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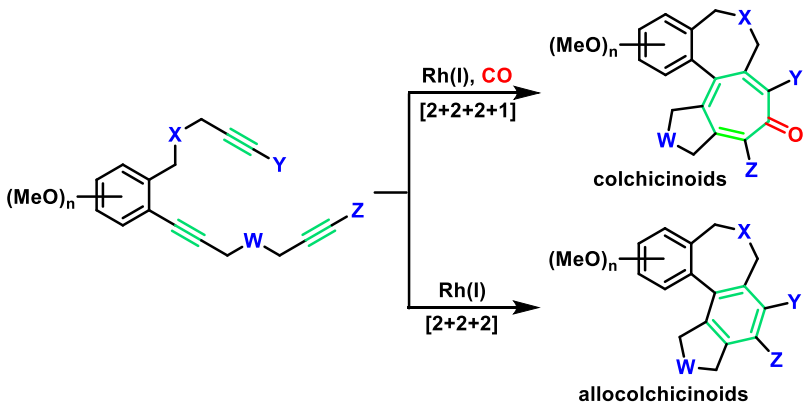
Synthesis of Colchicinoids and Allocolchicinoids through Rh(I)-catalyzed [2+2+2+1] and [2+2+2] Cycloadditions of *o*-Phenylenetriynes with and without CO

Chih-Wei Chien,[†] Yu-Han Gary Teng,[†] Tadashi Honda, [†,‡] and Iwao Ojima*[,†,‡]

[†]Department of Chemistry, Stony Brook University, Stony Brook, New York 11794-3400, [‡]Institute of Chemical Biology and Drug Discovery, Stony Brook University, Stony Brook, New York 11794-3400

Email: iwao.ojima@stonybrook.edu

ABSTRACT



The non-benzenoid aromatics, tropones and tropolones, are found in various natural products such as colchicine and hinokitol, which possess significant biological activities. The traditional methods to construct the tropone skeletons include oxidation of cycloheptatriene and [4+3] cycloadditions. In addition, the total synthesis of colchicine and its analogues requires laborious organic transformations in the formations of 6-7-7 fused rings systems. Transition metal-catalyzed carbocyclization and cycloaddition reactions have proven to be among the most efficient methods for constructing complex polycyclic systems. On the basis of our recent discovery of the Rh-catalyzed carbonylative [2+2+2+1] cycloaddition of triynes to the formation of fused tropone system, we report here the application of this methodology to the one-step formation of the 6-7-7-5 fused-tetracyclic scaffold of colchicinoids based on the [2+2+2+1] cycloaddition of *o*-phenylenetriynes with CO. In addition, the one-step formation of allocolchicinoids bearing the 6-7-6-5 fused tetracyclic system through the Rh-catalyzed [2+2+2] cycloaddition of *o*-phenylenetriynes is also described.

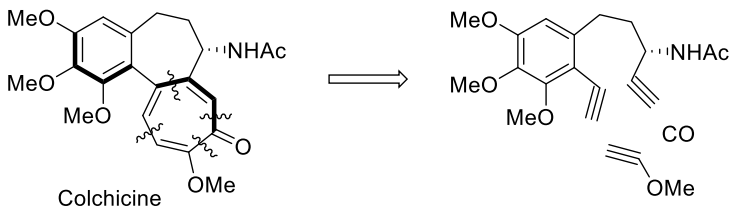
INTRODUCTION

Colchicine, a cytotoxic natural product and secondary metabolite of autumn crocus, is originally extracted from the poisonous plant meadow saffron (*Colchicum autumnale* L.). Owing to the capability in suppressing inflammation, colchicine is one of the oldest known drugs and has been used for treatment of rheumatic complaints and especially gout for thousands of years. In addition to gout, colchicine has also been used for treatment of familial Mediterranean fever, pericarditis, and Behçet's disease, due to its anti-inflammatory effect. In recent years, colchicine and its analogues have received considerable interest for cancer chemotherapy. After the structural confirmation in 1952, a number of synthetic approaches have been elaborated following fundamentally different strategies towards colchicine.[1, 2] In spite of all available modern methodologies, the development of a synthetic method with satisfactory efficiency towards colchicine and its derivatives is still challenging. The difficulties inherent to the target structure lie in the regioselective construction of the highly oxidized ring C with an unusual 6,7,7 fused ring system,[3] which appears to have hindered the discovery of more active colchicine analogues. Therefore, in order to further explore the pharmaceutical potential and study the structure-activity relationships, it is of great importance to develop a synthetic method which enables an efficient construction of colchicine derivatives and analogs.

