Cis-selective double spirocyclization via dearomatization and isomerization under thermodynamic control

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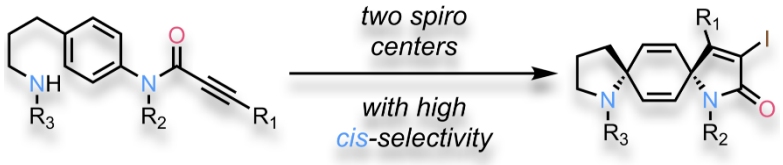
Supporting Information Placeholder



ABSTRACT: Spiro compounds have been considered key scaffolds for pharmaceutical applications. Although many synthetic methods exist for monospirocycles, fewer approaches are known for dispirocycles. Here, we report a highly *cis*-selective method for constructing a 5/6/5-dispirocyclic structure containing pyrrolidine and γ-lactam rings with various substituents from a series of *N*-arylpropiolamides. The high *cis*-selectivity would result from isomerization under thermodynamic control. *Cis*- and *trans*-diastereomers can be in equilibrium, favoring *cis*-adducts.

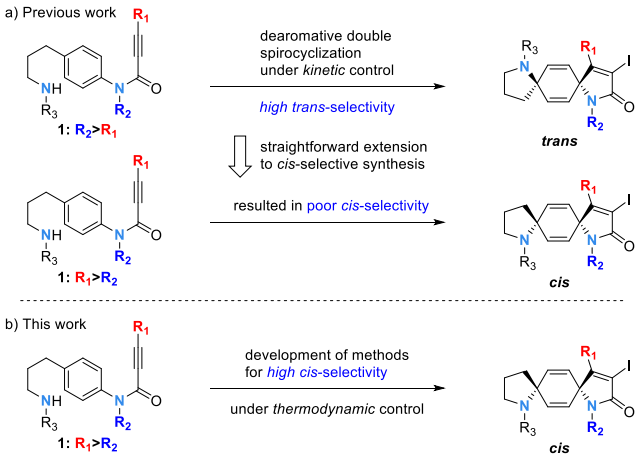
Spirocyclic structures, which are widely found in bioactive natural products and therapeutic drugs, have recently been recognized as an important class of structural motifs that can improve clinical success in drug discovery and development.[1-3] The distinctive three-dimensionality and conformational rigidity of the spirocycles embedded in the potential drug candidates can enhance the drug-likeness of the candidates, restricting the molecular conformation and the spatial arrangement of functional groups, and thereby facilitating interaction between the candidates and target biological molecules.[4] These structures have thus attracted much attention for pharmaceutical applications.

Continuous efforts have been made to develop efficient methods for the construction of the spirocyclic structures.[5] In particular, a strategy of spirocyclization through dearomatization, *ipso*-cyclization, [6] has attracted much attention, providing these structures in short steps from easily available compounds.[7] Although there has been significant progress in the synthesis of *mono*spirocycles with this direct strategy, the availability of *di*spirocyclic counterparts is relatively limited despite the high demand for a wide variety of spirocyclic structures.[7j,k,8] To expand the diversity of the spiro compounds currently available, there is an urgent need to develop efficient synthetic methods to realize previously unexplored spirocyclic structures.

Previously, we reported diastereoselective double spirocyclization of *N*-arylpropiolamide **1** through a dearomatization initiated by electrophilic activation of the alkyne (Scheme 1a).[7k] Higher *trans*-selectivity was observed when bulkier substituents R_2 and a small R_1 were employed. However, a straightforward extension of this strategy to *cis*-selective synthesis gave unsatisfactory results. The combination of a small R_2 and a bulky R_1 under the developed reaction conditions resulted in poor diastereoselectivity.

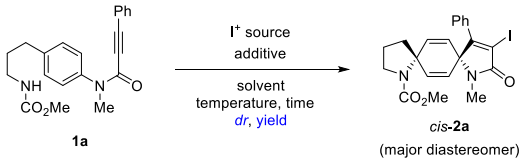
Here, we report highly *cis*-selective dearomative double spirocyclization (Scheme 1b). We established two methods, Methods A and B, for the diastereoselective synthesis of a 5/6/5-dispircyclic framework containing pyrrolidine[9] and γ-lactam[10] rings with various substituents from a series of *N*-arylpropiolamides.

Scheme 1. Diastereoselective double spirocyclization through dearomatization



We selected **1a** as a substrate for developing and optimizing the reaction conditions (Table 1). Entry 1 is the previously reported result in which treatment of **1a** with *N*-iodosuccinimide (NIS) as an I^+ source and AgTFA in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) solvent gave *cis*-**2a** in 56% yield with a low *cis*:*trans* diastereomeric ratio (dr) of 60:40.[7k] We initiated this investigation by examining I^+ sources. Molecular iodine required a prolonged reaction time, and the dr was not improved (entry 2). When iodine chloride (ICl) was used in CH_2Cl_2 from –78 °C to room temperature (rt), the reaction was completed in one hour albeit with low selectivity and 60:40 dr (entry 3). Next, the solvent effect was examined. Switching CH_2Cl_2 to MeCN dramatically improved the selectivity, and the reaction of **1a** with ICl in MeCN solvent from –45 °C to rt occurred with >95:5 dr, and the desired *cis*-**2a** was isolated in 80% yield (entry 4). Lowering the reaction temperature further provided a better result. With a reaction in EtCN solvent from –78 ºC to rt, *cis*-**2a** was obtained in 95% yield with >95:5 dr (entry 5), while the yield was decreased when this reaction was conducted at rt (entry 6). We set the optimal conditions in entry 5 for Method A. Furthermore, three additional experiments in entries 7–9 provided key insights into the mechanism for the diastereoselective outcome. Keeping the reaction temperature at –78 °C (entry 7), adding Na_2CO_3 base (entry 8) or using NIS instead of ICl (entry 9) afforded a mixture of *cis*- and *trans*-**2a** with low diastereoselectivity. These results suggested that the higher temperature and acidic conditions were necessary for higher diastereoselectivity.

Table 1. Optimization of the Reaction Conditions

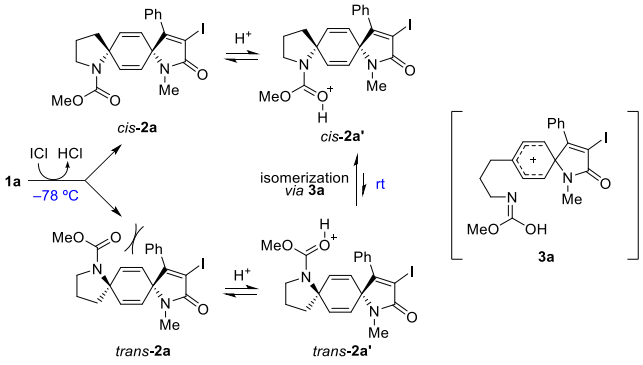


entry	I^+ source	additive	solvent	temperature	time (h)	dr[a]	yield (%)[b]
1	NIS (1.1 equiv)	AgTFA (0.1 equiv)	HFIP	0 °C	24	60:40	56
2	I_2 (2.0 equiv)	$NaHCO_3$ (2.0 equiv)	CH_2Cl_2	rt	68	64:36	46
3	ICl (1.5 equiv)	–	CH_2Cl_2	–78 °C~rt	1	60:40	42
4	ICl (1.5 equiv)	–	MeCN	–45 °C~rt	1	>95: 5	80
5	ICl (1.5 equiv)	–	EtCN	–78 °C~rt	1	>95: 5	95
6	ICl (1.5 equiv)	–	EtCN	rt	1	>95: 5	81
7	ICl (2.2 equiv)	–	EtCN	–78 °C	1	62:38	49
8	ICl (1.5 equiv)	Na_2CO_3 (1.5 equiv)	EtCN	–78 °C~rt	3	58:42	53
9	NIS (1.5 equiv)	–	EtCN	–78 °C~rt	24	60:40	41

[a]The diastereomeric ratio (*cis*:*trans*) was determined by ^{1}H NMR analysis of crude material; [b]Isolated yield of *cis*-**2a**.

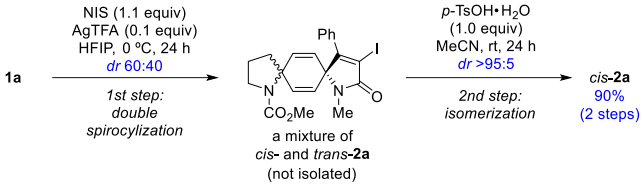
We proposed a possible mechanism for the diastereoselective outcome in Scheme 2. At low temperature of –78 ºC, the reaction of **1a** with ICl would afford a mixture of *cis*- and *trans*-**2a** involving HCl release. The mixture would be converted into *cis*-**2a** upon warming to rt. *Cis*- and *trans*-**2a** could be in equilibrium through their protonated forms *cis*-**2a'**, *trans*-**2a'**, and cyclohexadienyl cation **3a**. The equilibrium favors *cis*-**2a** presumably because *trans*-**2a** is less thermodynamically stable due to the steric repulsion between the methoxycarbonyl and the phenyl groups.[11,12]

Scheme 2. Possible mechanism for the diastereoselective outcome.



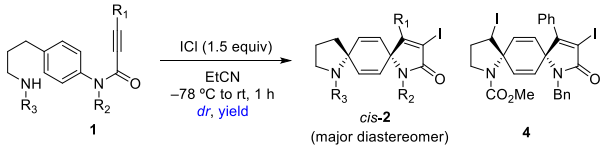
These findings allowed us to establish an alternative two-step procedure consisting of the double spirocyclization step and the following isomerization step (Scheme 3). A crude mixture of diastereomers with 60:40 dr synthesized by NIS/AgTFA/HFIP was treated with *p*-TsOH•H_2O in MeCN to force the isomerization. This procedure provided the desired *cis*-**2a** in 90% yield in two steps with >95:5 dr, and we set this as Method B. For the first step, we selected NIS/AgTFA/HFIP rather than ICl/EtCN since the latter conditions were not suitable for some substrates (vide infra).

Scheme 3. Alternative procedure for the *cis*-selective double spirocyclization in two steps [Method B].



With the *cis*-selective double spirocyclization established, we next explored the scope and limitations of substrates with Method A (Table 2). The modification of the R_1 substituent was first studied with the same R_2 and R_3 for **1a**. In entries 1–5, variations of substitution at the *para*-position of the phenyl ring were explored. While substrates with the methyl and the methoxy groups, and the chlorine atom gave *cis*-**2b**, *cis*-**2c**, and *cis*-**2d** in high yields, electron-deficient substituents such as the trifluoromethyl and the nitro groups afforded *cis*-**2e** and *cis*-**2f** in lower yields. Moreover, the *ortho*-methoxy group afforded *cis*-**2g** in 90% yield (entry 6). In entries 7 and 8, the 2-naphthyl and the 3-benzothiophene rings were tolerated, and *cis*-**2h** and *cis*-**2i** were obtained in high yields. In all cases, *cis*-**2b**–**i** were formed with high diastereoselectivity of >95:5, and iodination on the aromatic ring core was not observed. Next, in entry 9, the benzyl group for R_2 was employed with the same R_1 and R_3 for **1a**. However, the reaction was complicated, and many products were observed in the crude ^{1}H NMR. Isolable products were *cis*-**2j** in 16% yield and diiodide **4** in 4% yield. In entry 10, the methanesulfonyl group for R_3 was tested with the same R_1 and R_2 for **1a**. However, many byproducts were formed and they prevented the isolation of *cis*-**2k** in its pure form.

Table 2. Scope and limitations of *cis*-selective double spirocyclization with iodine chloride [Method A]

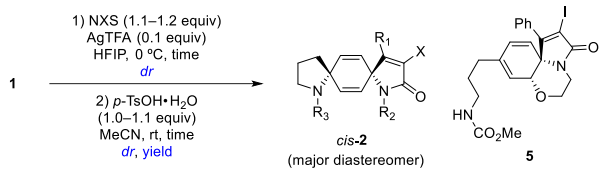


entry	1	R_1	R_2	R_3	dr[a]	yield (%)[b]
1	b	R = Me	Me	CO_2Me	>95: 5	95
2[c]	c	R = OMe	Me	CO_2Me	>95: 5	85
3[c]	d	R = Cl	Me	CO_2Me	>95: 5	80
4[c]	e	R = CF_3	Me	CO_2Me	>95: 5	57
5[d]	f	R = NO_2	Me	CO_2Me	>95: 5	68
6	g	MeO	Me	CO_2Me	>95: 5	90
7	h		Me	CO_2Me	>95: 5	91
8	i		Me	CO_2Me	>95: 5	89
9[c]	j	Ph	Bn	CO_2Me	–	16[e]
10	k	Ph	Me	SO_2Me	–	–[f]

[a]The diastereomeric ratio (*cis*:*trans*) was determined by ^{1}H NMR analysis of crude material; [b]Isolated yield of *cis*-**2**; [c]1.0 equiv of ICl was used; [d]2.2 equiv of ICl was used; [e]**4** was also isolated in 4% yield; [f]Many byproducts were formed.

