylethyl ester (TMSE).

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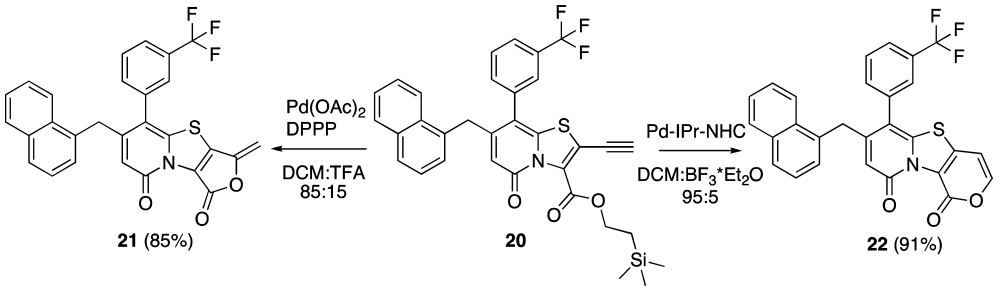
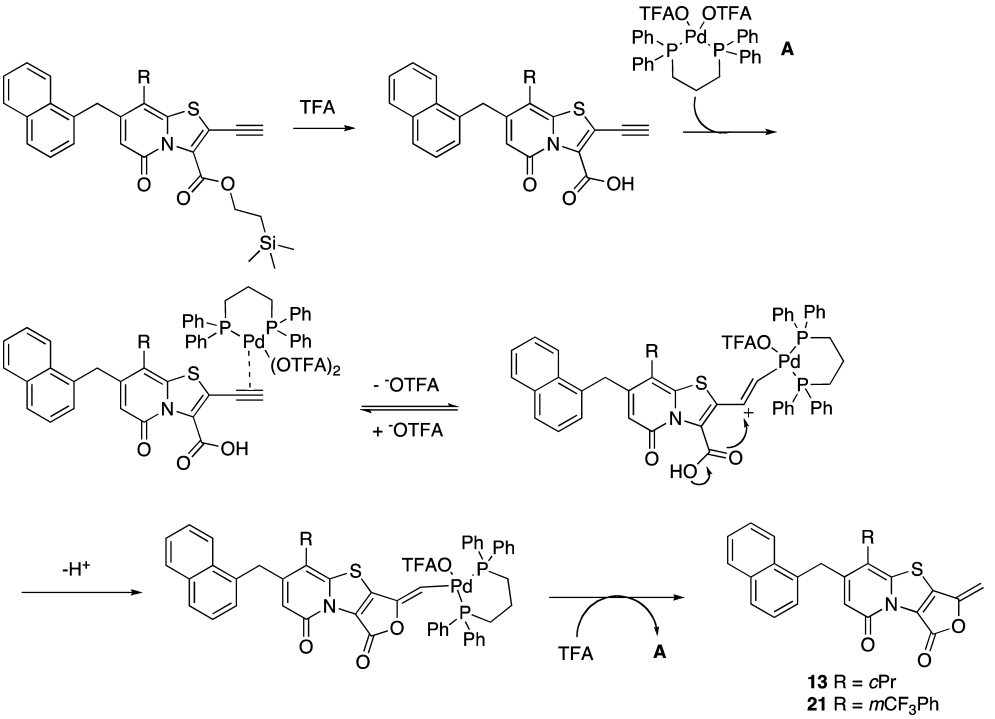
Scheme 3. Selective Cyclizations of the *m*CF_3Ph Substituted Bicyclic 2-Pyridone



Scheme 4. Tentative Mechanism of the $Pd(OAc)_2$/DPPP Catalyzed Selective 5-*exo*-dig Cyclization



The TMSE esters (**15** and **16**) were synthesized via the corresponding acid chlorides to give the racemic TMSE esters **15** and **16** in excellent yields (Scheme 2). The following oxidation/bromination with excess NaH and $BrCCl_3$ in MeCN, previously developed,[6] was slightly modified by changing MeOH for 2-(trimethylsilyl)ethanol (TMSE−OH) because of problems with transesterification. The reaction was yielding surprisingly well, considering that TMSE esters have been reported labile toward NaH in some cases.[17] The bromides **17** and **18** were exposed to a $Pd(PPh_3)_2Cl_2$/CuI catalyzed Sonogashira coupling with TMSA followed by deprotection of the TMS group with K_2CO_3 in MeOH/THF 4:1 to yield the TMSE protected key intermediates **19** and **20** in 61 and 62% yield, respectively (Scheme 2).

To our delight, this time the following ring closure worked, and the 6-*endo*-dig (**12**) and 5-*exo*-dig (**13**) products were obtained in a 1:1 ratio. Since the first conditions (20% TFA in DCM at room temperature) did not give any selectivety, a screen with different catalysts and conditions was performed (Table 1). Although most of the conditions tested resulted in a preference for the 5-*exo*-dig (**13**) product with almost complete selectivity with $Pd(OAc)_2$ and 1,3-bis(diphenylphosphino)-propane (DPPP) (Table 1, entry 3). Catalysts based upon N-heterocyclic carbenes (NHC) gave rewarding selectivity in favor of the 6-*endo*-dig product **12** (Table 1, entries 4 and 5).

In an attempt to further increase the selectivity between 5-*exo*-dig and 6-*endo*-dig cyclization in the Pd-NHC catalyzed reactions, a set of Lewis acid additives were screened, and here BF_3*Et_2O was by far the most effective Lewis acid (Table 2, entry 7). Indeed, complete selectivity for the 6-*endo*-dig product **12** was obtained. As a control, the reaction was also performed without Pd-catalyst, and under these conditions, fast deprotection of the TMSE ester was observed but no cyclization. Even when the BF_3*Et_2O amount was increased to 20%, only TMSE ester deprotection was observed.

Changing the *c*Pr substituent on the 2-pyridone scaffold (**19**) for the more electron withdrawing *m*CF_3Ph substituent (**20**) had a surprisingly large impact on the cyclization rate, even though it is located far away from the reaction center. Under noncatalyzed conditions, the reaction only reached 20% conversion after 18 h reaction at room temperature with DCM/TFA 80:20 as solvent. However, the catalyzed reactions were efficient and carried out with excellent regioselectivity between the 5-*exo*-dig (**21**) and 6-*endo*-dig (**22**) in 1 and 3 h, respectively (Scheme 3).