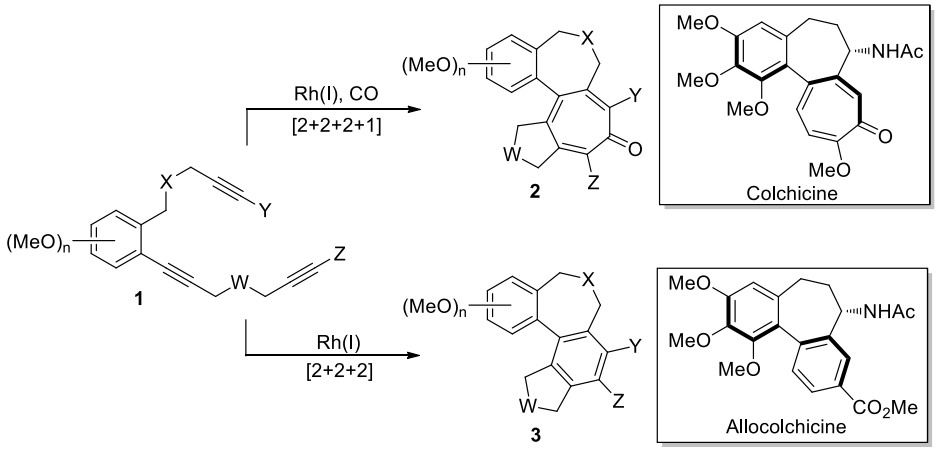
To rapidly implement molecular complexity from readily available simple starting materials, transition metal-catalyzed carbocyclization and cycloaddition reactions are recognized as synthetically very important processes.[4-7] Considerable advances have been made recently in the development of higher order cycloaddition reactions such as [2+2+2+1],[8-11] [3+3+1],[12] [2+2+2+2],[13-15] [4+2+2],[16-18] [5+2+1],[19-24] and [5+1+2+1][25] processes. Various polycyclization reactions have been employed for the construction of natural and unnatural fused-ring systems that

can be further elaborated into specific targets. Recently, we discovered the Rh-catalyzed [2+2+2+1] cycloaddition of linear 1,6,11-, 1,6,12- and 1,6,13-triynes with CO, forming the corresponding fused tricyclic tropone systems.[26] [*Note*: After the submission of this article, a related [2+2+2+1] carbonylative cycloaddition of triyens was published,[27] which followed up the Ph.D. dissertation works[26, 28] of the two authors (C.-W.C. and Y,-H.G.T.) of this article.] Conceptually, the tropone moiety of colchicine can be constructed through the [2+2+2+1] cycloaddition of a tethered diyne, methoxyethyne and CO (Scheme 1). However, this three-component higher cycloaddition is obviously very challenging, partly due to regioselectivity control in addition to energetics. Accordingly, we came up with a rational design of using tethered *o*-phenylenetriynes as the substrates for the [2+2+2+1] cycloaddition with CO (Scheme 2).[28] We envisioned that the colchicine scaffold should be constructed in a single step using this methodology (Scheme 2). We report here the Rh-catalyzed carbonylative [2+2+2+1] cycloaddition approach to the rapid synthesis of novel colchicinoids. Besides colchicine, allocolchicine bearing a bisbenzocycloheptane 6-7-6 ring system is also known as a tubulin-interacting agent, exhibiting apoptosis-inducing activity,[29] and several synthetic routes to allocolchicine variants and their biological activities have been reported.[29-34] Accordingly, in the present work, we also examined the formation of novel allocolchicinoid *via* [2+2+2] cycloaddition of *o*-phenylenetriynes (Scheme 2).