The scope and limitations of Method B are summarized in Table 3. In entry 1, **1j**, which failed with Method A, was tested. In the double spirocyclization step, **1j** gave almost equal amounts of *cis*- and *trans*-**2j** with a 52:48 dr. Then this crude mixture was applied to the isomerization step. Treatment with one equivalent of *p*-TsOH•H_2O in MeCN gave *cis*-**2j** in 86% yield for two steps with >95:5 dr. During the two steps, byproduct **4** was not observed. Method B seemed to be mild enough for exploring other functional groups on R_2. We then found that ester **1l** (entry 2) and ketone **1m** (entry 3) provided the desired dispiro compounds in high yield with high dr. In entry 4, the reaction with **1n** having the hydroxy group provided oxatricycle **5** as a major product in the first step with a small amount of *cis*- and *trans*-**2n**. After the second step, this mixture was smoothly converted into *cis*-**2n** in 92% yield with dr >95:5, and **5** was not detected. In entry 5, the propargyl group was tested, and the electrophilic activation of the alkyne of propiolamide occurred chemoselectively, providing *cis*-**2o** in high yield with high dr. The reaction was performed at rt without AgTFA because only unreacted **1o** was recovered for the reaction at 0 ºC with AgTFA. The silver salt would be deactivated by coordinating with the two alkynyl groups to form a tight complex. In entry 6, the nitrile group was also available for the reaction. Two equivalents of the acid were needed to complete the isomerization. We assume that this result can be attributed to the destabilization of the cationic intermediate **3p** by the highly electron-withdrawing nature of the cyanomethyl substituent,[13] therefore the stronger acidic conditions were required to accelerate the reaction. Next, R_3 substituents were explored in entries 7–11. In addition to phenyl carbamate, relatively acid-labile benzyl carbamate[14] was tolerated and afforded *cis*-**2q** and *cis*-**2r** in high yields with >95:5 dr (entries 7, 8). Dispiro compounds having methanesulfonamide *cis*-**2k**, which was not obtained with Method A, could be synthesized in 81% yield with >95:5 dr (entry 9). Substrate **1s** with the *p*-toluenesulfonyl group was also obtained with high efficiency (entry 10). For *cis*- and *trans*-**2t** having acetamide, the *cis*:*trans* ratio was nearly unchanged after the second step, resulting in the low yield of *cis*-**2t** (entry 11). The reactivity toward acid-mediated isomerization seems to depend on the nature of R_3 substituents. Presumably, the weaker leaving group ability of the acetamide moiety[15] would be insufficient for the generation of the cationic intermediate under these conditions. The reaction of **1a** with *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS) were also examined. While *cis*-**2a-Br** was isolated in 94% yield (entry 12), *cis*-**2a-Cl** was obtained in 43% yield (entry 13), because the reaction with NCS did not complete even after 41 h under reflux conditions.

Table 3. Alternative milder reaction conditions for the *cis*-selective double spirocyclization in two steps [Method B]

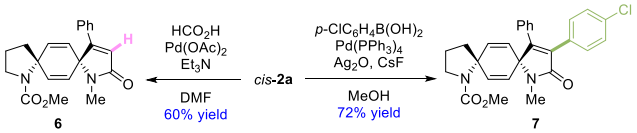


entry	1	*cis*-2	X	R_1	R_2	R_3	time (h) 1st step	time (h) 2nd step	dr[a] 1st step	dr[a] 2nd step	yield[b]
1	j	j	I	Ph	Bn	CO_2Me	8	24	52:48	>95: 5	86
2	l	l	I	Ph	CH_2CO_2Et	CO_2Me	22	22	58:42	>95: 5	85
3	m	m	I	Ph	cyclopropyl-CO	CO_2Me	23	23	75:25	>95: 5	83
4	n	n	I	Ph	CH_2CH_2OH	CO_2Me	24	22	–[c]	>95: 5	92
5	o	o	I	Ph	$CH_2C{\equiv}CH$	CO_2Me	24[d]	22	72:28	>95: 5	85
6	p	p	I	Ph	CH_2CN	CO_2Me	22	22[e]	53:47	>95: 5	82
7	q	q	I	Ph	Me	CO_2Bn	2	19	56:44	>95: 5	90
8	r	r	I	Ph	Me	CO_2Ph	2	22	55:45	>95: 5	86
9	k	k	I	Ph	Me	SO_2Me	1	24	90:10	>95: 5	81
10	s	s	I	Ph	Me	SO_2(*p*-tol)	1.3	19	77:23	94: 6	76
11	t	t	I	Ph	Me	COMe	2.5	24	72:28	74:26	29[f]
12	a	a-Br	Br	Ph	Me	CO_2Me	24	24	50:50	>95: 5	94
13	a	a-Cl	Cl	Ph	Me	CO_2Me	41[g]	24	57:43	>95: 5	43[f]

[a]The diastereomeric ratio (*cis*:*trans*) determined by ^{1}H NMR of crude material; [b]Isolated yield of *cis*-**2** for 2 steps; [c]**5** was observed as a major product in the first step; [d]The reaction was run without AgTFA at rt; [e]2.0 equiv of *p*-TsOH•H_2O was used; [f]NMR yield; [g]The reaction was conducted under reflux.

Synthetic elaboration of *cis*-**2a** is shown in Scheme 4. The iodine atom was reductively removed to give **6** with formic acid and $Pd(OAc)_2$.[16] Moreover, *p*-chlorophenyl derivative **7** was obtained under Suzuki–Miyaura cross coupling reaction conditions.[17]

Scheme 4. Synthetic elaboration of *cis*-2a.



In summary, we have developed two new methods (Method A and Method B) for highly *cis*-selective double spirocyclization through dearomatization and isomerization. The key to success was the development of the Method A with a simple operation and short reaction time, the discovery of the equilibrium between *cis*- and *trans*-dispiro adducts in favoring thermodynamically more stable *cis*-diastereomer under acidic conditions, and the development of Method B with a wider functional group tolerance and substrate scope. With these methods, we have constructed a 5/6/5-dispirocyclic ring system with pyrrolidine

and γ-lactam moieties with various substituents in high yield and high dr. The methods developed here would be applied to more complex dispirocyclic molecules.

EXPERIMENTAL SECTION

Materials and Methods. All non-aqueous reactions were performed in dried glassware under positive pressure of argon. Acetonitrile, propionitrile and HFIP were dried over activated 3A molecular sieves. Dichloromethane (Fujifilm Wako Chemical, super dehydrated) was used. NIS was recrystallized prior to use. All other reagents were used as received.

Flash column chromatography was performed on silica gel (Kanto Chemical spherical neutral 40–50 μm). Preparative thin-layer chromatography (PTLC) was performed with Merck silica gel plate 60 F_{254} 250 μm, and compuonds were visualized with UV light.

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Brucker Avance III 400, JEOL ECZL 400, and JEOL ECA 600 II spectrometers at rt. Chemical shifts are expressed in ppm values. ^{1}H NMR spectra were referenced to the solvent resonances $CHCl_3$ (δ 7.26 ppm), ^{13}C NMR spectra were referenced to $CDCl_3$ (δ 77.0 ppm), and ^{19}F NMR spectra were referenced to C_6F_6 (δ –164.9 ppm). Peak multiplicities were designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet. High resolution mass spectra (HRMS) were recorded on JEOL JMS T100LP and JEOL JMS-700 spectrometers.

General Experimental Procedures.

*General Procedure A. Synthesis of N-arylpropiolamides **1b–c, e, g**.*

To a stirred solution of methyl (3-(4-aminophenyl)propyl)carbamate (**S-1**)[7k] in CH_2Cl_2 were successively added substituted propiolic acid derivative and EDC. The reaction was diluted with $CHCl_3$ and water. After the organic layer separation, the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. To the residue were successively added MeCN, K_2CO_3, and MeI at rt, and this mixture was stirred at the same temperature. The reaction mixture was filtered through Celite and concentrated in vacuo, then purified to give **1b–c, e, g**.

*General Procedure B. Synthesis of N-arylpropiolamides **1d, f, h, i**.*

Li's arylation protocol[19] was modified. To a stirred solution of methyl (3-(4-(*N*-methylpropiolamido)phenyl)propyl)carbamate (**S-2**)[7k] in MeOH were successively added boronic acid, $Pd(OAc)_2$, Ag_2O, and CsF at rt, then the reaction mixture was stirred at the same temperature. The reaction mixture was filtered through a pad of Celite and rinsed with $CHCl_3$, and concentrated in vacuo. The crude product was purified to give **1d**, **f**, **h**, **i**.

*General procedure C. Synthesis of N-arylpropiolamides **1j**, **l**–**m, o**–**p**.*

To a stirred solution of methyl (3-(4-(3-phenylpropiolamido)phenyl)propyl)carbamate (**S-3**)[7k] in MeCN were successively added K_2CO_3, TBAI (if necessary), and halide at rt, and the stirring was continued at the same temperature. The reaction mixture was filtered through Celite and concentrated in vacuo. The crude product was purified to give **1j, l–m, o–p**.

*General procedure D. Synthesis of N-arylpropiolamides **1k**, **q**–**t**.*

To a stirred solution of *tert*-butyl (3-(4-(*N*-methyl-3-phenylpropiolamido)phenyl)propyl)carbamate (**S-4**) in CH_2Cl_2 or $CHCl_3$ was added TFA at rt, and the stirring was continued at rt for CH_2Cl_2 or at 50 °C for $CHCl_3$. The reaction mixture was concentrated in vacuo. To the residue were successively added CH_2Cl_2, K_2CO_3, and halide or anhydride at 0 °C, and the stirring was continued. The reaction was quenched with aqueous saturated NH_4Cl. After the organic layer was separated, the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude was purified to give **1k, q–t.**

*General procedure E. Synthesis of diazadispirocycles cis-**2a**–**j**: [Method A]*.

To a stirred solution of **1a-j** in EtCN was added dropwise ICl solution (1.0 mol/L solution in MeCN) at –78 °C. After being stirred at the same temperature for 10 min, the reaction mixture was allowed to stir at rt for 50 min. The reaction was quenched with 10% aqueous Na_2SO_3 at rt and diluted with $CHCl_3$. After the organic layer was separated, the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude was purified to give *cis*-**2a-j**.

*General procedure F. Synthesis of diazadispirocycles cis-**2j**–**t**, **2a-Br**,**Cl**: [Method B]*

To a stirred solution of **1a,j-t** in HFIP were successively added AgTFA and NIS (NBS for *cis*-**2a-Br**, NCS for *cis*-**2a-Cl**) at 0 °C and the stirring was continued. The reaction was quenched with 10% aqueous Na_2SO_3 and diluted with $CHCl_3$. After the organic layer was separated, the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue thus obtained was dissolved in MeCN. Then, to the solution was added *p*-TsOH•H_2O at rt. and the stirring was continued at the same temperature. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ at rt. After the organic layer was separated, the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude was purified to give *cis*-**2j-t, 2a-Br,Cl**.

Synthesis and Characterization Data.

Methyl (3-(4-(N-methyl-3-(p-tolyl)propiolamido)phenyl)propyl)carbamate (**1b**). Compound **1b** was obtained in 78% yield (337 mg, 0.837 mmol) for 2 steps as a colorless solid according to the **general procedure A**; **S-1** (223 mg, 1.07 mmol), EDC (226 mg, 1.18 mmol, 1.1 equiv), 3-(*p*-tolyl)propiolic acid (189 mg, 1.18 mmol, 1.1 equiv), CH_2Cl_2 (10 mL), 0 °C to rt, 2 min; K_2CO_3 (383 mg, 2.77 mmol, 3.0 equiv), MeI (0.173 mL, 2.77 mmol, 3.0 equiv), MeCN (9.0 mL), rt, 24h; silica gel column chromatography (70% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 85:15, only the data for the major isomer is given) δ 7.22-7.29 (4H, m), 7.02-7.05 (4H, m), 4.70 (1H, s), 3.68 (3H, s), 3.36 (3H, s), 3.23 (2H, q, *J* = 6.5 Hz), 2.70 (2H, t, *J* = 7.7 Hz), 2.31 (3H, s), 1.84-1.89 (2H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) δ (Asterisks indicate peaks for minor rotamer) 157.05, 154.52, 141.26, 140.40, 132.41*, 132.31, 129.34*, 129.07, 128.98, 127.40, 125.45* , 117.37, 91.20, 82.27, 52.09, 40.49,39.69*, 36.34, 32.57, 31.73, 21.69*, 21.59; **HRMS** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{25}N_2O_3$ 365.1865, found 365.1854.

Methyl (3-(4-(3-(4-methoxyphenyl)-N-methylpropiolamido)phenyl)propyl)carbamate (**1c**). Compound **1c** was obtained in 41% yield (181 mg, 0.476 mmol) for 2 steps as a pale yellow solid according to the **general procedure A**; **S-1** (240 mg, 1.15 mmol), EDC (287 mg, 1.50 mmol, 1.3 equiv), 3-(4-methoxyphenyl)propiolic acid (264 mg, 1.50 mmol, 1.3 equiv), CH_2Cl_2 (10 mL, 0.1 mol/L), –20 °C to rt, 90 min; K_2CO_3 (226 mg, 1.64 mmol, 3.0 equiv), MeI (0.102 mL, 1.64 mmol, 3.0 equiv), MeCN (2.7 mL), rt, 24h; silica gel column chromatography (80% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 85:15, only the data for the major isomer is given) δ 7.26 (2H, d, *J* = 8.4 Hz), 7.40 (2H, *J* = 8.4 Hz), 7.07 (2H, d, *J* = 8.7 Hz), 6.75 (2H, d, *J* = 8.7 Hz), 4.71 (1H, brs), 3.78 (3H, s), 3.67 (3H, brs), 3.36 (3H, s), 3.23 (2H, m), 2.71 (2H, t, *J* = 7.7 Hz), 1.86 (2H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 160.9, 157.1, 154.7, 141.3, 141.2, 134.2, 129.0, 127.4, 114.0, 112.3, 91.4, 82.0, 55.3, 52.1, 40.5, 36.3, 32.6, 31.7; **HRMS** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{25}N_2O_4$ 381.1814, found 381.1800.