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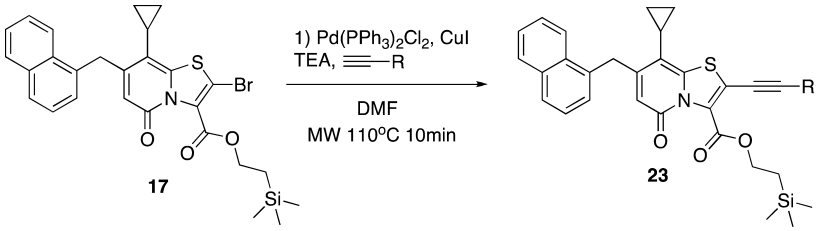
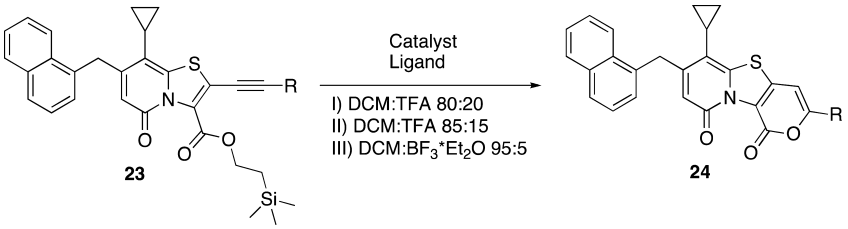
Table 3. Synthesis of the Internal Acetylenes



compound	R	yield (%)
23a	*n*Pr	86
23b	*c*Pr	84
23c	Ph	95
23d	*p*MeOPh	89
23e	*m*CF_3Ph	86
23f	3-thienyl	95

Table 4. Cyclization of the Internal Acetylenes



entry	compound	R	catalyst (5 mol %)	ligand (5 mol %)	solvent	time (h)	conversion (isolated yield) (%)
1	**24a**	*n*Pr			I	28	100 (99)
2	**24a**	*n*Pr	$Pd(OAc)_2$	DPPP	II	1	100[a]
3	**24a**	*n*Pr	Pd-IPr-NHC		III	2	100[a]
4	**24b**	*c*Pr			I	1	100 (99)
5	**24b**	*c*Pr	$Pd(OAc)_2$	DPPP	II	1	100[a]
6	**24b**	*c*Pr	Pd-IPr-NHC		III	4	100[a]
7	**24c**	Ph			I	18	100 (98)
8	**24c**	Ph	$Pd(OAc)_2$	DPPP	II	1	100[a]
9	**24c**	Ph	Pd-IPr-NHC		III	18	100[a]
10	**24d**	*p*MeOPh			I	1	100 (99)
11	**24d**	*p*MeOPh	$Pd(OAc)_2$	DPPP	II	1	100[a]
12	**24d**	*p*MeOPh	Pd-IPr-NHC		III	2.5	100[a]
13	**24e**	*m*CF_3Ph			I	96	90 (88)
14	**24e**	*m*CF_3Ph	$Pd(OAc)_2$	DPPP	II	2	100[a]
15	**24e**	*m*CF_3Ph	Pd-IPr-NHC		III	2	100[a]
16	**24f**	3-thienyl			I	20	100 (99)
17	**24f**	3-thienyl	$Pd(OAc)_2$	DPPP	II	1	100[a]
18	**24f**	3-thienyl	Pd-IPr-NHC		III	1.5	100[a]

[a]No byproducts detected by HPLC.

The mechanism of the selective Pd-IPr-NHC catalyzed 6-*endo*-dig cyclization in DCM/BF_3*Et_2O 95:5 is still not known. The selective $Pd(OAc)_2$/DPPP catalyzed 5-*exo*-dig cyclization is believed to proceed via the Pd(II) catalytic cycle shown in Scheme 4.[18] The $Pd(OAc)_2$/DPPP catalyzed reaction was also performed with 5% TFA in DCM as solvent, but these conditions gave less selectivity, with about 5% of the 6-*endo*-dig product **22** formed.

The great results obtained with the terminal acetylenes, regarding regioselectivity and yields in the ring-forming reaction, encouraged further studies but with substituted acetylenes. Hence, a set of different internal acetylenes was synthesized in high yields from the bromo intermediate **17** (Table 3).

Next, the internal acetylenes **23a**−**f** were exposed to the ring closing procedure under the optimized conditions (Table 4). Surprisingly, the reactions only gave the 6-*endo*-dig products **24a**−**f** regardless of which conditions were used; without catalyst the reaction rates were much slower (Table 4, entries 1, 7, 10, 13, and 16). The faster ring-closure of the *c*Pr substituted acetylene under noncatalyzed conditions (Table 4, entry 4) is attributed to the cation stabilizing properties of the "sp2-like" hybridization of the *c*Pr carbons.[19]

CONCLUSIONS

In conclusion, we have shown that the 2-furanone or the 2-pyrone containing tricyclic scaffolds (**12**, **13**, **21**, **22**) can be synthesized with excellent selectivity in good yields from the

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TMSE protected terminal acetylenes **19** and **20** under Pd-catalysis. In the latter case, it was discovered that exchanging TFA for BF_3*Et_2O as an acidic additive gave complete 6-*endo*-dig selectivity in the Pd-NHC catalyzed reaction. The substituted 2-pyrone tricyclic scaffolds **24a−f** were synthesized in quantitative yields from the corresponding internal acetylenes **23a−f**. This was proven to work excellently for alkyl, cycloalkyl, aryl, and heteroaryl substituted acetylenes. Hence, two new rigid tricyclic central fragments, which both have a peptide backbone connectivity, onto which it is easy to introduce substituents and fuctional groups, have been constructed. These central fragments are interesting in the synthesis of future peptidomimetics.

EXPERIMENTAL SECTION

General Methods. Unless stated otherwise, all reagents and solvents were used as received from commercial suppliers. DMF was distilled under a vacuum and stored over 3 Å molecular sieves. MeCN and MeOH were dried with 3 Å molecular sieves for at least 20 h before use. CuI was purified by refluxing with DCM for 20 h in a Soxhlet apparatus and stored under dark and dry conditions. All HPLC was performed on a C18 reversed-phase column with H_2O/MeCN mixtures as eluent. Microwave heated reactions were performed in a microwave reactor; temperatures were monitored with an IR-probe. TLC was performed on silica gel detected with UV light. Column chromatography was employed on normal phase silica gel (eluents given in brackets). Optical rotation was measured with a polarimeter at 20 °C and 589 nm. IR was recorded on a spectrometer equipped with an ATR device. ^{1}H and ^{13}C NMR spectra were recorded on a 400 or 500 MHz spectrometer at 298 K and calibrated using the residual peak of solvent as internal standard [$CDCl_3$ ($CHCl_3$ δ_H 7.26 ppm, $CDCl_3$ δ_C 77.16 ppm), DMSO-d_6 (DMSO-d_5 δ_H 2.49 ppm, DMSO-d_6 δ_C 39.5 ppm), DCM-d_2 (DCM-d_1 δ_H 5.32 ppm, DCM-d_2 δ_C 53.84 ppm)]. HRMS was performed using a mass spectrometer with electrospray ionization (ES^+); sodiumformate was used as calibration chemical.