Scheme 1. Retrosynthetic analysis of colchicine based on [2+2+2+1] cycloaddition approach



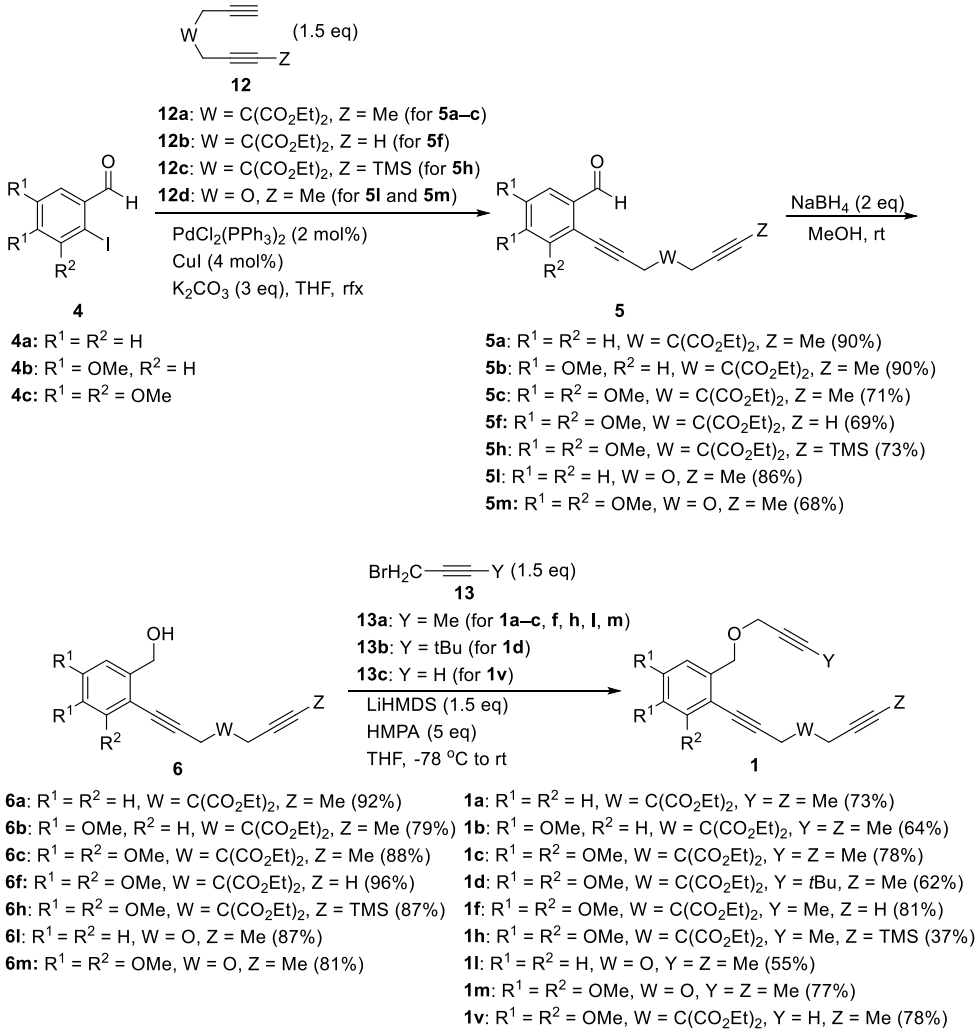
Scheme 2. Colchicinoid and allocolchicinoid formations via higher cycloadditions of *o*-phenylenetriynes



■ RESULTS AND DISCUSSION

Synthesis of *o*-phenylenetriynes. In order to prove our hypothesis on the possible rapid construction of colchicinoide skeleton based on the Rh-catalyzed [2+2+2+1] cycloaddition of designed triynes with CO, ***o*-phenylenetriynes,** **1a**–**d**, **1f**, **1h**, **1l**, **1m**, and **1v**, were synthesized according to the sequence shown in Scheme 3. Diynealdehydes **5a**–**5c** were obtained in good yield by Sonogashira coupling[35] of iodobenzaldehydes **4a**–**4c** with diethyl 2-(but-2-ynyl)-2-(prop-2-ynyl)malonate (**12a**).[36] The diynealdehydes **5a**–**5c** were then reduced with $NaBH_4$ in MeOH to give diynealcohol **6a**–**6c**, and subsequent alkylation with 1-bromobut-2-yne (**13a**) in the presence of LiHMDS in THF afforded the desired triynes **1a**–**1c**. *o*-Phenylenetriyne **1d** was prepared through alkylation of **6c** with1-bromo-4,4-dimethylpent-2-yne (**13b**).