Methyl (3-(4-(3-(4-chlorophenyl)-N-methylpropiolamido)phenyl)propyl)carbamate (**1d**). Compound **1d** was obtained in 64% yield (44.6 mg, 0.116 mmol) as a colorless oil according to the **general procedure B**; **S-2** (50.0 mg, 0.182 mmol), (4-chlorophenyl)boronic acid (37.1 mg, 0.237 mmol, 1.3 equiv), $Pd(OAc)_2$ (2.05 mg, 9.11 µmol, 0.05 equiv), CsF (36.0 mg, 0.237 mmol, 1.3 equiv), Ag_2O (84.5 mg, 0.365 mmol, 2.0 equiv), MeOH (1.0 mL), rt, 24 h; silica gel column chromatography (60% AcOEt/hexane); gel permeation chromatography (Shodex GPC H-2001 and Shodex GPC H-2002, $CHCl_3$, flow rate 3.5 mL/min, detection λ 254 nm).

Methyl (3-(4-(N-methyl-3-(4-(trifluoromethyl)phenyl)propiolamido)phenyl)propyl)carbamate (**1e**). Compound **1e** was obtained in 95% yield (76.0 mg, 0.180 mmol) for 2 steps as a colorless solid according to the **general procedure A**; **S-1** (40.0 mg, 0.190 mmol), EDC (41 mg, 0.210 mmol, 1.1 equiv), 3-(4-(trifluoromethyl)phenyl)propiolic acid (45.0 mg, 0.210 mmol, 1.1 equiv), CH_2Cl_2 (2.0 mL, 0.1 mol/L), 0 °C to rt, 4 h; K_2CO_3 (82 mg, 0.59 mmol, 3.0 equiv), MeI (0.037 mL, 0.59 mmol, 3.0 equiv), MeCN (2.0 mL, 0.1 mol/L), rt, 24 h; silica gel column chromatography (60% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 85:15, only the data for the major isomer is given) δ 7.51 (2H, d, *J* = 8.2 Hz), 7.23-7.29 (6H, m), 4.69 (1H, s), 3.67 (3H, s), (3H, s), 3.23 (2H, q, *J* = 6.6 Hz), 2.71 (2H, t, *J* = 7.9 Hz), 1.84-1.89 (2H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) (Asterisks indicate peaks of minor rotamer) δ 157.03, 153.71, 141.59, 140.76, 139.07*, 132.53* , 132.46 , 131.31 (q, *J* = 33 Hz), 129.07 , 127.24 , 125.42, 125.29, 125.18 (q, *J* = 4.2 Hz) 124.17, 123.46 (q, *J* = 270 Hz), 88.63, 84.16, 51.92, 40.39, 39.58*, 36.34, 32.46, 31.56, 31.39*; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –66.3; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{22}F_3N_2O_3$ 419.1583, found 419.1577.

Methyl (3-(4-(N-methyl-3-(4-nitrophenyl)propiolamido)phenyl)propyl)carbamate (**1f**). Compound **1f** was obtained in 29% yield (20.7 mg, 0.0523 mmol) as a colorless oil according to the **general procedure B**; **S-2** (50.0 mg, 0.182 mmol), (4-nitrophenyl)boronic acid (39.6 mg, 0.237 mmol, 1.3 equiv), $Pd(OAc)_2$ (2.05 mg, 9.11 µmol, 0.05 equiv), CsF (36.0 mg, 0.237 mmol, 1.3 equiv), Ag_2O (84.5 mg, 0.365 mmol, 2.0 equiv), MeOH (1.0 mL), rt, 3 h; silica gel column chromatography (60% AcOEt/hexane); gel permeation chromatography (Shodex GPC H-2001 and Shodex GPC H-2002, $CHCl_3$, flow rate 3.5 mL/min, detection λ 254 nm). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 85:15, only the data for the major isomer is given) δ 8.12 (2H, d, *J* = 9.0 Hz), 7.31 (2H, d, *J* = 9.0 Hz), 7.27 (4H, brs), 4.70 (1H, brs), 3.68 (3H, brs), 3.38 (3H, s), 3.22 (2H, q, *J* = 7.2 Hz), 2.71 (2H, t, *J* = 7.2 Hz), 1.86 (2H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 157.1, 153.4, 148.0, 141.7, 140.7, 133.1, 129.2, 127.3, 127.1, 123.5, 87.8, 86.3, 52.1, 40.4, 36.5, 32.5, 31.6; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{22}N_3O_5$ 396.1560, found 396.1541.

Methyl (3-(4-(3-(2-methoxyphenyl)-N-methylpropiolamido)phenyl)propyl)carbamate (**1g**). Compound **1g** was obtained in 97% yield (394 mg, 0.104 mmol) for 2 steps as a pale brown oil according to the **general procedure A**; **S-1** (223 mg, 0.107 mmol), EDC (226 mg, 1.18 mmol, 1.1 equiv), 3-(2-methoxyphenyl)propiolic acid (208 mg, 1.18 mmol, 1.1 equiv), CH_2Cl_2 (10 mL, 0.1 mol/L), –20 °C to rt, 1 h; K_2CO_3 (403 mg, 2.92 mmol, 3.0 equiv), MeI (0.183 mL, 2.92 mmol, 3.0 equiv), MeCN (9.0 mL, 0.1 mol/L), rt, 24h; silica gel column chromatography (80% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 85:15, only the data for the major isomer is given) δ 7.29-7.25 (3H, m), 7.22 (2H, t, *J* = 7.9 Hz), 7.06 (1H, d, *J* = 7.6 Hz), 6.81-6.76 (2H, m), 4.69 (1H, brs), 3.71 (3H, s), 3.67 (3H, brs), 3.36 (3H, s), 3.23 (2H, q, *J* = 6.9 Hz), 2.67 (2H, t, *J* = 6.9 Hz), 1.86 (2H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 160.7, 157.0, 154.2, 140.9, 134.0, 131.3, 128.7, 127.0, 120.0, 110.5, 109.3, 87.6, 86.2, 55.5, 51.7, 40.3, 36.2, 32.3, 31.3; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{25}N_2O_4$ 381.1814, found 381.1812.

Methyl (3-(4-(N-methyl-3-(naphthalen-2-yl)propiolamido)phenyl)propyl)carbamate (**1h**). Compound **1h** was obtained in 61% yield (44.6 mg, 0.111 mmol) as a colorless oil according to the **general procedure B**; **S-2** (50.0 mg, 0.182 mmol), 2-naphthaleneboronic acid (40.8 mg, 0.237 mmol, 1.3 equiv), $Pd(OAc)_2$ (2.05 mg, 9.11 µmol, 0.05 equiv), CsF (36.0 mg, 0.237 mmol, 1.3 equiv), Ag_2O (84.5 mg, 0.365 mmol, 2.0 equiv), MeOH (0.75 mL), rt, 3 h; silica gel column chromatography (60% AcOEt/hexane); gel permeation chromatography (Shodex GPC H-2001 and Shodex GPC H-2002, $CHCl_3$, flow rate 3.5 mL/min, detection λ 254 nm). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 85:15, only the data for the major isomer is given) δ 7.76 (1H, d, *J* = 7.2 Hz), 7.72-7.66 (3H, m), 7.52-7.45 (2H, m), 7.34-7.26 (4H, m), 7.11 (1H, d, *J* = 8.2 Hz), 4.70 (1H, brs), 3.62 (3H, s), 3.41 (3H, s), 3.24 (2H, q, *J* = 6.3 Hz), 2.73 (2H, t, *J* = 7.7 Hz), 1.91-1.85 (2H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 157.0, 154.3, 141.4, 141.1, 133.4, 133.1, 132.4, 129.0, 128.0, 127.99, 127.95, 127.7, 127.5, 127.3, 126.7, 117.6, 91.2, 82.8, 52.0, 40.5, 36.3, 32.5, 31.7; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{25}N_2O_3$ 401.1865, found 401.1885.

Methyl (3-(4-(3-(benzo[b]thiophen-3-yl)-N-methylpropiolamido)phenyl)propyl)carbamate (**1i**). Compound **1i** was obtained in 65% yield (48.0 mg, 0.118 mmol) as a colorless oil according to the **general procedure B**; **S-2** (50.0 mg, 0.182 mmol), *B*-benzo[*b*]thien-3-ylboronic acid (42.2 mg, 0.237 mmol), $Pd(OAc)_2$ (2.05 mg, 9.11 µmol), CsF (36.0 mg, 0.237 mmol), Ag_2O (84.5 mg, 0.365 mmol), MeOH (1.0 mL), rt, 30 min; silica gel column chromatography (60% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 85:15, only the data for the major isomer is given) δ 7.76 (1H, d, *J* = 7.8 Hz), 7.67 (1H, s), 7.33-7.28 (5H, m), 7.21 (1H, t, *J* = 7.8 Hz), 6.99 (1H, d, *J* = 7.8 Hz), 4.75 (1H, brs), 3.67 (3H, s), 3.39 (3H, s), 3.22 (2H, q, *J* = 6.5 Hz), 2.74 (2H, t, *J* = 7.7 Hz), 1.89-1.84 (2H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 157.0, 154.3, 141.7, 141.2, 138.5, 138.5, 134.5, 129.3, 127.6, 125.2, 124.6, 122.7, 122.5, 115.8, 85.2, 84.7, 52.0, 40.5, 36.5, 32.6, 31.7; **HRMS** (ESI) *m/z* $[M+Na]^+$ calcd for $C_{23}H_{22}N_2NaO_3S$ 429.1249, found 429.1226.

Methyl (3-(4-(N-benzyl-3-phenylpropiolamido)phenyl)propyl)carbamate (**1j**). Compound **1j** was obtained in 87% yield (329 mg, 0.771 mmol) as a colorless oil according to the **general procedure C**; **S-3** (300 mg, 0.892 mmol), K_2CO_3 (616 mg, 4.46 mmol, 5.0 equiv), TBAI (32.9 mg, 0.0892 mmol, 0.1 equiv), benzyl bromide (0.111 mL, 0.936 mmol, 1.05 equiv), MeCN (4.0 mL), rt, 24 h; silica gel column chromatography (40% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 85:15, only the data for the major isomer is given) δ 7.33-7.25 (6H, m), 7.22 (2H, t, *J* = 7.4 Hz), 7.16-7.13 (2H, d, *J* = 7.8 Hz), 7.09 (2H, d, *J* = 8.4 Hz), 7.07 (2H, d, *J* = 8.4 Hz), 4.98 (2H, s), 4.67 (1H, brs), 3.65 (3H, s), 3.20 (2H, m), 2.66 (2H, t, *J* = 7.8 Hz), 1.83 (2H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 157.0, 154.5, 141.5, 139.6, 136.7, 132.4, 129.9, 128.9, 128.7, 128.6, 128.5, 128.3, 127.5, 120.4, 91.4, 82.6, 52.3, 52.1, 40.5, 32.6, 31.6; **HRMS** (ESI) *m/z* $[M+Na]^+$ calcd for $C_{27}H_{26}N_2NaO_3$ 449.1841, found 449.1831.

tert-Butyl (3-(4-(N-methyl-3-phenylpropiolamido)phenyl)propyl)carbamate (**S-4**). To a stirred solution of *tert*-butyl (3-(4-(*N*-methyl-3-phenylpropiolamido)phenyl)propyl)carbamate[19] (65.0 mg, 0.260 mmol, 1.0 eq.) in CH_2Cl_2 (2.0 mL) were successively added phenyl propiolic acid (45.5 mg, 0.312 mmol, 1.2 eq.) and EDC (65.7 mg, 0.343 mmol, 1.32 eq.) at –30 °C. The reaction was stirred at the same temperature for 15 min before diluted with $CHCl_3$ and water. After the organic layer was separated, the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. To the residue were successively added MeCN (2.0 mL), K_2CO_3 (108 mg, 0.780 mmol,

3.0 equiv), and MeI (0.049 mL, 0.780 mmol, 3.0 equiv) at rt, and this mixture was stirred at the same temperature for 24 h. The reaction mixture was filtered through Celite and concentrated in vacuo, then purified through silica gel column chromatography to give **S-4** (78.1 mg, 77% yield for 2 steps) as a colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$) (A mixture of rotamers in 85:15, only the data for the major isomer is given) δ 7.59-7.22 (7H, m), 7.14-7.12 (2H, m), 4.55 (1H, brs), 3.65 (0.45H, s), 3.34 (2.55H, s), 3.22-3.15 (2H, m), 2.72-2.64 (2H, m), 1.88-1.80 (2H, m), 1.44 (9H, s); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.9, 154.4, 141.5, 141.1, 132.4, 129.9, 129.0, 128.3, 127.4, 120.5, 90.74, 82.64, 79.3, 40.1, 36.3, 32.7, 31.8, 28.4; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{29}N_2O_3$ 393.2178, found 393.2172.