Methyl 8-Cyclopropyl-2-ethynyl-7-(naphthalen-1-ylmethyl)-5-oxo-5*H*-thiazolo[3,2-a]pyridine-3-carboxylate (11). Compound **10** (1.73 mmol, 0.81 g), CuI (0.17 mmol, 32 mg), $Pd(PPh_3)_3Cl_2$ (0.09 mmol, 63 mg), and TEA (3.46 mmol, 0.48 mL) were dissolved in dry DMF (15 mL). Ethynyltrimethylsilane (5.19 mmol, 0.73 mL) dissolved in dry DMF (0.5 mL) was added, and the reaction was heated in the microwave oven at 110 °C for 10 min. The reaction mixture was diluted with saturated $NaHCO_3$ (aq) and extracted with EtOAc; the organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude product was dissolved in MeOH/THF 4:1 (15 mL), and K_2CO_3 (1.73 mmol, 239 mg) was added; the reaction was stirred at rt for 15 min. The reaction mixture was diluted with saturated $NaHCO_3$ and extracted with EtOAc; the organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude reaction mixture was purified by column chromatography on silica gel (heptane/EtOAc 90:10 → 70:30) to give the desired compound (0.52 g, 73%) as a yellow foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00−7.92 (m, 1H), 7.92−7.83 (m, 2H), 7.57−7.43 (m, 3H), 7.39−7.31 (m, 1H), 5.56 (s, 1H), 5.15 (s, 1H), 4.55 (s, 2H), 3.82 (s, 3H), 1.89−1.79 (m, 1H), 1.02−0.94 (m, 2H), 0.77−0.70 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.5, 157.1, 155.1, 144.9, 134.3, 133.8, 133.4, 131.4, 128.6, 127.5, 127.4, 126.3, 125.8, 125.6, 123.9, 112.0, 110.1, 108.9, 92.9, 70.5, 53.2, 35.4, 10.6, 7.4 (2C); IR λ 1739, 1655, 1567, 1468, 1430; HRMS (ES) calcd [M + Na] for $C_{25}H_{19}NNaO_3S$ 436.0984, obsd 436.0972.

(3*RS*)-2-(Trimethylsilyl)ethyl 8-Cyclopropyl-7-(naphthalen-1-ylmethyl)-5-oxo-3,5-dihydro-2*H*-thiazolo[3,2-a]pyridine-3-carboxylate (15). Compound **9** (2.55 mmol, 1 g) was dissolved in THF (20 mL), and 1 M LiOH (5.1 mmol, 5.1 mL) was added; the reaction was stirred at rt for 20 min. The reaction mixture was quenched with acidic water (pH ∼ 1, set with 1 M HCl) and extracted with EtOAc; the organic phase was dried (Na_2SO_4), filtered, and concentrated. The solid material was suspended in DCM (30 mL), and oxalylchloride (2.81 mmol, 0.25 mL), together with DMF (5 drops), was added; the reaction was stirred at rt for 10 min. 2-(Trimethylsilyl)ethanol (7.65 mmol, 1.1 mL) was added, and the reaction was stirred at rt for additional 20 min. The reaction mixture was diluted with DCM and washed with saturated $NaHCO_3$ (aq); the organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 90:10 → 60:40) to give the desired compound (1.15 g, 94%) as a colorless foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92−7.87 (m, 1H), 7.85−7.78 (m, 2H), 7.52−7.40 (m, 3H), 7.32−7.29 (m, 1H), 5.78 (s, 1H), 5.55 (dd, J = 2.2, 8.6 Hz, 1H), 4.54−4.35 (m, 2H), 4.35−4.24 (m, 2H), 3.67 (dd, J = 8.6, 11.7 Hz, 1H), 3.51 (dd, J = 2.2, 11.7 Hz, 1H), 1.71−1.62 (m, 1H), 1.08−0.88 m, 4H), 0.80−0.71 (m, 2H), 0.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 161.4, 156.7, 147.1, 134.1, 134.0, 132.0, 128.9, 127.7, 127.6, 126.3, 125.8, 125.6, 123.9, 115.5, 113.6, 65.0, 63.0, 36.3, 31.8, 17.3, 11.3, 7.8, 7.5, −1.5 (3C); IR λ 1734, 1653, 1577, 1483, 1425; $[\alpha]_D$ = 0 (c0.5, $CHCl_3$); HRMS (ES) calcd [M + Na] for $C_{27}H_{31}NNaO_3SSi$ 500.1692, obsd 500.1694.

(3*RS*)-2-(Trimethylsilyl)ethyl 7-(Naphthalen-1-ylmethyl)-5-oxo-8-(3-(trifluoromethyl)phenyl)-3,5-dihydro-2*H*-thiazolo-[3,2-a]pyridine-3-carboxylate (16). Compound **14** (2.02 mmol, 1 g) was dissolved in THF (20 mL), and 1 M LiOH (4.0 mmol, 4 mL) was added; the reaction was stirred at rt for 15 min. The reaction mixture was quenched with acidic water (pH ∼ 1, set with 1 M HCl) and extracted with EtOAc; the organic phase was dried (Na_2SO_4), filtered, and concentrated. The solid material was suspended in DCM (30 mL), and oxalylchloride (2.22 mmol, 0.19 mL), together with DMF (5 drops), was added; the reaction was stirred at rt for 10 min. 2-(Trimethylsilyl)ethanol (6.1 mmol, 0.87 mL) was added, and the reaction was stirred at rt for additional 15 min. The reaction mixture was diluted with DCM and washed with saturated $NaHCO_3$ (aq); the organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 90:10 → 60:40) to give the desired compound (1.06 g, 90%) as a colorless foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.80 (m, 1H), 7.75−7.71 (m, 1H), 7.61−7.53 (m, 3H), 7.51−7.32 (m, 5H), 7.21−7.16 (m, 1H), 5.99−5.92 (m, 1H), 5.60 (dd, J = 2.3, 8.6 Hz, 1H), 4.39−4.24 (m, 2H), 4.04−3.87 (m, 2H), 3.72−3.63 (m, 1H), 3.51−3.43 (m, 1H), 1.08−1.00 (m, 2H), 0.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 161.3, 153.9, 147.3, 137.2, 133.9, 133.6 (d, J = 41 Hz, 1C), 133.4, 131.7, 131.4 (splitted q, J = 32 Hz, 1C), 129.6, 128.9, 127.9, 127.8, 127.0 (splitted d, J = 31 Hz, 1C), 126.2, 125.7, 125.4, 125.2, 123.9 (q, J = 270 Hz, 1C), 123.5, 115.8, 114.6, 65.3, 63.9, 36.9, 31.9, 17.4, −1.4 (3C); IR λ 1740, 1653, 1579, 1482, 1436, 1331; $[\alpha]_D$ = 0 (c0.5, $CHCl_3$); HRMS (ES) calcd [M + Na] for $C_{31}H_{30}F_3NNaO_3SSi$ 604.1566, obsd 604.1566.