Scheme 3. Synthesis of *o*-phenylenetriynes **1**

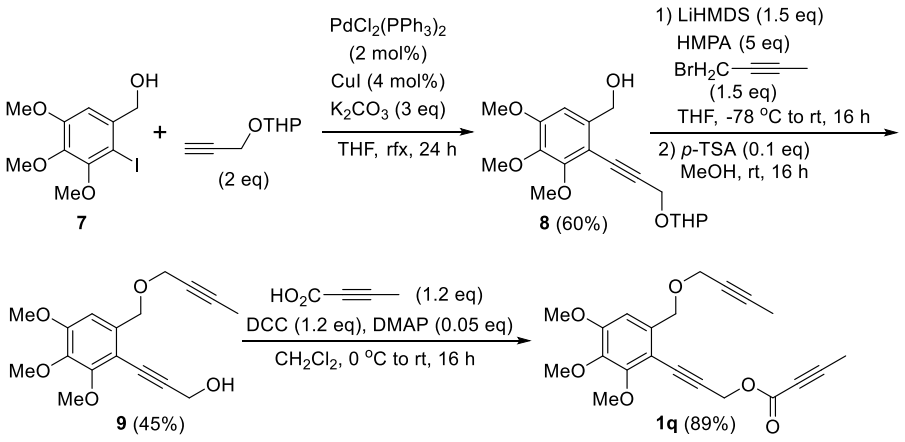


Diynealdehydes **5f**, **5h**, and **5m** were prepared by Sonogashira coupling of **4c** with diethyl 2,2-di(prop-2-yn-1-yl)malonate (**12b**),[37] (diethyl 2-(prop-2-yn-1-yl)-2-(3-(trimethylsilyl)prop-2-yn-1-yl)malonate (**12c**),[36] and 1-(prop-2-yn-1-yloxy)but-2-yne (**12d**),[38] respectively. Diynealdehyde **5l** was obtained from **4a** using **12d**. After reduction of the aldehydes to the corresponding alcohols, *o*-phenylenetriynes **1f**, **1h**, **1l**, and **1m** were prepared by alkylation of alcohols **6f, 6h**, **6l**, and **6m** with **13a**, respectively. It is noteworthy that during the synthesis of **1h**, a product without the TMS group, *o*-phenylenetriyne **1f** was also isolated in 38% yield. Alkylation of **6c** with 3-bromoprop-1-yne (**13c**) gave **1v**.

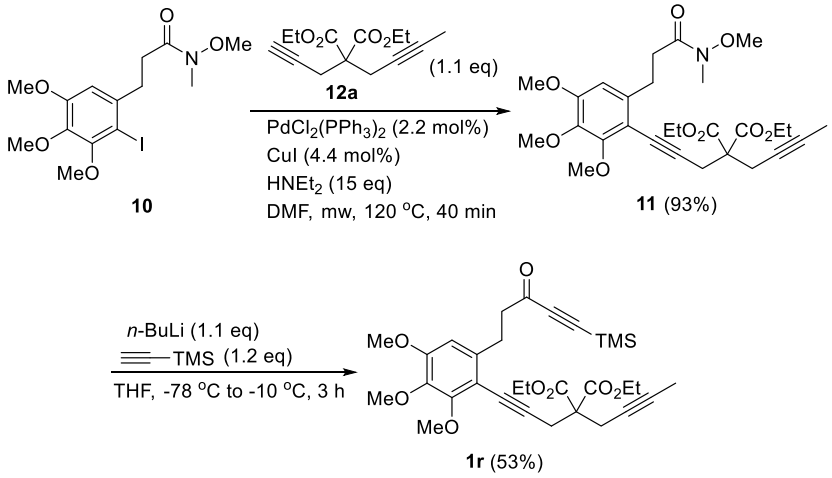
o-Phenylenetriyne **1q** was synthesized by the sequence shown in Scheme 4. Sonogashira coupling of iodinated benzyl alcohol **7**[39] with THP-protected propagyl alcohol gave **8**. Diyne **9** was obtained by etherification of **8**, followed by deprotection. The Steglich esterification of **9** with 2-butynoic acid afforded **1q**.

o-Phenylenetriyne **1r** was synthesized by Sonogashira coupling of **10**[40, 41] with **12a**, followed by substitution of the *N*,*O*-dimethylhydroxylamino moiety with a trimethylsilylacetylene group (Scheme 5).