N-Methyl-N-(4-(3-(methylsulfonamido)propyl)phenyl)-3-phenylpropiolamide (**1k**). Compound **1k** was obtained in 82% yield (174 mg, 0.470 mmol) for 2 steps as a colorless oil according to the **general procedure D**; **S-4** (224 mg, 0.571 mmol), TFA (0.440 mL, 5.71 mmol, 10 equiv), CH_2Cl_2 (1.1 mL), rt, 2 h 10 min; MsCl (0.0700 mL, 0.571 mmol, 1.0 equiv), K_2CO_3 (236 mg, 1.71 mmol, 3 equiv), CH_2Cl_2 (1.1 mL), rt, 22 h; silica gel column chromatography (60% AcOEt/hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) (A mixture of rotamers in 85:15, only the data for the major isomer is given) δ 7.36-7.22 (7H, m), 7.15-7.13 (2H, m), 4.61 (1H, brt, *J* = 6.0 Hz), 3.37 (3H, s), 3.17 (2H, brq, *J* = 6.7 Hz), 2.94 (3H, s), 2.77-2.74 (2H, m), 1.97-1.90 (2H, m); **^{13}C NMR** (100 MHz, $CDCl_3$) (one carbon missing) δ 154.3, 141.3, 140.8, 132.3, 129.9, 129.0, 128.3, 127.4, 120.4, 90.8, 82.6, 42.6, 40.2, 36.4, 32.3, 31.8; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{23}N_2O_3S$ 371.1429, found 371.1401.

Ethyl N-(4-(3-((methoxycarbonyl)amino)propyl)phenyl)-N-(3-phenylpropioloyl)glycinate (**1l**). Compound **1l** was obtained in 67% yield (251 mg, 0.594 mmol) as a colorless oil according to the **general procedure C**; **S-3** (300 mg, 0.892 mmol), K_2CO_3 (370 mg, 2.68 mmol, 3.0 equiv), ethyl bromoacetate (0.099 mL, 0.892 mmol, 1.0 equiv), MeCN (6.0 mL), rt, 24 h; silica gel column chromatography (60% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 85:15, only the data for the major isomer is given) δ 7.39 (2H, d, *J* = 8.2 Hz), 7.31 (1H, m), 7.24 (4H, m), 7.14-7.12 (2H, m), 4.69 (1H, brs), 4.48 (2H, s), 4.22 (2H, q, *J* = 7.2 Hz), 3.67 (3H, s), 3.23 (2H, m), 2.70 (2H, brt, *J* = 7.7 Hz), 1.85 (2H, m), 1.29 (3H, t, *J* = 7.2 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 168.3, 157.0, 154.5, 141.9, 139.9, 132.3, 130.0, 129.0, 128.2, 128.1, 120.1, 91.6, 82.0, 61.4, 51.9, 50.3, 40.4, 32.5, 31.5, 14.0; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{27}N_2O_5$ 423.1920, found 423.1920.

*Methyl (3-(4-(N-(2-cyclopropyl-2-oxoethyl)-3-phenylpropiolamido)phenyl)propyl)carbamat*e (**1m**). Compound **1m** was obtained in 89% yield (332 mg, 0.793 mmol) as a pale yellow oil according to the **general procedure C**; **S-3** (300 mg, 0.892 mmol), K_2CO_3 (370 mg, 2.68 mmol, 3.0 equiv), 2-bromo-1-cyclopropylethanone (0.0871 mL, 0.892 mmol, 1.0 equiv), MeCN (15.0 mL), rt, 24 h; silica gel column chromatography (60% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 85:15, only the data for the major isomer is given) δ 7.34 (2H, d, *J* = 8.4 Hz), 7.33 (1H, m), 7.23 (4H, m), 7.13 (2H, d, *J* = 7.2 Hz), 4.73 (2H, s), 3.67 (3H, s), 3.23 (2H, brq, *J* = 6.3 Hz), 2.69 (2H, t, *J* = 7.7 Hz), 1.98 (1H, m), 1.85 (2H, m), 1.13 (2H, m), 0.96 (2H, td, *J* = 7.5, 3.9 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 203.7, 157.0, 154.2, 141.7, 139.9, 132.2, 129.9, 128.8, 128.1, 128.0, 120.0, 91.4, 82.0, 58.3, 51.8, 40.3, 32.4, 31.4, 18.1, 11.4, 11.2; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{27}N_2O_4$ 419.19708, found 419.1948.

Methyl (3-(4-((2-((tert-butyldimethylsilyl)oxy)ethyl)amino)phenyl)propyl)carbamate (**S-5**). Chusov's reductive amination protocol[20] was used. Aniline **S-1** (209 mg, 0.835 mmol) and 2-((*tert*-butyldimethylsilyl)oxy)acetaldehyde (249 mg, 0.835 mmol, 1.0 equiv) were dissolved in THF (7.5 mL). To the solution was added $Ti(OiPr)_4$ (0.49 mL, 1.67 mmol, 2 equiv) at rt, and the stirring was kept for 3 h. After THF was removed under reduced pressure, to the residue were added dichloroethane (3.5 mL) and $NaBH(OAc)_3$ (248 mg, 1.17 mmol, 1.4 equiv) at rt, and stirred for 23 h at the same temperature. The reaction was quenched with aqueous saturated $NaHCO_3$ and the mixture was filtered through a pad of Celite and rinsed with $CHCl_3$. The filtrate was diluted with H_2O and $CHCl_3$. The organic layer was separated and dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude was chromatographed on silica gel with 40% AcOEt/hexane to give **S-5** (300 mg, 0.563 mmol, 67% yield) as a colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.98 (2H, d, *J* = 8.4 Hz), 6.58 (2H, d, *J* = 8.4 Hz), 4.63 (1H, brs), 3.81 (2H, t, *J* = 5.4 Hz), 3.66 (3H, brs), 3.19 (4H, t, *J* = 5.4 Hz), 2.54 (2H, t, *J* = 7.7 Hz), 1.80-1.75 (2H, m), 0.90 (9H, s), 0.06 (6H, s); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 157.0, 146.5, 130.3, 129.0, 113.4, 61.6, 51.9, 46.2, 40.6, 32.0, 31.8, 25.9, 18.3, –5.4; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{35}N_2O_3Si$ 367.2417, found 367.2399.

Methyl (3-(4-(N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-3-phenylpropiolamido)phenyl)propyl)carbamate (**S-6**). To a stirred solution of aniline **S-5** (0.253 g, 0.691 mmol) in CH_2Cl_2 (4.9 mL) were successively added phenylpropiolic acid (0.111 g, 0.760 mmol, 1.1 equiv) then EDC (0.146 g, 0.760 mmol, 1.1 equiv) at –30 °C, and stirred for 1 h. The reaction was quenched with water. After the organic layer separation, the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo, and chromatographed on silica gel with 35% AcOEt/hexane to give **S-6** (0.320 g, 0.647 mmol, 94% yield) as a pale yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 70:30, only the data for the major isomer is given) δ 7.32-7.30 (3H, m), 7.23-7.19 (4H, m), 7.12-7.10 (2H, m), 4.72 (1H, s), 3.90 (2H, t, *J* = 5.8 Hz), 3.82 (2H, t, *J* = 5.8 Hz), 3.67 (3H, s), 3.23 (2H, brq, *J* = 6.4 Hz), 2.69 (2H, brt, *J* = 7.7 Hz), 1.88-1.83 (2H, m), 0.86 (9H, s), 0.03 (6H, s); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 157.0, 154.4, 141.3, 140.4, 132.3, 129.8, 129.1, 128.7, 128.4, 128.2, 127.1, 120.5, 90.7, 82.8, 60.0, 54.2, 52.0, 51.2, 40.5, 32.5, 31.7, 25.8, 25.7, 18.1, –5.5; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{39}N_2O_4Si$ 495.2679, found 495.2660.

Methyl (3-(4-(N-(2-hydroxyethyl)-3-phenylpropiolamido)phenyl)propyl)carbamate (**1n**). **S-6** (11.5 mg, 23.2 μmol), THF (0.50 mL), and TBAF (23.2 μL, 23.2 μmol, 1.1 equiv) were mixed at 0 °C, and stirred for 10 h at the same temperature. To the reaction was added water and diluted with $CHCl_3$ After the organic layer was separated, the organic layer was extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo, and chromatographed on silica gel with AcOEt to give **1n** (7.00 mg, 18.4 μmol, 79% yield) as a colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 70:30, only the data for the major isomer is given) δ 7.45-7.22 (7H, m), 7.10 (2H, dd, *J* = 8.4, 0.9 Hz), 4.69 (1H, brs), 3.99 (2H, t, *J* = 5.3 Hz), 3.85 (2H, t, *J* = 5.3 Hz), 3.68 (3H, brs), 3.23 (2H, q, *J* = 6.3 Hz), 2.71 (2H, t, *J* = 7.8 Hz), 1.87 (2H, m), 1.58 (1H, brs).**^{13}C NMR** (150 MHz, $CDCl_3$) δ 157.1, 156.0, 141.9, 140.0, 132.4, 130.1, 129.2, 128.35, 128.31, 120.2, 92.0, 82.4, 61.2, 52.1 (two peaks, overlap), 40.5, 32.6, 31.7; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{25}N_2O_4$ 381.1814, found 381.1795.

Methyl (3-(4-(3-phenyl-N-(prop-2-yn-1-yl)propiolamido)phenyl)propyl)carbamate (**1o**). Compound **1o** was obtained in 79% yield (133 mg, 0.354 mmol) as a pale brown oil according to the **general procedure C**; **S-3** (150 mg, 0.446 mmol), K_2CO_3 (370 mg, 2.68 mmol, 6.0 equiv), propargyl bromide (0.0923 mL, 1.07 mmol, 2.4 equiv), MeCN (8.0 mL), rt, 24 h; silica gel column chromatography (60% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 85:15, only the data for the major isomer is given) δ 7.38-7.20 (7H, m), 7.09-7.08 (2H, m), 4.93 (1H, brs), 4.54 (2H, s), 3.65 (3H, s), 3.25-3.18 (2H, m), 2.71-

2.69 (2H, m), 2.24 (1H, t, *J* = 2.4 Hz), 1.85 (2H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 157.1, 153.9, 142.1, 138.9, 132.4, 130.0, 129.0, 128.4, 128.2, 120.1, 91.6, 82.1, 78.2, 72.5, 51.9, 40.4, 37.7, 32.5, 31.6; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{23}N_2O_3$ 375.1709, found 375.1705.

Methyl (3-(4-(N-(cyanomethyl)-3-phenylpropiolamido)phenyl)propyl)carbamate (**1p**). Compound **1p** was obtained in 79% yield (133 mg, 0.354 mmol) as a brown oil according to the **general procedure C**; **S-3** (150 mg, 0.446 mmol), K_2CO_3 (370 mg, 2.68 mmol, 6.0 equiv), 2-bromoacetonitrile (0.0619 mL, 0.892 mmol, 2.0 equiv), MeCN (8.0 mL), rt, 24h; silica gel column chromatography (60% AcOEt/hexane); PTLC (50% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 85:15, only the data for the major isomer is given) δ 7.36-7.31 (5H, m), 7.26-7.23 (2H, m), 7.11 (2H, d, *J* = 8.2 Hz), 4.80 (1H, brs), 4.68 (2H, s), 3.67 (3H, s), 3.23 (2H, brq, *J* = 6.4 Hz), 2.73 (2H, t, *J* = 7.7 Hz), 1.87 (2H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 157.1, 154.1, 143.1, 137.9, 132.5, 130.5, 129.6, 128.4, 128.1, 119.6, 114.8, 93.2, 81.1, 52.0, 40.4, 36.2, 32.6, 31.6; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{22}N_3O_3$ 376.1661, found 376.1652.

Benzyl (3-(4-(N-methyl-3-phenylpropiolamido)phenyl)propyl)carbamate (**1q**). Compound **1q** was obtained in 90% yield (174 mg, 0.470 mmol) for 2 steps as a colorless oil according to the **general procedure D**; **S-4** (202 mg, 0.513 mmol), TFA (0.400 mL, 5.23 mmol, 10 equiv), $CHCl_3$ (1.0 mL), 50 °C, 1.5 h; benzyl chloroformate (0.0900 mL, 0.635 mmol, 1.4 equiv), K_2CO_3 (214 mg, 1.55 mmol, 3.3 equiv), CH_2Cl_2 (1.5 mL), rt, 22 h; silica gel column chromatography (60% AcOEt/hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) (A mixture of rotamers in 85:15, only the data for the major isomer is given) δ 7.41-7.21 (12H, m), 7.13 (2H, d, *J* = 7.1 Hz), 5.11 (2H, s), 4.80 (1H, brs), 3.36 (3H, s), 3.25 (2H, brq, *J* = 6.7 Hz), 2.69 (2H, t, *J* = 7.7 Hz), 1.90-1.83 (2H, m); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.3, 154.2, 141.3, 141.0, 136.4, 132.2, 129.8, 128.9, 128.4, 128.2, 128.0, 127.2, 125.3, 120.3, 90.7, 82.5, 66.5, 40.4, 36.2, 32.5, 31.5; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{27}N_2O_3$ 427.2022, found 427.2028.