2-(Trimethylsilyl)ethyl 2-Bromo-8-cyclopropyl-7-(naphthalen-1-ylmethyl)-5-oxo-5*H*-thiazolo[3,2-a]pyridine-3-carboxylate (17). Compound **15** (2.76 mmol, 1.32 g) was dissolved in dry MeCN (30 mL, dried over 3 Å MS), NaH (8.3 mmol, 200 mg), $BrCCl_3$ (8.3 mmol, 0.82 mL), and 2-(trimethylsilyl)ethanol (5.52 mmol, 0.79 mL); the reaction was stirred at rt for 8 h. MeCN was evaporated, and the crude material was quenched with saturated $NaHCO_3$ (aq) and extracted with EtOAc. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 95:5 → 85:15) to give the desired compound (1.1 g, 72%) as a yellow foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.84 (m, 1H), 7.81−7.75 (m, 2H), 7.50−7.43 (m, 2H), 7.43−7.36 (m, 1H), 7.24−7.19 (m, 1H), 5.89 (s, 1H), 4.50 (s, 2H), 4.52−4.44 (m, 2H), 1.81−1.71 (m, 1H), 1.20−1.12 (m, 2H), 1.07−1.00 (m, 2H), 0.78−0.71 (m, 2H), 0.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 158.1, 153.9, 146.8, 134.1, 134.0, 132.0, 131.2, 129.0, 127.9, 127.5, 126.4, 125.9, 125.6, 123.7, 112.2, 112.1, 103.1, 65.7, 36.4, 17.3, 11.0, 7.9 (2C), −1.4 (3C); IR λ 1723, 1654, 1567, 1469; HRMS (ES) calcd [M + Na] for $C_{27}H_{28}BrNNaO_3SSi$ 576.0640, obsd 576.0635.

2-(Trimethylsilyl)ethyl 2-Bromo-7-(naphthalen-1-ylmethyl)-5-oxo-8-(3-(trifluoromethyl)phenyl)-5*H*-thiazolo[3,2-a]-pyridine-3-carboxylate (18). Compound **16** (1.01 mmol, 0.59 g)

was dissolved in dry MeCN (15 mL), NaH (3.03 mmol, 73 mg), $BrCCl_3$ (3.03 mmol, 0.3 mL) and 2-(trimethylsilyl)ethanol (2.02 mmol, 0.29 mL); the reaction was stirred at rt for 10 h. MeCN was evaporated, and the crude material was quenched with saturated $NaHCO_3$ (aq) and extracted with EtOAc. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 95:5 → 85:15) to give the desired compound (0.55 g, 83%) as a yellow foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.78 (m, 1H), 7.74−7.70 (m, 1H), 7.65−7.61 (m, 1H), 7.58−7.50 (m, 3H), 7.47−7.30 (m, 4H), 7.16−7.11 (m, 1H), 6.10 (s, 1H), 4.57−4.47 (m, 2H), 4.06 (s, 2H), 1.25−1.15 (m, 2H), 0.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 158.0, 151.3, 147.1, 136.1, 133.9, 133.4, 133.3, 132.1 (q, J = 33 Hz, 1C), 131.5, 131.3, 130.3, 128.9, 128.0, 127.8, 126.7 (q, J = 3 Hz, 1C), 126.3, 125.9 (q, J = 3 Hz, 1C), 125.8, 125.4, 123.7 (q, J = 271 Hz, 1C), 123.4, 113.3, 112.3, 102.9, 65.9, 36.8, 17.3, −1.4 (3C); IR λ 1734, 1661, 1570, 1467, 1436; HRMS (ES) calcd [M + Na] for $C_{31}H_{27}BrF_3NNaO_3SSi$ 680.0514, obsd 680.0528.

2-(Trimethylsilyl)ethyl 8-Cyclopropyl-2-ethynyl-7-(naphthalen-1-ylmethyl)-5-oxo-5*H*-thiazolo[3,2-a]pyridine-3-carboxylate (19). Compound **17** (1.8 mmol, 1 g), CuI (0.18 mmol, 34 mg), $Pd(PPh_3)_3Cl_2$ (0.09 mmol, 63 mg) and TEA (3.6 mmol, 0.5 mL) were dissolved in dry DMF (15 mL). Ethynyltrimethylsilane (5.4 mmol, 0.76 mL) dissolved in dry DMF (1 mL) was added, and the reaction was heated in the microwave oven at 110 °C for 10 min. The reaction mixture was diluted with saturated $NaHCO_3$ (aq) and extracted with EtOAc; the organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude product was dissolved in MeOH/THF 4:1 (15 mL), and K_2CO_3 (1.8 mmol, 0.25 g) was added; the reaction was stirred at rt for 10 min. The reaction mixture was diluted with saturated $NaHCO_3$ and extracted with EtOAc; the organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude reaction mixture was purified by column chromatography on silica gel (heptane/EtOAc 95:5 → 85:15) to give the desired compound (0.55 g, 61%) as a yellow foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98−7.92 (m, 1H), 7.90−7.83 (m, 2H), 7.54−7,43 (m, 3H), 7.36−7.31 (m, 1H), 5.53 (s, 1H), 5.11 (s, 1H), 4.54 (s, 2H), 4.36−4.28 (m, 2H), 1.88−1.79 (m, 2H), 1.04−0.93 (m, 4H), 0.76−0.69 (m, 2H), −0.02 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.0, 157.1, 155.1, 144.9, 134.3 (splitted, 2C), 133.5, 131.5, 128.6, 127.6, 127.4, 126.4, 125.8, 125.7, 123.9, 112.0, 110.1, 108.5, 92.8, 70.6, 64.7, 35.5, 16.6, 10.6, 7.4 (2C), −1.6 (3C); IR λ 1732, 1654, 1568, 1466, 1247; HRMS (ES) calcd [M + Na] for $C_{29}H_{29}NNaO_3SSi$ 522.1535, obsd 522.1530.