Phenyl (3-(4-(N-methyl-3-phenylpropiolamido)phenyl)propyl)carbamate (**1r**). Compound **1r** was obtained in 96% yield (207 mg, 0.502 mmol) for 2 steps as a colorless oil according to the **general procedure D**; **S-4** (205 mg, 0.521 mmol), TFA (0.400 mL, 5.23 mmol, 10 equiv), $CHCl_3$ (1.0 mL), 50 °C, 2 h; phenyl chloroformate (0.0920 mL, 0.729 mmol, 1.4 equiv), K_2CO_3 (217 mg, 1.56 mmol, 3 equiv), CH_2Cl_2 (1.0 mL), rt, 18 h; silica gel column chromatography (60% AcOEt/hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) (A mixture of rotamers in 85:15, only the data for the major isomer is given) δ 7.38-7.32 (3H, m), 7.30-7.15 (7H, m), 7.12 (4H, m), 5.16 (1H, brs), 3.36 (3H, s), 3.30-3.28 (2H, m), 2.74 (2H, brt, *J* = 7.7 Hz), 1.96-1.89 (2H, m); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.6, 154.1, 150.8, 141.2, 140.7, 132.1, 129.7, 129.0, 128.8, 128.1, 127.0, 124.9, 121.3, 120.0, 90.6, 82.3, 40.3, 36.1, 32.3, 31.1; **HRMS** (ESI) *m/z* $[M+Na]^+$ calcd for $C_{26}H_{24}N_2NaO_3$ 435.1685, found 435.1675.

N-methyl-N-(4-(3-((4-methylphenyl)sulfonamido)propyl)phenyl)-3-phenylpropiolamide (**1s**). Compound **1s** was obtained in 77% yield (180 mg, 0.403 mmol) for 2 steps as a colorless oil according to the **general procedure D**; **S-4** (205 mg, 0.521 mmol), TFA (0.400 mL, 5.23 mmol, 10 equiv), $CHCl_3$ (1.0 mL), 50 °C, 1 h; *p*-toluenesulfonyl chloride (111 mg, 0.574 mmol, 1.1 equiv), K_2CO_3 (219 mg, 1.57 mmol, 3 equiv), CH_2Cl_2 (1.0 mL), rt, 21 h; silica gel column chromatography (60% AcOEt/hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) (A mixture of rotamers in 85:15, only the data for the major isomer is given) δ 7.75 (2H, d, *J* = 8.2 Hz), 7.38-7.07 (11H, m), 5.37 (1H, brs), 3.34 (3H, d, *J* = 4.4 Hz), 2.97-2.94 (2H, m), 2.68-2.58 (2H, m), 2.38 (3H, s), 1.85-1.78 (2H, m); **^{13}C NMR** (100 MHz, $CDCl_3$) (one carbon missing) δ 154.3, 143.2, 141.0, 136.8, 132.2, 129.8, 129.6, 129.0, 128.2, 127.2, 126.9, 120.2, 90.8, 82.5, 42.3, 36.3, 32.1, 31.1, 21.4; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{27}N_2O_3S$ 447.1742, found 447.1735.

N-(4-(3-Acetamidopropyl)phenyl)-N-methyl-3-phenylpropiolamide (**1t**). Compound **1t** was obtained in 68% yield (122 mg, 0.365 mmol) for 2 steps as a pale yellow oil according to the **general procedure D**; **S-4** (211 mg, 0.537 mmol), TFA (0.411 mL, 5.37 mmol, 3.5 equiv), $CHCl_3$ (1.0 mL), 50 °C, 1 h; acetyl chloride (0.120 mL, 1.87 mmol, 1.5 equiv), K_2CO_3 (223 mg, 1.61 mmol, 3 equiv), CH_2Cl_2 (1.0 mL), rt, 21 h; silica gel column chromatography (2% MeOH/AcOEt). **^{1}H NMR** (400 MHz, $CDCl_3$) (A mixture of rotamers in 85:15, only the data for the major isomer is given) δ 7.38-7.24 (7H, m), 7.17-7.15 (2H, m), 5.55 (1H, brs), 3.39 (3H, s), 3.33 (2H, brq, *J* = 6.7 Hz), 2.73 (2H, brt, *J* = 7.9 Hz), 2.00 (3H, s), 1.93-1.85 (2H, m); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.1, 154.3, 141.4, 141.0, 132.3, 129.9, 129.0, 128.3, 127.3, 120.3, 90.8, 82.5, 39.1, 36.3, 32.7, 31.2, 23.3; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{23}N_2O_2$ 335.1760, found 335.1745.

Methyl (5s,8s)-11-iodo-9-methyl-10-oxo-12-phenyl-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate (*cis*-**2a**). Compound *cis*-**2a** was obtained in 95% yield (64.8 mg, 0.136 mmol) as a colorless solid according to the **general procedure E**; **1a** (50.0 mg, 0.143 mmol), ICl (1 mol/L MeCN solution, 0.214 mL, 0.214 mmol, 1.5 equiv), EtCN (1.4 mL), –78 °C to rt, 1 h; silica gel column chromatography (80% AcOEt/hexane). The compound data were consistent with the literature[7k]. Compound *cis*-**2a** was obtained in 90% yield (61.3 mg, 0.129 mmol) for 2 steps as a colorless solid according to the **general procedure F**; **1a** (50.0 mg, 0.143 mmol), NIS (35.4 mg, 0.157 mmol, 1.1 equiv), AgTFA (3.16 mg, 15.7 μmol, 0.1 equiv), HFIP (1.4 mL), 0 °C, 24 h; *p*-TsOH•H_2O (27.2 mg, 0.143 mmol, 1.0 equiv), MeCN (1.4 mL), rt, 24 h; silica gel column chromatography (80% AcOEt/hexane). The compound data were consistent with the literature[7k].

Methyl (5s,8s)-11-iodo-9-methyl-10-oxo-12-(p-tolyl)-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate (*cis*-**2b**). Compound *cis*-**2b** was obtained in 95% yield (75.0 mg, 0.153 mmol) as a colorless solid according to the **general procedure E**; **1b** (59.1 mg, 0.162 mmol), ICl (1 mol/L MeCN solution, 0.162 mL, 0.162 mmol, 1.0 equiv), EtCN (1.6 mL), –78 °C to rt, 1 h; silica gel column chromatography (80% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 65:35 ratio) δ 7.16 (2H, d, *J* = 7.9 Hz), 7.13 (1.3H, d, *J* = 7.6 Hz), 7.07-7.08 (0.7H, m), 5.99 (2H, dd, *J* = 9.6 Hz), 5.42 (1.3H, d, *J* = 9.6 Hz), 5.34 (0.7H, d, *J* = 8.9 Hz), 3.63 (1.95H, s), 3.59 (1.05H, s), 3.52-3.58 (0.7H, m), 3.48 (1.3H, t, *J* = 6.5 Hz), 3.10 (1.95H, s), 2.97 (1.05H, s), 2.36 (3H, s), 1.71-1.76 (2H, m), 1.22-1.28 (2H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) (Asterisks indicate peaks for the minor rotamer) δ 167.12, 163.17, 154.45, 139.09, 137.23*, 136.38, 130.77, 128.70, 128.16, 123.71, 122.83*, 96.58, 69.85, 59.17, 52.09, 48.40*, 47.50, 41.71*, 40.43, 27.30, 26.76*, 22.77, 22.18*, 21.40; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{24}IN_2O_3$ 491.0832, found 491.0833.

Methyl (5s,8s)-11-iodo-12-(4-methoxyphenyl)-9-methyl-10-oxo-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate (*cis*-**2c**). Compound *cis*-**2c** was obtained in 85% yield (68.6 mg, 0.135 mmol) as a colorless solid according to the **general procedure E**; **1c** (60.8 mg, 0.160 mmol), ICl (1 mol/L MeCN solution, 0.160 mL, 0.160 mmol, 1.0 equiv), EtCN (1.4 mL), –78 °C to rt, 1 h; silica gel column chromatography (80% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 65:35 ratio) δ 7.17 (1.3H, brd, *J* = 7.6 Hz) 7.13 (0.7H, m), 6.87 (2H, d, *J* = 8.9 Hz), 5.98 (2H, d, *J* = 10.0 Hz), 5.41 (1.3H, brd, *J* = 9.3 Hz), 5.31 (0.7H, m), 3.81 (3H, s), 3.62 (1.95H, s), 3.58 (1.05H, s), 3.55 (0.7H, m), 3.48 (1.3H, brt, *J* = 6.3 Hz), 3.09 (1.95H, s), 2.96 (1.05H, s), 1.75 (2H, m), 1.33 (1.3H, brt, *J* = 6.0 Hz), 1.29 (0.7H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 167.1, 162.8, 160.1, 154.5, 137.2*, 136.4, 129.7, 126.0, 123.8, 123.0*, 113.4, 96.5, 69.8,

59.2, 55.3, 52.1, 47.5, 40.5, 27.3, 22.8; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{24}IN_2O_4$ 507.0781, found 507.0784.

Methyl (5s,8s)-12-(4-chlorophenyl)-11-iodo-9-methyl-10-oxo-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate (*cis*-**2d**). Compound *cis*-**2d** was obtained in 80% yield (40.2 mg, 0.0787 mmol) as a colorless solid according to the **general procedure E**; **1d** (50.3 mg, 0.0985 mmol), ICl (1 mol/L MeCN solution, 0.0985 mL, 0.0985 mmol, 1.0 equiv), EtCN (1.0 mL), –78 °C to rt, 1 h; silica gel column chromatography (60% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 65:35 ratio) δ 7.34 (2H, d, *J* = 8.0 Hz), 7.15 (1.3H, d, *J* = 8.0 Hz), 7.12-7.14 (0.7H, m), 6.01 (2H, d, *J* = 9.6 Hz), 5.41 (1.3H, d, *J* = 9.6 Hz), 5.34 (0.7H, d, *J* = 9.6 Hz), 3.64 (1.95H, s), 3.60 (1.05H, s), 3.56-3.64 (0.7H, m), 3.50 (1.3H, t, *J* = 6.7 Hz), 3.11 (1.95H, s), 2.99 (1.05H, s), 1.79-1.75 (2H, m), 1.29-1.23 (2H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) (Asterisks indicate peaks for the minor rotamer) δ 166.8, 166.6*, 161.9, 154.4, 137.7*, 136.8, 135.2, 132.20, 129.8, 128.4, 123.4, 122.5*, 97.6, 69.8, 59.1, 52.1, 47.5, 40.6, 27.3, 22.8, 22.2*; **HRMS** (ESI) *m/z* $[M+Na]^+$ calcd for $C_{21}H_{20}ClIN_2NaO_3$ 533.0105, found 533.0114.

Methyl (5s,8s)-11-iodo-9-methyl-10-oxo-12-(4-(trifluoromethyl)phenyl)-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate (*cis*-**2e**). Compound *cis*-**2e** was obtained in 57% yield (7.40 mg, 0.0140 mmol) as a colorless solid according to the **general procedure E**; **1e** (60.8 mg, 0.160 mmol), ICl (1 mol/L MeCN solution, 0.0239 mL, 0.0239 mmol, 1.0 equiv), EtCN (0.24 mL), –78 °C to rt, 1 h; silica gel column chromatography (70% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 65:35 ratio) δ 7.64 (2H, d, *J* = 8.3 Hz), 7.34 (1.3H, d, *J* = 8.3 Hz), 7.31 (0.7H, m), 6.01 (2H, d, *J* = 9.8 Hz), 5.44 (1.3H, dd, *J* = 9.8 Hz), 5.36 (0.7H, brd, *J* = 9.8 Hz), 3.63 (1.95H, s), 3.59 (1.05H, s), 3.55 (0.7H, m), 3.48 (1.3H, brt, *J* = 6.6 Hz), 3.12 (1.95H, s), 2.99 (1.05H, s), 1.76-1.71 (2H, m), 1.16 (1.3H, brt, *J* = 7.2 Hz), 1.10 (0.7H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) (Asterisks indicate peaks for the minor rotamer) δ 166.6, 161.7, 154.4, 137.8*, 137.5, 137.0, 131.1 (q, *J* = 33.0 Hz), 128.9, 125.1, 123.8 (q, J = 271 Hz), 123.1, 122.3*, 98.0, 69.8, 59.0, 52.1, 48.4*, 47.5, 41.7*, 40.4, 27.4, 26.8*, 22.7, 22.1*;**^{19}F NMR** (376 MHz, $CDCl_3$) δ –65.9; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{21}F_3IN_2O_3$ 545.0549, found 545.0563.

Methyl (5s,8s)-11-iodo-9-methyl-12-(4-nitrophenyl)-10-oxo-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate (*cis*-**2f**). Compound *cis*-**2f** was obtained in 68% yield (9.8 mg, 0.0190 mmol) as a yellow solid according to the **general procedure E**; **1f** (11.0 mg, 0.0278 mmol), ICl (1 mol/L MeCN solution, 0.0612 mL, 0.0612 mmol, 2.2 equiv), EtCN (0.40 mL), –78 °C to rt, 1.5 h; silica gel column chromatography (80% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 70:30 ratio) δ 8.25 (2H, d, *J* = 8.6 Hz), 7.43 (1.4H, d, *J* = 8.6 Hz) 7.40-7.37 (0.6H, m), 6.04 (2H, d, *J* = 9.8 Hz), 5.45 (1.4H, d, *J* = 9.8 Hz), 5.38 (0.6H, brd, *J* = 8.6 Hz), 3.64 (2.1H, s), 3.60 (0.9H, s), 3.57-3.55 (0.6H, m), 3.49 (1.4H, t, *J* = 6.7 Hz), 3.13 (2.1H, s), 3.00 (0.9H, s), 1.78-1.73 (2H, m), 1.22 (1.4H, t, *J* = 6.9 Hz), 1.18-1.14 (0.6H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) (Asterisks indicate peaks for the minor rotamer) δ 166.3, 160.8, 154.4, 148.0, 140.5*, 138.1, 137.3, 129.7, 123.4, 123.0, 122.1*, 98.9, 69.8, 58.9, 52.2, 47.5, 40.7, 27.4, 22.8. **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{21}IN_3O_5$ 522.0526, found 522.0548.

Methyl (5s,8s)-11-iodo-12-(2-methoxyphenyl)-9-methyl-10-oxo-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate (*cis*-**2g**). Compound *cis*-**2g** was obtained in 90% yield (67.2 mg, 0.133 mmol) as a yellow solid according to the **general procedure E**; **1g** (56.0 mg, 0.147 mmol), ICl (1 mol/L MeCN solution, 0.221 mL, 0.221 mmol, 1.5 equiv), EtCN (1.5 mL), –78 °C to rt, 1 h; silica gel column chromatography (80% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 30:30:20:20) δ 7.35-7.32 (1H, m), 6.94-6.89 (3H, m), 6.00 (1H, brs), 5.80 (1H, brs), 5.43 (1.3H, m), 5.35 (0.7H, brs), 3.76-3.72 (3H, m), 3.65-3.54 (3H, m), 3.54-3.46 (0.8H, m), 3.46-3.39 (1.2H, m), 3.11-3.05 (1.8H, m), 2.99-2.95 (1.2H, m), 1.65 (2H, brs), 1.07 (1H, brs), 0.89 (1H, brs); **^{13}C NMR** (150 MHz, $CDCl_3$) (Asterisks indicate peaks for the minor rotamer) δ 167.2, 167.1*, 161.6*, 161.4, 156.4, 155.3*, 154.4, 137.5*, 136.8, 135.5*, 134.8, 130.5, 130.4*, 129.5, 124.0, 123.3, 122.5*, 122.4, 122.2*, 119.6, 111.1, 98.3, 98.0*, 70.5, 70.3, 59.1, 58.7*, 55.6, 52.0, 48.3*, 47.4, 41.6*, 40.4, 27.3, 26.8*, 22.7, 22.1*; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{24}IN_2O_4$ 507.0781, found 507.0783.

Methyl (5s,8s)-11-iodo-9-methyl-12-(naphthalen-2-yl)-10-oxo-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate (*cis*-**2h**). Compound *cis*-**2h** was obtained in 91% yield (19.0 mg, 0.0361 mmol) as a colorless solid according to the **general procedure E**; **1h** (15.9 mg, 0.0397 mmol), ICl (1 mol/L MeCN solution, 0.0596 mL, 0.0596 mmol, 1.5 equiv), EtCN (0.4 mL), –78 °C to rt, 1 h; silica gel column chromatography (80% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 65:35 ratio) δ 7.86-7.83 (3H, m), 7.75 (0.65 H, brs) 7.70 (0.35H, brs), 7.55-7.50 (2H, m), 7.36 (0.65H, brd, *J* = 8.4 Hz), 7.30 (0.35H, m), 6.00 (2H, d, *J* = 9.8 Hz), 5.51 (1.3H, brd, *J* = 9.8 Hz), 5.43 (0.7H, m), 3.63 (1.95H, s),3.60 (1.05H, s), 3.50 (0.7H, m), 3.43 (1.3H, brt, *J* = 6.6 Hz), 3.15 (1.95H, s), 3.01 (1.05H, s), 1.64-1.57 (2H, m), 1.15 (1.3H, m), 1.08 (0.7H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) (Asterisks indicate peaks for the minor rotamer) δ 167.1, 163.0, 154.4, 137.4*, 136.6, 133.2, 132.5, 131.2, 128.1, 127.8 (two peaks, overlap), 127.7, 126.9, 126.6, 125.8, 123.7, 122.8*, 97.2, 70.0, 59.1, 52.1, 48.3*, 47.4, 41.7*, 40.4, 27.3, 22.7, 22.1*; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{24}IN_2O_3$ 527.0832, found 527.0830.

Methyl (5s,8s)-12-(benzo[b]thiophen-3-yl)-11-iodo-9-methyl-10-oxo-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate (*cis*-**2i**). Compound *cis*-**2i** was obtained in 89% yield (8.0 mg, 0.0150 mmol) as a colorless solid according to the **general procedure E**; **1i** (6.9 mg, 0.0170 mmol), ICl (1 mol/L MeCN solution, 0.0250 mL, 0.0250 mmol, 1.5 equiv), EtCN (0.4 mL), –78 °C to rt, 1.0 h; silica gel column chromatography (80% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 30:30:20:20) δ 7.89-7.86 (1H, m), 7.55-7.48 (1H, m), 7.42-7.39 (2H, m), 7.34 (0.6H, brs), 7.31 (0.4H, brs), 6.19 (0.5H, brs), 6.17 (0.5H, brs), 5.74 (1H, brs), 5.58 (0.6H, m), 5.50 (0.4H, m), 5.35 (0.6H, m), 5.29 (0.4H, m), 3.62 (1.8H, s), 3.59 (1.2H, s), 3.52 (0.8H, s), 3.45 (1.2H, t, *J* = 6.7 Hz), 3.15 (1.8H, s), 3.03 (1.2H, s), 1.78-1.58 (2H, m), 1.48-1.38 (1H, m), 1.05-0.98 (1H, m); **^{13}C NMR** (100 MHz, $CDCl_3$) (Asterisks indicate peaks for the minor rotamer) δ 166.97, 166.85*, 158.7*, 158.5, 155.2*, 154.4, 139.3, 138.8*, 138.0, 136.8*, 136.3, 136.0, 128.6*, 128.4, 125.7*, 125.5, 124.8, 124.4, 123.6, 123.4*, 123.3*, 122.8, 122.6*, 122.5*, 121.7*, 98.6, 98.5*, 70.5, 70.3*, 59.1, 58.7*, 52.1, 48.4*, 47.5, 42.0*, 40.7, 27.5, 26.9*, 22.7, 22.2*; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{22}IN_2O_3S$ 533.0396, found 533.0392.

Methyl (5s,8s)-9-benzyl-11-iodo-10-oxo-12-phenyl-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate (*cis*-**2j**) and *methyl (5s,8s)-9-benzyl-4,11-diiodo-10-oxo-12-phenyl-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate* (**4**). Compound *cis*-**2j** was isolated in 16% yield (23.6 mg, 0.0427 mmol) as a colorless solid, and compound **4** was isolated in 4% yield (8.9 mg, 0.013 mmol) as a pale yellow oil, according to the **general procedure E**; **1j** (130 mg, 0.305 mmol), ICl (1 mol/L MeCN solution, 0.305 mL, 0.305 mmol, 1.0 equiv), EtCN (2.6 mL), –78 °C to rt, 1 h; silica gel column chromatography (30% AcOEt/hexane). Compound *cis*-**2j** was obtained in 86% yield (43.3 mg, 0.0784 mmol) for 2 steps as a colorless solid according to the **general procedure F**; **1j** (38.8 mg, 0.0910 mmol), NIS (22.5 mg, 0.100 mmol, 1.1 equiv), AgTFA (2.34 mg, 9.10 μmol, 0.1 equiv), HFIP (0.5 mL), 0 °C, 8 h; *p*-TsOH•H_2O (17.3 mg, 0.0910 mmol, 1.0 equiv), MeCN (1.0 mL), rt, 24 h; silica gel column

chromatography (40% AcOEt/hexane). *Cis*-**2j**:**^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 65:35) δ 7.62 (1.3H, brd, *J* = 7.2 Hz), 7.48 (0.7H, m), 7.35-7.21 (6H, m), 7.14 (1.3H, m), 7.10 (0.7H, m), 6.00 (0.7H, brd, *J* = 9.2 Hz), 5.92 (1.3H, brd, *J* = 9.6 Hz), 5.39 (0.7H, brd, *J* = 9.2 Hz), 5.34 (1.3H, brd, *J* = 9.6 Hz), 4.77 (1.3H, s), 4.54 (0.7H, s), 3.64 (1.95H, s), 3.61 (1.05H, s), 3.55 (0.7H, m), 3.46 (1.3H, brt, *J* = 6.6 Hz), 1.69 (2H, m), 1.10 (1.3H, m), 1.03 (0.7H, m); **^{13}C NMR** (100 MHz, $CDCl_3$) (Asterisks indicate peaks for the minor rotamer) δ 167.3, 163.6, 154.3, 139.1, 137.0*, 136.2, 133.8, 129.7, 129.0, 128.3, 128.0 (two peaks, overlap), 126.9, 123.8, 123.2*, 96.9, 70.8, 59.1, 52.1, 48.6*, 47.4, 44.8, 41.8*, 40.3, 22.7, 22.1*; **HRMS** (ESI) *m*/*z* $[M+Na]^+$ calcd for $C_{27}H_{25}IN_2NaO_3$ 575.0808, found 575.0813. **4**: **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 70:30 ratio) δ 7.56 (1.5H, d, *J* = 7.2 Hz), 7.43-7.35 (3.5H, m), 7.28-7.19 (3H, m), 7.16-7.07 (2H, m), 6.23-6.18 (1H, m), 5.93 (0.3H, brd, *J* = 9.6 Hz), 5.81 (0.7H, d, *J* = 9.6 Hz), 5.53-5.49 (1H, m), 5.30 (0.3H, brd, *J* = 9.6 Hz), 5.26 (0.7H, d, *J* = 9.6 Hz), 4.80 (0.7H, d, *J* = 15.0 Hz), 4.69 (0.3H, brd, J = 13.8 Hz), 4.56 (0.7H, d, *J* = 15.0 Hz), 4.26 (0.3H, brd, *J* = 13.8 Hz), 3.86 (0.3H, m), 3.77 (1H, m), 3.69 (3H, s), 3.69-3.63 (0.7H, m), 3.03 (0.7H, brd, *J* = 4.5 Hz), 2.89 (0.3H, brs), 2.34-2.30 (1H, m), 2.12 (1H, dd, *J* = 14.4, 5.8 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) (Asterisks indicate peaks for the minor rotamer) δ 167.3, 162.1, 154.2, 141.6, 138.9, 133.4, 131.1, 129.6, 129.4, 128.5, 128.2, 128.0, 127.0, 126.6, 124.2, 97.2, 70.6, 61.5, 52.4, 46.1, 44.9, 39.1, 35.3; **HRMS** (EI) *m*/*z* $[M]^+$ calcd for $C_{27}H_{24}IN_2O_3$ 677.9876, found 677.9878.

(5s,8s)-3-Iodo-1-methyl-9-(methylsulfonyl)-4-phenyl-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-3,6,13-trien-2-one (*cis*-**2k**). Compound *cis*-**2k** was obtained in 81% yield (41.1 mg, 0.0829 mmol) for 2 steps as a colorless solid according to the **general procedure F**; **1k** (37.9 mg, 0.102 mmol), NIS (25.3 mg, 0.113 mmol, 1.1 equiv), AgTFA (2.30 mg, 10.2 μmol, 0.1 equiv), HFIP (1.0 mL), 0 °C, 1 h; *p*-TsOH•H_2O (18.8 mg, 0.102 mmol, 1.0 equiv), MeCN (1.0 mL), rt, 24 h; silica gel column chromatography (80% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38-7.37 (3H, m), 7.17-7.15 (2H, m), 6.11 (2H, d, *J* = 10.2 Hz), 5.46 (2H, d, *J* = 9.6 Hz), 3.50 (2H, t, *J* = 7.2 Hz), 3.02 (3H, s), 2.28 (3H, s), 1.82 (2H, quint, *J* = 7.1 Hz), 1.24 (2H, t, *J* = 7.2); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.97, 162.91, 135.87, 133.44, 129.17, 128.24, 128.04, 124.03, 96.97, 69.60, 61.66, 48.90, 41.39, 39.66, 27.19, 22.55; **HRMS** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{20}H_{22}IN_2O_3S$ 497.0396, found 497.0384.

Methyl (5s,8s)-9-(2-ethoxy-2-oxoethyl)-11-iodo-10-oxo-12-phenyl-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate (*cis*-**2l**). Compound *cis*-**2l** was obtained in 85% yield (56.4 mg, 0.103 mmol) for 2 steps as a pale yellow solid according to the **general procedure F**; **1l** (51.0 mg, 0.121 mmol), NIS (29.9 mg, 0.133 mmol, 1.1 equiv), AgTFA (2.67 mg, 12.1 μmol, 0.1 equiv), HFIP (1.4 mL), 0 °C, 22 h; *p*-TsOH•H_2O (23.0 mg, 0.121 mmol, 1.0 equiv), MeCN (0.5 mL), rt, 22 h; silica gel column chromatography (80% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 60:40) δ 7.37 (3H, brs), 7.26 (1.2H, brs), 7.16 (0.8H, s), 5.97-5.89 (2H, m), 5.56 (1.2H, d, *J* = 9.3 Hz), 5.48 (0.8H, *J* = 9.3 Hz), 4.38 (1.1H, brs), 4.23-4.15 (2H, m), 4.10 (0.9H, brs), 3.63-3.56 (3H, m), 3.52 (0.8H, m) 3.44 (1.2H, brt, *J* = 6.4 Hz), 1.75-1.65 (2H, m), 1.29-1.24 (1.1H, m), 1.26 (3H, t, *J* = 7.2 Hz) 1.10 (0.9H, m); **^{13}C NMR** (100 MHz, $CDCl_3$) (Asterisks indicate peaks for the minor rotamer) δ 169.4, 168.6*, 167.2, 167.1*, 164.1, 155.2*, 154.1, 137.3*, 136.1, 133.6, 133.4*, 129.2, 128.2, 128.0, 123.3, 122.2*, 95.7, 69.8, 61.4*, 61.0, 58.8, 58.6*, 52.1*, 51.9, 48.5*, 47.3, 42.4, 41.9*, 41.7*, 40.1, 22.7, 22.0*, 14.1; **HRMS** (ESI) *m*/*z* $[M+Na]^+$ calcd for $C_{24}H_{25}IN_2NaO_5$ 571.0706, found 571.0708.