2-(Trimethylsilyl)ethyl 2-Ethynyl-7-(naphthalen-1-ylmethyl)-5-oxo-8-(3-(trifluoromethyl)phenyl)-5*H*-thiazolo[3,2-a]pyridine-3-carboxylate (20). Compound **18** (0.8 mmol, 525 mg), CuI (0.08 mmol, 15 mg), $Pd(PPh_3)_3Cl_2$ (0.04 mmol, 28 mg), and TEA (1.6 mmol, 0.22 mL) were dissolved in dry DMF (10 mL). Ethynyltrimethylsilane (2.4 mmol, 0.34 mL) dissolved in dry DMF (1 mL) was added, and the reaction was heated in the microwave oven at 110 °C for 10 min. The reaction mixture was diluted with saturated $NaHCO_3$ (aq) and extracted with EtOAc; the organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude product was dissolved in MeOH/THF 4:1 (10 mL), and K_2CO_3 (0.8 mmol, 0.11 g) was added; the reaction was stirred at rt for 10 min. The reaction mixture was diluted with saturated $NaHCO_3$ and extracted with EtOAc; the organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude reaction mixture was purified by column chromatography on silica gel (heptane/EtOAc 95:5 → 85:15) to give the desired compound (0.3 g, 62%) as a yellow foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91−7.85 (m, 1H), 7.82−7.63 (m, 6H), 7.49−7.34 (m, 3H), 7.26−7.20 (m, 1H), 5.89 (s, 1H), 5.11 (s, 1H), 4.42−4.32 (m, 2H), 4.14 (s, 2H), 1.09−1.01 (m, 2H), 0.02 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.8, 157.1, 152.1, 145.5, 136.0, 134.4, 134.1, 133.8, 133.3, 131.1, 130.6, 130.1 (q, J = 31 Hz, 1C), 128.5, 127.5, 127.4, 126.6 (q, J = 3 Hz, 1C), 126.2, 125.7, 125.6 (q, J = 3 Hz, 1C), 125.4, 123.8 (q, J = 272 Hz, 1C), 123.6, 113.1, 110.5, 108.3, 93.1, 70.2, 64.9, 35.8, 16.6, −1.6 (3C); IR λ 1734, 1662, 1570, 1471, 1329; HRMS (ES) calcd [M + Na] for $C_{33}H_{28}F_3NNaO_3SSi$ 626.1409, obsd 626.1412.

6-Cyclopropyl-7-(naphthalen-1-ylmethyl)-1*H*,9*H*-pyrano-[3′,4′:4,5][1,3]thiazolo[3,2-a]pyridine-1,9-dione (12). Compound **19** (0.04 mmol, 20 mg) and Pd-NHC (0.002 mmol, 1.4 mg) were dissolved in DCM/BF_3*Et_2O 95:5 (2 mL), and the reaction was stirred at rt for 3 h. The reaction mixture was diluted with DCM and washed with saturated $NaHCO_3$ (aq); the organic phase was dried (Na_2SO_4) filtered and concentrated. The crude material was purified by HPLC and freeze-dried to give the desired compound (14 mg, 88%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90−7.85 (m, 1H), 7.82−7.76 (m, 2H), 7.56 (d, J = 8 Hz, 1H), 7.51−7.43 (m, 2H), 7.43−7.37 (m, 1H), 7.27−7.22 (m, 1H), 6.57 (d, J = 8 Hz, 1H), 6.04 (s, 1H), 4.51 (s, 2H), 1.82−1.73 (m, 1H), 1.10−1.03 (m, 2H), 0.80−0.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 153.2, 150.3, 149.4, 143.6, 142.5, 134.1, 134.0, 132.0, 129.0, 127.9, 127.6, 126.4, 125.9, 125.6, 123.7, 122.8, 115.8, 112.7, 100.7, 36.2, 11.2, 8.2 (2C); IR λ 1735, 1655, 1602, 1477; HRMS (ES) calcd [M + Na] for $C_{24}H_{17}NNaO_3S$ 422.0827, obsd 422.0818.

5-Cyclopropyl-3-methylidene-6-(naphthalen-1-ylmethyl)-8*H*-furo[3′,4′:4,5][1,3]thiazolo[3,2-a]pyridine-1,8(3*H*)-dione (13). Compound **19** (0.04 mmol, 20 mg), $Pd(OAc)_2$ (0.002 mmol, 0.4 mg), and DPPP (0.002 mmol, 0.8 mg) were dissolved in DCM/TFA 85:15 (2 mL), and the reaction was stirred at rt for 1 h. The reaction mixture was diluted with DCM and washed with saturated $NaHCO_3$ (aq); the organic phase was dried (Na_2SO_4) filtered and concentrated. The crude material was purified by HPLC and freeze-dried to give the desired compound (14 mg, 88%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.85 (m, 1H), 7.83−7.74 (m, 2H), 7.52−7.38 (m, 3H), 7.27−7.21 (m, 1H), 6.01 (s, 1H), 5.34 (d, J = 3.4 Hz, 1H), 5.03 (d, J = 3.4 Hz, 1H), 4.52 (s, 2H), 1.82−1.72 (m, 1H), 1.14−1.05 (m, 2H), 0.84−0.76 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 154.7, 153.3, 149.8, 145.8, 141.1, 134.2, 133.7, 133.3, 131.9, 129.1, 128.1, 127.6, 126.5, 126.0, 125.7, 123.7, 115.4, 114.0, 96.8, 36.5, 11.8, 8.2 (2C); IR λ 1782, 1664, 1569, 1464, 1134; HRMS (ES) calcd [M + Na] for $C_{24}H_{17}NNaO_3S$ 422.0827, obsd 422.0815.

3-Methylidene-6-(naphthalen-1-ylmethyl)-5-[3-(trifluoromethyl)phenyl]-8*H*-furo[3′,4′:4,5][1,3]thiazolo[3,2-a]-pyridine-1,8(3*H*)-dione (21). Compound **20** (0.07 mmol, 40 mg), $Pd(OAc)_2$ (0.004 mmol, 0.8 mg), and DPPP (0.004 mmol, 1.6 mg) were dissolved in DCM/TFA 85:15 (4 mL), and the reaction was stirred at rt for 1 h. The reaction mixture was diluted with DCM and washed with saturated $NaHCO_3$ (aq); the organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by HPLC and freeze-dried to give the desired compound (30 mg, 85%) as a yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92−7.87 (m, 1H), 7.83−7.68 (m, 6H), 7.50−7.37 (m, 3H), 7.25−7.20 (m, 1H), 5.96 (s, 1H), 5.64 (d, J = 4 Hz, 1H), 5.43 (d, J = 4 Hz, 1H), 4.15 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.2, 152.8, 151.6, 151.3, 144.7, 140.7, 135.6, 134.3, 133.7, 133.2, 132.3, 131.1, 130.6, 130.1 (q, J = 30 Hz, 1C), 128.4, 127.4, 127.3, 126.6 (splitted 1C), 126.1, 125.6 (2C), 125.3, 123.7 (q, J = 271 Hz, 1C), 123.5, 114.2, 113.0, 98.8, 35.7; IR λ 1798, 1680, 1583, 1479, 1332; HRMS (ES) calcd [M + Na] for $C_{28}H_{16}F_3NNaO_3S$ 526.0701, obsd 526.0698.