Methyl (5s,8s)-9-(2-cyclopropyl-2-oxoethyl)-11-iodo-10-oxo-12-phenyl-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate (*cis*-**2m**). Compound *cis*-**2m** was obtained in 83% yield (11.3 mg, 0.0207 mmol) for 2 steps as a pale yellow solid according to the **general procedure F**; **1m** (10.4 mg, 0.0249 mmol), NIS (6.15 mg, 0.2073 mmol, 1.1 equiv), AgTFA (0.55 mg, 2.49 μmol, 0.1 equiv), HFIP (0.5 mL), 0 °C, 23 h; *p*-TsOH•H_2O (4.74 mg, 0.0249 mmol, 1.0 equiv), MeCN (0.5 mL), rt, 23 h; silica gel column chromatography (70% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 80:20) δ 7.37-7.36 (3H, m), 7.28-7.26 (2H, m), 5.98-5.85 (2H, m), 5.56-5.45 (2H, m), 4.67 (1.6H, s), 4.31 (0.4H, s), 3.64 (0.6H, m), 3.60 (2.4H, brs), 3.57-3.49 (0.4H, m), 3.46 (1.6H, t, *J* = 6.8 Hz), 2.00 (1H, m), 1.75 (1.6H, m), 1.70-1.62 (0.4H, m), 1.33 (1.6H, m), 1.16-1.02 (2.4H, m), 1.00-0.92 (0.4H, m), 0.92-0.84 (1.6H, m); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 204.7, 167.0, 163.7, 154.1, 135.7, 133.8, 129.1, 128.2, 128.0, 123.6, 96.1, 69.7, 58.9, 51.9, 50.1, 47.3, 40.1, 22.7, 18.5, 10.5; **HRMS** (ESI) *m*/*z* $[M+Na]^+$ calcd for $C_{25}H_{25}IN_2NaO_4$ 567.0757, found 567.0765.

Methyl (5s,8s)-9-(2-hydroxyethyl)-11-iodo-10-oxo-12-phenyl-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate (*cis*-**2n**). Compound *cis*-**2n** was obtained in 92% yield (5.70 mg, 0.110 mmol) for 2 steps as a colorless solid according to the **general procedure F**; **1n** (4.70 mg, 0.0120 mmol), NIS (3.10 mg, 0.0140 mmol, 1.1 equiv), AgTFA (0.27 mg, 1.2 μmol, 0.1 equiv), HFIP (0.5 mL), 0 °C, 24 h; *p*-TsOH•H_2O (2.28 mg, 0.0120 mmol, 1.0 equiv), MeCN (0.5 mL), rt, 22 h; silica gel column chromatography (80% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 85:15) δ 7.37 (3H, d, *J* = 6.9 Hz), 7.23-7.27 (1.7H, m), 7.09-7.19 (0.3H, m), 6.0 (0.3H, brd, *J* = 9.5 Hz), 5.94 (1.7H, d, *J* = 10.0 Hz), 5.49 (1.7H, d, *J* = 10.0 Hz), 5.42 (0.3H, brd, *J* = 9.5 Hz), 3.78-3.86 (3.4H, m), 3.58-3.64 (0.6H, m), 3.61 (3H, s), 3.54 (0.3H, m), 3.48 (1.7H, t, *J* = 6.9 Hz), 1.76 (1.7H, m), 1.68 (0.3H, m), 1.58 (1H, s), 1.30 (1.7H, t, *J* = 7.0 Hz), 1.10 (0.3H, m); **^{13}C NMR** (100 MHz, $CDCl_3$) (Asterisks indicate peaks for the minor rotamer) δ 168.4, 164.0, 154.5, 137.5*, 135.8, 133.5, 129.2, 128.1, 128.0, 123.8, 122.1*, 95.9, 70.4, 62.9, 58.9, 52.2, 47.5, 44.8, 40.2, 22.7; **HRMS** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{24}IN_2O_4$ 507.0781, found 507.0790.

Methyl (3-((7aR,11aR*)-2-iodo-3-oxo-1-phenyl-5,6-dihydro-3H,7aH-benzo[b]pyrrolo[2,1-c][1,4]oxazin-9-yl)propyl)carbamate* (**5**). To a stirred solution of **1n** (10.0 mg, 0.0263 mmol) in HFIP (0.5 mL) were successively added AgTFA (0.68 mg, 2.63 μmol), NIS (6.51 mg, 0.0289 mmol) at 0 °C, then the stirring was continued at the same temperature for 24 h. The reaction mixture was quenched with 10% aqueous Na_2SO_3 and diluted with $CHCl_3$. After the organic layer was separated, the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified on PTLC (80% AcOEt/hexane) to give **5** (8.80 mg, 0.0263 mmol, 66% yield) as a yellow solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36-7.30 (3H, m), 7.03-7.01 (2H, m), 6.10 (1H, d, *J* = 9.4 Hz), 5.54 (1H, d, *J* = 9.4 Hz), 5.46 (1H, brd, *J* = 5.7 Hz), 4.52 (1H, brs), 4.34 (1H, dd, *J* = 13.4, 2.1 Hz), 3.89 (1H, dd, *J* = 11.3, 3.3 Hz), 3.70 (1H, dd, *J* = 5.7, 1.5 Hz), 3.66 (3H, brs), 3.36 (1H, td, *J* = 11.3, 2.5 Hz), 3.27-3.22 (1H, m), 2.88-2.83 (2H, m), 1.82-1.75 (1H, m), 1.72-1.64 (1H, m), 1.18-1.13 (1H, m), 0.97-0.91 (1H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.0, 162.6, 156.9, 139.6, 134.2, 131.9, 128.7, 127.9, 127.8, 125.2, 119.1, 99.0, 74.1, 70.2, 66.5, 52.1, 40.0, 32.1, 29.7, 27.6; **HRMS** (EI) *m*/*z* $[M]^+$ calcd for $C_{22}H_{23}IN_2O_4$ 506.0703, found 506.0705.

Methyl (5s,8s)-11-iodo-10-oxo-12-phenyl-9-(prop-2-yn-1-yl)-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate (*cis*-**2o**). Compound *cis*-**2o** was obtained in 85% yield (52.2 mg, 0.0912 mmol) for 2 steps as a pale yellow solid according to the **general procedure F**; **1o** (40.0 mg, 0.107 mmol), NIS (26.4 mg, 0.118 mmol, 1.1 equiv), HFIP (1.1 mL), rt, 24 h; *p*-TsOH•H_2O (18.4 mg, 0.107 mmol, 1.0 equiv), MeCN (0.5 mL), rt, 22 h; silica gel column chromatography (60% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 55:45) δ 7.40-7.36 (3H, m), 7.25-7.22 (1.1H, m), 7.18-7.13 (0.9H, m), 5.99 (2H, d, *J* = 9.2

Hz), 5.53 (1.1H, d, *J* = 9.2 Hz), 5.45 (0.9H, *J* = 9.2 Hz) 4.40 (1.1H, s), 4.16 (0.9H, s), 3.67 (1.35H, brs), 3.64 (1.65H, brs), 3.54 (0.9H, brs), 3.47 (1.1H, brs), 2.20 (1H, s), 1.78-1.62 (2H, m), 1.27 (1.1H, brs), 1.12 (0.9H, brs); **^{13}C NMR** (100 MHz, $CDCl_3$) (Asterisks indicate peaks for the minor rotamer) δ 166.6, 166.4*, 164.3*, 163.8, 155.3*, 154.4, 137.4*, 136.5, 133.6, 133.4*, 129.2*, 128.3, 128.14, 128.06, 123.2*, 122.3, 96.3, 96.0*, 80.3, 79.5*, 71.3*, 70.6, 70.0, 58.9, 58.7*, 52.1, 48.4*, 47.4, 41.6, 40.2*, 30.3*, 29.9, 22.7, 22.1*; **HRMS** (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{22}IN_2O_3$ 501.0676, found 501.0693.

Methyl (5s,8s)-9-(cyanomethyl)-11-iodo-10-oxo-12-phenyl-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate (*cis*-**2p**). Compound *cis*-**2p** was obtained in 82% yield (31.4 mg, 0.0626 mmol) for 2 steps as a pale brown solid according to the **general procedure F**; **1p** (28.7 mg, 0.0764 mmol), AgTFA (1.69 mg, 7.64 µmol, 0.1 equiv), NIS (18.9 mg, 0.0841 mmol, 1.1 equiv), HFIP (0.8 mL), 0 °C, 22 h; *p*-TsOH•H_2O (26.3 mg, 0.153 mmol, 2.0 equiv), MeCN (0.5 mL), rt, 22 h; silica gel column chromatography (60% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 85:15 ratio) δ 7.42-7.36 (3H, m), 7.31 (1.7H, d, *J* = 6.6 Hz), 7.18 (0.3H, brs), 6.11 (0.3H, brd, *J* = 10.4 Hz), 6.05 (1.7H, d, *J* = 9.6 Hz), 5.52 (1.7H, d, *J* = 9.6 Hz), 5.46 (0.3H, brd, *J* = 9.0 Hz), 4.63 (1.7H, s), 4.30 (0.3H, s), 3.71 (0.45H, brs), 3.63 (2.55H, s), 3.57 (0.3H, brs), 3.51 (1.7H, t, *J* = 6.6 Hz), 1.81 (1.7H, quint, *J* = 6.6 Hz), 1.72 (0.3H, brs), 1.44 (1.7H, t, *J* = 7.0 Hz), 1.27 (0.3H, brs); **^{13}C NMR** (150 MHz, $CDCl_3$) (Asterisks indicate peaks for the minor rotamer) δ 166.6, 164.5, 154.3, 138.9*, 137.5, 133.1, 129.6, 128.2, 128.0, 122.5, 121.3*, 116.3, 94.5, 69.5, 58.8, 52.2, 47.4, 40.0, 28.5, 22.7; **HRMS** (ESI) *m/z* $[M+Na]^+$ calcd for $C_{22}H_{20}IN_3NaO_3$ 524.0447, found 524.0448.

Benzyl (5s,8s)-11-iodo-9-methyl-10-oxo-12-phenyl-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate (*cis*-**2q**). Compound *cis*-**2q** was obtained in 90% yield (67.1 mg, 0.121 mmol) for 2 steps as a colorless solid according to the **general procedure F**; **1q** (57.7 mg, 0.135 mmol), NIS (33.5 mg, 0.149 mmol, 1.1 equiv), AgTFA (3.4 mg, 14.0 µmol, 0.1 equiv), HFIP (1.4 mL), 0 °C, 2 h; *p*-TsOH•H_2O (25.8 mg, 0.135 mmol, 1.0 equiv), MeCN (1.4 mL), rt, 19 h; decantation (40% AcOEt/hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) (A mixture of rotamers in 65:35 ratio) δ 7.38-7.26 (8H, m), 7.21 (1.3H, m), 7.10 (0.7H, m), 6.01 (2H, d, *J* = 10.0 Hz), 5.45 (1.3H, d, *J* = 10.0 Hz), 5.31 (0.7H, brd, *J* = 10.0 Hz), 5.06 (2H, s), 3.53 (2H, brt, *J* = 6.8 Hz), 3.13 (1.95H, s), 2.55 (1.05H, s), 1.74-1.65 (2H, m), 1.19 (1.3H, brt, *J* = 7.0 Hz), 1.00 (0.7H, m); **^{13}C NMR** (100 MHz, $CDCl_3$) (Asterisks indicate peaks for the minor rotamer) δ 167.0, 163.3, 153.7, 137.5*, 136.5, 136.4, 133.7, 129.1, 128.4, 128.3, 128.0, 127.9, 127.7, 123.5, 122.6*, 96.7, 69.9, 66.9*, 66.5, 59.2, 48.6*, 47.5, 41.8*, 40.3, 27.3, 26.5*, 22.7, 22.0*; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{26}IN_2O_3$ 553.0988, found 553.0974.

Phenyl (5s,8s)-11-iodo-9-methyl-10-oxo-12-phenyl-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate (*cis*-**2r**). Compound *cis*-**2r** was obtained in 86% yield (62.2 mg, 0.116 mmol) for 2 steps as a colorless solid according to the **general procedure F**; **1r** (55.6 mg, 0.135 mmol), NIS (34.3 mg, 0.152 mmol, 1.1 equiv), AgTFA (3.2 mg, 14.5 µmol, 0.1 equiv), HFIP (1.4 mL), 0 °C, 2 h; *p*-TsOH•H_2O (25.9 mg, 0.136 mmol, 1.1 equiv), MeCN (1.4 mL), rt, 22 h; silica gel column chromatography (50% AcOEt/hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) (A mixture of rotamers in 55:45 ratio) δ 7.40-7.30 (5H, m), 7.22-7.15 (3H, m), 7.09 (1.1H, brd, *J* = 7.6 Hz), 6.96 (0.9H, brd, *J* = 7.6 Hz), 6.15 (0.9H, d, *J* = 10.0 Hz), 6.05 (1.1H, d, *J* = 10.0 Hz), 5.43 (1.1H, d, *J* = 10.0 Hz), 5.42 (0.9H, *J* = 10.0 Hz), 3.71 (1.1H, t, *J* = 6.8 Hz), 3.61 (0.9H, t, *J* = 6.7 Hz), 3.01 (1.65H, s), 2.63 (1.35H, s), 1.71-1.85 (2H, m), 1.24 (1.1H, t, *J* = 6.9 Hz), 1.18 (0.9H, t, *J* = 6.8 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) (Asterisks indicate peaks for the minor rotamer) δ 166.9, 166.7*, 163.3, 163.1*, 153.2*, 151.7, 150.8*, 150.7, 136.9*, 136.0, 133.7, 133.5*, 129.3*, 129.2, 129.1*, 129.0, 128.28*, 128.25, 128.0*, 127.97, 125.6*, 125.1, 123.8, 123.1*, 121.8*, 121.7, 96.8, 69.8, 69.7*, 59.4, 48.5*, 48.1, 41.5*, 40.4, 27.4, 26.9*, 22.7, 22.2*; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}IN_2O_3$ 539.0832, found 539.0808.