7-(Naphthalen-1-ylmethyl)-6-[3-(trifluoromethyl)phenyl]-1*H*,9*H*-pyrano[3′,4′:4,5][1,3]thiazolo[3,2-a]pyridine-1,9-dione (22). Compound **20** (0.07 mmol, 40 mg) and Pd-NHC (0.004 mmol, 2.7 mg) were dissolved in DCM/BF_3*Et_2O 95:5 (4 mL), and the reaction was stirred at rt for 3 h. The reaction mixture was diluted with DCM and washed with saturated $NaHCO_3$ (aq); the organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by HPLC and freeze-dried to give the desired compound (32 mg, 91%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.78 (m, 1H), 7.76−7.70 (m, 1H), 7.67−7.61 (m, 1H), 7.60−7.49 (m, 3H), 7.57 (d, J = 4 Hz, 1H), 7.48−7.29 (m, 4H), 7.15−7.09 (m, 1H), 6.46 (d, J = 4 Hz, 1H), 6.28 (s, 1H), 4.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 150.7, 150.6, 149.2, 143.8, 142.2, 136.3, 134.0, 133.5, 133.3, 132.2 (q, J = 33 Hz, 1C), 131.6, 130.4, 129.0, 128.1, 127.9, 126.9 (splitted 1C), 126.4, 126.0 (splitted 1C), 125.8, 125.4, 123.7 (q, J = 272 Hz, 1C), 123.4, 122.9, 115.9, 114.2, 100.5, 36.9; IR λ 1748, 1660, 1603, 1482, 1328; HRMS (ES) calcd [M + Na] for $C_{28}H_{16}F_3NNaO_3S$ 526.0701, obsd 526.0705.

Typical Procedure for Synthesis of Internal Acetylenes 23. 2-(Trimethylsilyl)ethyl 8-Cyclopropyl-7-(naphthalen-1-ylmethyl)-5-oxo-2-(pent-1-ynyl)-5*H*-thiazolo[3,2-a]pyridine-3-carboxylate (23a). Compound **17** (0.47 mmol, 0.26 g), CuI (0.047 mmol, 9 mg), $Pd(PPh_3)_3Cl_2$ (0.023 mmol, 16 mg), and TEA (0.94 mmol, 0.13 mL) were dissolved in dry DMF (4.5 mL). 1-Pentyne (1.41 mmol, 0.14 mL) dissolved in dry DMF (0.5 mL) was added, and the reaction was heated in the microwave oven at 110 °C for 10 min. The reaction mixture was diluted with saturated $NaHCO_3$ (aq) and extracted with EtOAc; the organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude reaction mixture was purified by column chromatography on silica gel (heptane/EtOAc 95:5 → 85:15) to give the desired compound (0.22 g, 86%) as a yellow foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88−7.83 (m, 1H), 7.82−7.74 (m, 2H), 7.50−7.42 (m, 2H), 7.42−7.36 (m, 1H), 7.24−7.19 (m, 1H) 5.87 (s, 1H), 4.50 (s, 2H), 4.49−4.42 (m, 2H), 2.43 (t, J = 8 Hz, 2H) 1.79−1.70 (m, 1H), 1.63 (m, 2H), 1.18−1.11 (m, 2H), 1.04−0.97 (m, 2H) 1.03 (t, J = 4 Hz, 3H), 0.76−0.71 (m, 2H), 0.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 158.4, 154.0, 145.7, 134.2, 134.0, 133.2, 132.0, 128.9, 127.7, 127.5, 126.3, 125.8, 125.6, 123.8, 111.8 (2C), 111.1, 102.7, 68.4, 65.2, 36.3, 21.9, 21.7, 17.3, 13.5, 11.0, 8.0 (2C), −1.4 (3C); IR λ 1734, 1662, 1474; HRMS (ES) calcd [M + Na] for $C_{32}H_{35}NNaO_3SSi$ 564.2005, obsd 564.2016.

2-(Trimethylsilyl)ethyl 8-Cyclopropyl-2-(cyclopropylethynyl)-7-(naphthalen-1-ylmethyl)-5-oxo-5*H*-thiazolo[3,2-a]pyridine-3-carboxylate (23b). Following the procedure for **23a**, the title compound (82 mg, 84%) was isolated as a yellow foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.83 (m 1H), 7.82−7.74 (m, 2H), 7.50−7.42 (m, 2H), 7.39 (t, J = 8 Hz, 1H), 7.21 (d, J = 8 Hz, 1H), 5.86 (s, 1H), 4.50 (s, 2H), 4.50−4.42 (m, 2H), 1.78−1.68 (m, 1H), 1.52−1.44 (m, 1H), 1.18−1.10 (m, 2H), 1.04−0.97 (m, 2H), 0.97−0.90 (m, 2H), 0.89−0.82 (m, 2H), 0.77−0.70 (m, 2H), 0.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 158.4, 154.0, 145.7, 134.2, 134.0, 133.3, 132.0, 128.9, 127.7, 127.5, 126.3, 125.8, 125.6, 123.8, 111.9 (2C), 111.2, 105.9, 65.2, 63.2, 36.4, 17.3, 11.0, 9.4 (2C), 8.0 (2C), 0.7, −1.4 (3C); IR λ 1732, 1659, 1569, 1473; HRMS (ES) calcd [M + Na] for $C_{32}H_{33}NNaO_3SSi$ 562.1848, obsd 562.1849.

2-(Trimethylsilyl)ethyl 8-Cyclopropyl-7-(naphthalen-1-ylmethyl)-5-oxo-2-(phenylethynyl)-5*H*-thiazolo[3,2-a]pyridine-3-carboxylate (23c). Following the procedure for **23a**, the title compound (147 mg, 95%) was isolated as a yellow foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90−7.85 (m, 1H), 7.84−7.76 (m, 2H), 7.54−7.45 (m, 4H), 7.44−7.34 (m, 4H), 7.24 (d, J = 4 Hz, 1H), 5.91 (s, 1H), 4.57−4.48 (m, 4H), 1.83−1.73 (m, 1H), 1.23−1.15 (m, 2H), 1.08−1.00 (m, 2H), 0.81−0.73 (m, 2H), 0.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 158.5, 154.2, 145.7, 134.1, 134.0, 133.9, 132.0, 131.9 (2C), 129.8, 128.9, 128.6 (2C), 127.8, 127.5, 126.3, 125.8, 125.6, 123.7, 121.4, 112.0 (2C), 110.4, 100.1, 76.7, 65.4, 36.4, 17.4, 11.0, 8.0 (2C), −1.5 (3C); IR λ 1733, 1665, 1570, 1473; HRMS (ES) calcd [M + Na] for $C_{35}H_{33}NNaO_3SSi$ 598.1848, obsd 598.1850.

2-(Trimethylsilyl)ethyl 8-Cyclopropyl-2-((4-methoxyphenyl)-ethynyl)-7-(naphthalen-1-ylmethyl)-5-oxo-5*H*-thiazolo[3,2-a]pyridine-3-carboxylate (23d). Following the procedure for **23a**, the title compound (145 mg, 89%) was isolated as a yellow foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98−7.91 (m, 1H), 7.91−7.82 (m, 2H), 7.55−7.42 (m, 5H), 7.34 (d, J = 8 Hz, 1H), 7.03−6.95 (m, 2H), 5.54 (s, 1H), 4.53 (s, 2H), 4.41−4.32 (m, 2H), 3.79 (s, 3H), 1.88−1.77 (m, 1H), 1.08−1.00 (m, 2H), 1.00−0.91 (m, 2H), 0.76−0.67 (m, 2H), −0.03 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.6, 159.2, 157.0, 154.6, 144.9, 134.3, 133.4, 133.3 (2C), 132.5, 131.4, 128.6, 127.5, 127.4, 126.3, 125.8, 125.6, 123.9, 114.6 (2C), 111.9, 111.7, 110.1, 109.8, 100.3, 75.1, 64.4, 55.4, 35.4, 16.8, 10.6, 7.4 (2C), −1.7 (3C); IR λ 1728, 1654, 1605, 1568, 1507, 1466; HRMS (ES) calcd [M + Na] for $C_{36}H_{35}NNaO_4SSi$ 628.1954, obsd 628.1945.

2-(Trimethylsilyl)ethyl 8-Cyclopropyl-7-(naphthalen-1-ylmethyl)-5-oxo-2-((3-(trifluoromethyl)phenyl)ethynyl)-5*H*-thiazolo[3,2-a]pyridine-3-carboxylate (23e). Following the procedure for **23a**, the title compound (145 mg, 86%) was isolated as a yellow foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.84 (m, 1H), 7.84−7.75 (m, 3H), 7.70−7.63 (m, 2H), 7.54−7.45 (m, 3H), 7.44−7.38 (m, 1H), 7.25 (d, J = 8 Hz, 1H), 5.91 (s, 1H), 4.57−4.49 (m, 4H), 1.84−1.72 (m, 1H), 1.23−1.14 (m, 2H), 1.10−1.01 (m, 2H), 0.82−0.74 (m, 2H), 0.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 158.5, 154.5, 145.6, 134.9, 134.7, 134.0 (2C), 132.0, 131.3 (q, J = 33 Hz, 1C), 129.2, 129.0, 128.6 (splitted, 1C), 127.8, 127.5, 126.4, 126.3 (splitted, 1C), 125.9, 125.6, 123.7, 123.5 (q, J = 271 Hz, 1C), 122.4, 112.1 (2C), 109.5, 98.1, 78.1, 65.6, 36.4, 17.4, 11.0, 8.0 (2C), −1.5 (3C); IR λ 1732, 1662, 1570, 1472, 1329; HRMS (ES) calcd [M + Na] for $C_{36}H_{32}F_3NNaO_3SSi$ 666.1722, obsd 666.1719.

2-(Trimethylsilyl)ethyl 8-Cyclopropyl-7-(naphthalen-1-ylmethyl)-5-oxo-2-(thiophen-3-ylethynyl)-5*H*-thiazolo[3,2-a]-pyridine-3-carboxylate (23f). Following the procedure for **23a**, the title compound (150 mg, 95%) was isolated as a yellow foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84−7.79 (m, 1H), 7.79−7.70 (m, 2H), 7.57−7.53 (m, 1H), 7.45−7.39 (m, 2H), 7.39−7.33 (m, 1H), 7.29−7.24 (m, 1H), 7.21−7.17 (m, 1H), 7.14−7.10 (m, 1H), 5.86 (s, 1H), 4.51−4.44 (m, 2H), 4.46 (s, 2H), 1.75−1.66 (m, 1H), 1.18−1.10 (m, 2H), 1.01−0.93 (m, 2H), 0.73−0.66 (m, 2H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 158.3, 154.1, 145.6, 134.0, 133.9, 133.6, 131.9, 130.9, 129.6, 128.8, 127.7, 127.4, 126.3, 126.0, 125.7, 125.5, 123.7, 120.4, 111.9 (2C), 110.3, 95.4, 76.2, 65.3, 36.2, 17.3, 10.9, 7.9 (2C), −1.5 (3C); IR λ 1724, 1654, 1560, 1466; HRMS (ES) calcd [M + Na] for $C_{33}H_{31}NNaO_3S_2Si$ 604.1412, obsd 604.1412.

6-Cyclopropyl-7-(naphthalen-1-ylmethyl)-3-propyl-1*H*,9*H*-pyrano[3′,4′:4,5][1,3]thiazolo[3,2-a]pyridine-1,9-dione (24a). Compound **23a** (0.18 mmol, 100 mg) was dissolved in DCM/TFA 80:20 (4 mL), and the reaction was stirred at rt for 28 h. The reaction mixture was diluted with DCM and washed with saturated $NaHCO_3$ (aq); the organic phase was dried (Na_2SO_4), filtered, and concentrated to give the desired product (79 mg, 99%) as a yellow foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.83 (m, 1H), 7.83−7.73 (m, 2H), 7.50−7.35 (m, 3 h), 7.23 (d, J = 8 Hz, 1H), 6.31 (s, 1H), 6.03 (s, 1H), 4.49 (s, 2H), 2.53 (t, J = 8 Hz, 2H), 1.79−1.65 (m, 3H), 1.09−1.00 (m, 2H), 0.97 (t, J = 4 Hz, 3H), 0.78−0.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 159.2, 152.9, 150.2, 144.1, 143.8, 134.0 (2C), 131.9, 129.0, 127.8, 127.5, 126.4, 125.8, 125.6, 123.7, 120.5, 115.7, 112.6, 97.1, 36.1, 35.6, 20.3, 13.5, 11.1, 8.2 (2C); IR λ 1734, 1654, 1616, 1578, 1474, 1420; HRMS (ES) calcd [M + Na] for $C_{27}H_{23}NNaO_3S$ 464.1296, obsd 464.1298.

3,6-Dicyclopropyl-7-(naphthalen-1-ylmethyl)-1*H*,9*H*-pyrano[3′,4′:4,5][1,3]thiazolo[3,2-a]pyridine-1,9-dione (24b). Compound **23b** (0.19 mmol, 100 mg) was dissolved in DCM/TFA 80:20 (4 mL), and the reaction was stirred at rt for 1 h. The reaction mixture was diluted with DCM and washed with saturated $NaHCO_3$ (aq); the organic phase was dried (Na_2SO_4), filtered, and concentrated to give the desired product (83 mg, 99%) as a yellow foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.82 (m, 1H), 7.82−7.73 (m, 2H), 7.50−7.35 (m, 3H), 7.23 (d, J = 8 Hz, 1H), 6.37 (s, 1H), 6.01 (s, 1H), 4.49 (s, 2H), 1.87−1.69 (m, 2H), 1.20−1.12 (m, 2H), 1.09−0.96 (m, 4H), 0.78−0.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 159.2, 152.7, 149.6, 144.7, 143.6, 134.0 (2C), 131.9, 128.9, 127.8, 127.5, 126.3, 125.8, 125.6, 123.7, 119.5, 115.6, 112.6, 95.5, 36.1, 14.5, 11.1, 9.1 (2C), 8.2 (2C); IR λ 1734, 1654, 1607, 1474; HRMS (ES) calcd [M + Na] for $C_{27}H_{21}NNaO_3S$ 462.1140, obsd 462.1135.