(5s,8s)-3-Iodo-1-methyl-4-phenyl-9-tosyl-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-3,6,13-trien-2-one (*cis*-**2s**). Compound *cis*-**2s** was obtained in 76% yield (52.2 mg, 0.0912 mmol) for 2 steps as a colorless solid according to the **general procedure F**; **1s** (53.4 mg, 0.120 mmol), NIS (30.9 mg, 0.137 mmol, 1.2 equiv), AgTFA (2.9 mg, 13.0 µmol, 0.1 equiv), HFIP (1.2 mL), 0 °C, 1 h 20 min; *p*-TsOH•H_2O (23.5 mg, 0.124 mmol, 1.1 equiv), MeCN (1.4 mL), rt, 19 h; silica gel column chromatography (40% AcOEt/hexane). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.67 (2H, d, *J* = 8.2 Hz), 7.34-7.30 (3H, m), 7.27-7.26 (2H, m), 7.10 (2H, dd, *J* = 7.7, 1.5 Hz), 5.98 (2H, d, *J* = 10.2 Hz), 5.41 (2H, d, *J* = 10.2), 3.41 (2H, t, *J* = 6.7 Hz), 3.15 (3H, s), 2.41 (3H, s), 1.71-1.67 (2H, m), 1.09 (2H, t, *J* = 7.0 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 167.0, 163.2, 143.3, 137.5, 136.5, 133.5, 129.4, 129.1, 128.3, 127.9, 127.3, 123.3, 96.8, 69.8, 62.2, 48.9, 41.4, 27.4, 22.8, 21.5; **HRMS** (ESI) *m/z* $[M+Na]^+$ calcd for $C_{26}H_{25}IN_2NaO_3S$ 595.0528, found 595.0510.

(5s,8s)-9-Acetyl-3-iodo-1-methyl-4-phenyl-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-3,6,13-trien-2-one (*cis*-**2t**). Compound *cis*-**2t** was obtained in 29% yield (10.1 mg, 0.0219 mmol, calculated by ^{1}H NMR) for 2 steps as a colorless solid according to the **general procedure F**; **1t** (25.1 mg, 0.0751 mmol), NIS (18.6 mg, 0.0826 mmol, 1.1 equiv), AgTFA (1.66 mg, 7.51 µmol, 0.1 equiv), HFIP (0.75 mL), 0 °C, 2.5 h; *p*-TsOH•H_2O (14.8 mg, 0.0778 mmol, 1.0 equiv), MeCN (0.78 mL), rt, 24 h; silica gel column chromatography (20% MeOH/AcOEt). A pure fraction of *cis*-**2t** could be obtained and was used for analysis. The other fractions contained *cis*-**2t** and inseparable byproducts, therefore yield of *cis*-**2t** was calculated by ^{1}H NMR. **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 70:30 ratio) δ 7.39-7.35 (3H, m), 7.21-7.19 (1.4H, m), 7.07-7.05 (0.6H, m), 6.08 (1.4H, d, *J* = 10.0 Hz), 5.95 (0.6H, d, *J* = 10.4 Hz), 5.54-5.53 (0.6H, d, *J* = 9.6 Hz), 5.40 (1.4H, d, *J* = 10.0 Hz), 3.58 (0.6H, t, *J* = 6.7 Hz), 3.53 (1.4H, t, *J* = 6.7 Hz), 3.12 (2.1H, s), 2.96 (0.9H, s), 2.02 (2.1H, s), 2.00 (0.9H, s), 1.82-1.77 (1.4H, m), 1.58 (0.6H, m), 1.18 (1.4H, t, *J* = 6.9 Hz), 0.92 (0.6H, t, *J* = 6.9 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) (Asterisks indicate peaks for the minor rotamer) δ 169.9*, 169.0, 166.9, 166.8*, 163.4, 163.3*, 137.4*, 136.4, 133.8, 133.3*, 129.3*, 129.0, 128.4*, 128.3, 128.2*, 128.0, 124.0*, 122.9, 97.2*, 96.7, 70.0, 69.8*, 59.8, 59.6*, 48.9, 48.2*, 42.2*, 40.1, 27.4, 27.3*, 23.7, 23.2, 22.5*, 21.4*; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{22}IN_2O_2$ 461.0726, found 461.0722.

Methyl (5s,8s)-11-bromo-9-methyl-10-oxo-12-phenyl-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate (*cis*-**2a-Br**). Compound *cis*-**2a-Br** was obtained in 94% yield (23.0 mg, 0.0536 mmol) for 2 steps as a colorless solid according to the **general procedure F**; **1a** (20.0 mg, 0.0571 mmol), NBS (11.2 mg, 0.0628 mmol, 1.1 equiv), AgTFA (1.26 mg, 5.71 µmol, 0.1 equiv), HFIP (0.60 mL), 0 °C, 24 h; *p*-TsOH•H_2O (10.9 mg, 0.0571 mmol, 1.0 equiv), MeCN (0.60 mL), rt, 24 h; silica gel column chromatography (60% AcOEt/hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) (A mixture of rotamers in 65:35 ratio) δ 7.38-7.35 (3H, m), 7.28-7.22 (2H, m), 6.00 (2H, d, *J* = 10.0 Hz), 5.44 (1.3H, brd, *J* = 10.0 Hz), 5.36 (0.7H, brd, *J* = 10.0 Hz), 3.65 (1.95H, s), 3.60 (1.05H, s), 3.55 (0.7H, m), 3.48 (1.3H, brt, *J* = 6.4 Hz) 3.10 (1.95H, s), 2.97 (1.05H, s), 1.73 (2H, m), 1.26 (1.3H, brt, *J* = 6.4 Hz), 1.20 (0.7H, m); **^{13}C NMR** (100 MHz, $CDCl_3$) (Asterisks indicate peaks for the minor rotamer) δ 165.6, 156.1, 154.4, 137.6*, 136.8, 131.8, 129.2, 128.4, 128.0, 123.4, 122.5*, 118.4, 68.0, 59.1, 52.1, 48.4*, 47.5, 41.8*, 40.5, 27.1, 26.5*, 22.7, 22.1*; **HRMS** (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{22}BrN_2O_3$ 429.0814, found 429.0842.

Methyl (5s,8s)-11-chloro-9-methyl-10-oxo-12-phenyl-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate

(*cis*-**2a-Cl**). Compound *cis*-**2a-Cl** was obtained in 43% yield (95.0 mg, 0.247 mmol, calculated by ^{1}H NMR) for 2 steps as a colorless solid according to the **general procedure F**; **1a** (200 mg, 0.571 mmol), NCS (83.8 mg, 0.628 mmol, 1.1 equiv), AgTFA (12.6 mg, 0.0571 mmol, 0.1 equiv), HFIP (6.0 mL), reflux, 41 h; *p*-TsOH•H_2O (109 mg, 0.571 mmol, 1.0 equiv), MeCN (6.0 mL), rt, 24 h; silica gel column chromatography (55% AcOEt/hexane). A pure fraction of *cis*-**2a-Cl** could be obtained and was used for spectral analysis. The other fractions contained *cis*-**2a-Cl** and inseparable byproducts, therefore yield of *cis*-**2t** was calculated by ^{1}H NMR. **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 65:35 ratio) δ 7.41-7.26 (5H, m), 6.02 (2H, d, *J* = 9.5 Hz), 5.44 (1.3H, brd, *J* = 9.5 Hz), 5.36 (0.7H, brd, *J* = 9.5 Hz), 3.62 (1.95H, s), 3.60 (1.05H, brs), 3.56 (0.70H, m), 3.50 (1.3H, brt, *J* = 6.0 Hz), 3.10 (1.95H, s), 2.96 (1.05H, brs), 1.78-1.72 (2H, m), 1.35 (1.3H, m), 1.28 (0.7H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) (Asterisks indicate peaks for the minor rotamer) δ 165.1, 154.4, 152.0, 137.7*, 136.8, 130.9, 129.3, 128.6, 128.1, 127.1, 123.6, 122.7*, 66.4, 59.1, 52.1, 48.4*, 47.5, 42.0*, 40.6, 26.9, 26.3*, 22.7, 22.2*; **HRMS** (ESI) *m*/*z* $[M+Na]^+$ calcd for $C_{21}H_{21}ClN_2NaO_3$ 407.1138, found 407.1147.

Methyl (5s,8s)-9-methyl-10-oxo-12-phenyl-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate (**6**). In a flask, *cis*-**2a** (43.0 mg, 0.0903 mmol) and $Pd(OAc)_2$ (2.03 mg, 9.03 μmol, 0.1 equiv) were placed, then to the flask was added DMF (degassed, 0.500 mL), Et_3N (37.7 μL, 0.271 mmol, 3.0 equiv), and formic acid (10.4 μL, 0.271 mmol, 3.0 equiv). The solution was stirred at 80 °C for 9 h. The reaction mixture was filtered through a pad of Celite and rinsed with AcOEt, and concentrated in vacuo. The crude product was chromatographed on silica gel with 80% AcOEt/hexane to give **6** (18.9 mg, 0.0539 mmol, 60% yield) as a colorless solid. **^{1}H NMR** (600 MHz, $CDCl_3$) (A mixture of rotamers in 65:35 ratio) δ 7.43-7.31 (5H, m), 6.32 (1H, brs), 6.04 (2H, d, *J* = 10.2 Hz), 5.48 (1.3H, m), 5.41 (0.7H, m), 3.65 (1.95H, brs), 3.62 (1.05H, brs), 3.55 (2H, m), 3.06 (1.95H, brs), 2.91 (1.05H, brs), 1.86 (2H, m), 1.71 (1.3H, m), 1.64 (0.7H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) (Asterisks indicate peaks for the minor rotamer) δ 170.0, 160.7, 154.4, 136.6*, 135.8, 133.1, 129.3, 128.1, 127.6, 125.1, 124.4, 124.1*, 67.2, 59.3, 52.1, 48.5*, 47.5, 42.1*, 40.6, 26.0, 25.5*, 22.8, 22.2*; **HRMS** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{23}N_2O_3$ 351.1709, found 351.1733.

Methyl (5s,8s)-11-(4-chlorophenyl)-9-methyl-10-oxo-12-phenyl-1,9-diazadispiro[4.2.4^8.2^5]tetradeca-6,11,13-triene-1-carboxylate (**7**). In a flask, *cis*-**2a** (10.0 mg, 0.0210 mmol), $Pd(PPh_3)_4$ (2.43 mg, 0.0113 mmol, 0.1 equiv), Ag_2O (7.30 mg, 0.0315 mmol, 1.5 equiv), CsF (11.2 mg, 0.0735 mmol, 3.5 equiv), and *p*-chlorophenylboronic acid (11.5 mg, 0.0735 mmol, 3.5 equiv) were weighed, then to the flask MeOH (1.00 mL) was added at rt to give black mixture. The mixture was stirred for 1 h at the same temperature. The reaction mixture was filtered through a pad of Celite and rinsed with $CHCl_3$, and concentrated in vacuo. The crude product was chromatographed on silica gel with 60% AcOEt/hexane to give **7** (7.00 mg, 0.0152 mmol, 72% yield) as a colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$) (A mixture of rotamers in 65:35 ratio) δ 7.38 (2H, d, *J* = 8.0 Hz), 7.29-7.28 (3H, m), 7.17 (2H, d, *J* = 8.0 Hz), 7.08 (2H, m), 5.98 (2H, d, *J* = 10.0 Hz), 5.49 (1.3H, brd, *J* = 10.0 Hz), 5.40 (0.7H, brd, *J* = 10.0 Hz), 3.65 (1.95H, brs), 3.62 (1.05H, brs), 3.55 (0.7H, m), 3.48 (1.3H, brt, *J* = 6.8 Hz), 3.12 (1.95H, brs), 2.99 (1.05H, brs), 1.71 (2H, m), 1.18-1.12 (2H, m); **^{13}C NMR** (100 MHz, $CDCl_3$) (Asterisks indicate peaks for the minor rotamer) δ 169.1, 154.7, 154.5, 137.0*, 136.2, 133.8, 133.3, 132.1, 130.6, 129.6, 129.1, 128.4, 128.1, 128.1, 124.3, 123.4*, 66.5, 59.2, 58.9*, 52.1, 48.4*, 47.5, 42.0*, 40.7, 26.6, 26.1*, 22.7, 22.1*; **HRMS** (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{27}H_{26}ClN_2O_3$ 461.1632, found 461.1622.

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