6-Cyclopropyl-7-(naphthalen-1-ylmethyl)-3-phenyl-1*H*,9*H*-pyrano[3′,4′:4,5][1,3]thiazolo[3,2-a]pyridine-1,9-dione (24c). Compound **23c** (0.25 mmol, 145 mg) was dissolved in DCM/TFA 80:20 (6 mL), and the reaction was stirred at rt for 18 h. The reaction mixture was diluted with DCM and washed with saturated $NaHCO_3$ (aq); the organic phase was dried (Na_2SO_4), filtered, and concentrated to give the desired product (117 mg, 98%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92−7.84 (m, 3H), 7.84−7.76 (m, 2H), 7.52−7.38 (m, 6H), 7.28−7.23 (m, 1H), 6.95 (s, 1H), 6.06 (s, 1H), 4.52 (s, 2H), 1.83−1.74 (m, 1H), 1.12−1.04 (m, 2H), 0.83−0.76 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 159.2, 153.1, 149.2, 144.1, 143.8, 134.2, 134.1, 132.1, 131.5, 130.5, 129.3 (2C), 129.1, 128.0, 127.6, 126.5, 126.1 (2C), 125.9, 125.7, 123.8, 121.2, 116.0, 112.8, 95.2, 36.2, 11.2, 8.3 (2C); IR λ 1748, 1663, 1605, 1482; HRMS (ES) calcd [M + Na] for $C_{30}H_{21}NNaO_3S$ 498.1140, obsd 498.1146.

6-Cyclopropyl-3-(4-methoxyphenyl)-7-(naphthalen-1-ylmethyl)-1*H*,9*H*-pyrano[3′,4′:4,5][1,3]thiazolo[3,2-a]pyridine-1,9-dione (24d). Compound **23d** (0.24 mmol, 145 mg) was

dissolved in DCM/TFA 80:20 (6 mL), and the reaction was stirred at rt for 1 h. The reaction mixture was diluted with DCM and washed with saturated $NaHCO_3$ (aq); the organic phase was dried (Na_2SO_4), filtered, and concentrated to give the desired product (120 mg, 99%) as a yellow solid: ^{1}H NMR (400 MHz, CD_2Cl_2 + 1% TFA) δ 7.99−7.88 (m, 4H), 7.71−7.66 (m, 1H), 7.58 (s, 1H), 7.56−7.47 (m, 3H), 7.38−7.33 (m, 1H), 7.11−7.05 (m, 2H), 6.53 (s, 1H), 4.79 (s, 2H), 3.91 (s, 3H), 2.23−2.11 (m, 1H), 1.45−1.36 (m, 2H), 1.04−0.96 (m, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2 + 1% TFA) δ 164.8, 162.9, 161.0, 157.8, 157.0, 152.2, 148.6, 134.6, 132.3, 131.9, 129.5 (3C), 129.2, 128.8, 127.3, 126.6, 126.2, 125.5, 123.6, 120.5, 119.2, 115.7 (2C), 112.8, 97.3, 56.2, 37.0, 11.9, 9.0 (2C); IR λ 1738, 1657, 1606, 1571, 1505, 1472; HRMS (ES) calcd [M + Na] for $C_{31}H_{23}NNaO_4S$ 528.1245, obsd 528.1250.

6-Cyclopropyl-7-(naphthalen-1-ylmethyl)-3-[3-(trifluoromethyl)phenyl]-1*H*,9*H*-pyrano[3′,4′:4,5][1,3]thiazolo-[3,2-a]pyridine-1,9-dione (24e). Compound **23e** (0.23 mmol, 145 mg) was dissolved in DCM/TFA 80:20 (6 mL), and the reaction was stirred at rt for 120 h. The reaction mixture was diluted with DCM and washed with saturated $NaHCO_3$ (aq); the organic phase was dried (Na_2SO_4), filtered, and concentrated to give the desired product (110 mg, 88%) as a yellow foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 8.02−7.95 (m, 1H), 7.86−7.79 (m, 1H), 7.79−7.70 (m, 2H), 7.67 (d, J = 8 Hz 1H), 7.57−7.49 (m, 1H), 7.46−7.38 (m, 2H), 7.38−7.32 (m, 1H), 7.21 (d, J = 8 Hz, 1H), 7.10 (s, 1H), 6.00 (s, 1H), 4.47 (s, 2H), 1.79−1.68 (m, 1H), 1.08−0.98 (m, 2H), 0.76−0.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 157.5, 153.3, 148.7, 144.0, 143.8, 133.9, 133.8, 131.8, 131.6 (q, J = 32 Hz, 1C), 131.0, 129.8, 129.0, 128.9, 127.8, 127.6 (splitted, 1C), 127.5, 126.3, 125.8, 125.5, 123.6 (q, J = 270 Hz, 1C), 123.6, 122.6 (splitted, 1C), 121.4, 115.4, 112.8, 96.6, 36.0, 11.0, 8.1 (2C); IR λ 1742, 1660, 1474, 1323; HRMS (ES) calcd [M + Na] for $C_{31}H_{20}F_3NNaO_3S$ 566.1014, obsd 566.1023.

6-Cyclopropyl-7-(naphthalen-1-ylmethyl)-3-(thiophen-3-yl)-1*H*,9*H*-pyrano[3′,4′:4,5][1,3]thiazolo[3,2-a]pyridine-1,9-dione (24f). Compound **23f** (0.18 mmol, 105 mg) was dissolved in DCM/TFA 80:20 (4 mL), and the reaction was stirred at rt for 20 h. The reaction mixture was diluted with DCM and washed with saturated $NaHCO_3$ (aq); the organic phase was dried (Na_2SO_4), filtered, and concentrated to give the desired product (86 mg, 99%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88−7.82 (m, 1H), 7.82−7.76 (m, 1H), 7.76−7.67 (m, 2H), 7.43−7.34 (m, 2H), 7.34−7.24 (m, 3H), 7.20−7.13 (m, 1H), 6.68 (s, 1H), 5.95 (s, 1H), 4.41 (s, 2H), 1.72−1.61 (m, 1H), 1.01−0.92 (m, 2H), 0.71−0.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 155.9, 153.0, 149.1, 144.4, 143.7, 134.1, 134.0, 132.7, 132.0, 129.0, 127.9, 127.6 (splitted, 2C), 127.0, 126.4, 125.9, 125.6, 124.5, 123.8, 120.5, 115.7, 112.7, 95.0, 36.1, 11.1, 8.2 (2C); IR λ 1747, 1662, 1606, 1475; HRMS (ES) calcd [M + Na] for $C_{28}H_{19}NNaO_3S_2$ 504.0704, obsd 504.0698.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet http://pubs.acs.org.

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