Scheme 4. Synthesis of *o*-phenylenetriyne **1q**

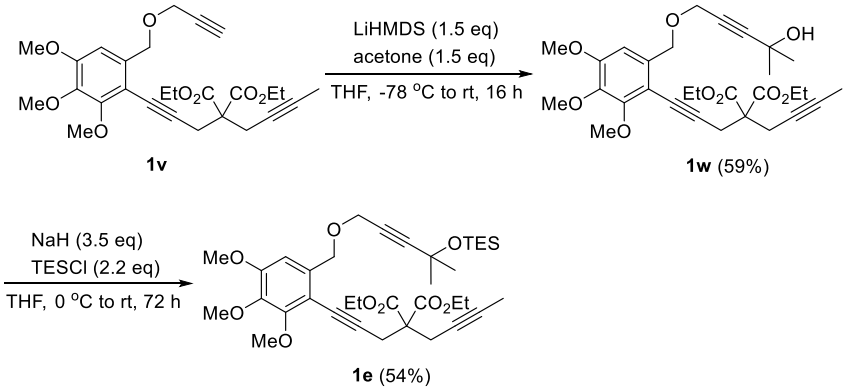


Scheme 5. Synthesis of *o*-phenylenetriyne **1r**



Treatment of lithium acetylide of **1v** with acetone gave **1w**. The hydroxyl group of **1w** was protected with TESCl to afford **1e** (Scheme 6).

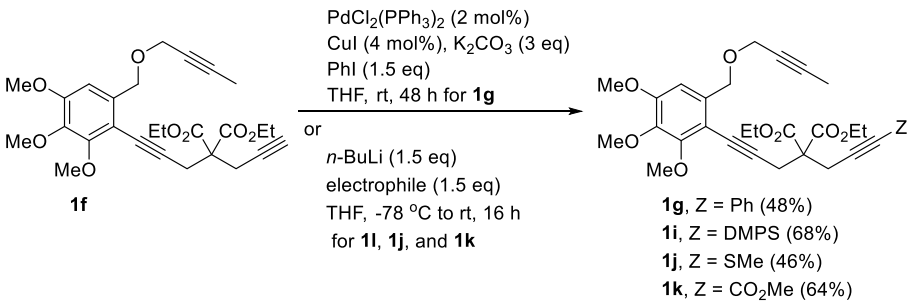
Scheme 6. Synthesis of *o*-phenylenetriynes **1w** and **1e**



1v **1w** (59%) **1e** (54%)

Sonogashira coupling of **1f** with phenyl iodide gave *o*-phenylenetriyne **1g**. Lithium acetylide of **1f** with dimethylphenylsilylchloride (DMPSCl), dimethyl disulfide, and methyl chroloformate gave **1i**, **1j**, and **1k**, respectively (Scheme 7).

Scheme 7. Synthesis of *o*-phenylenetriynes **1g**, **1i**, **1j**, and **1k**

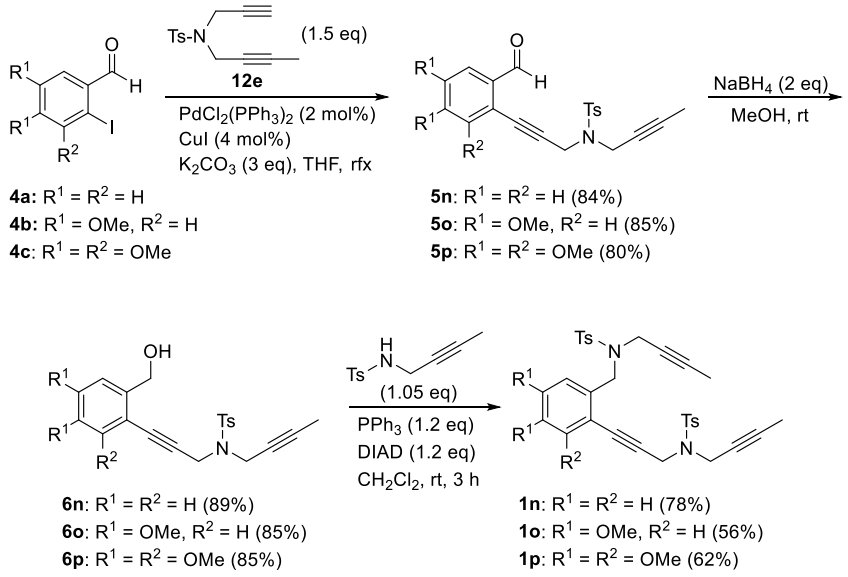


1f

1g, Z = Ph (48%)
1i, Z = DMPS (68%)
1j, Z = SMe (46%)
1k, Z = CO_2Me (64%)

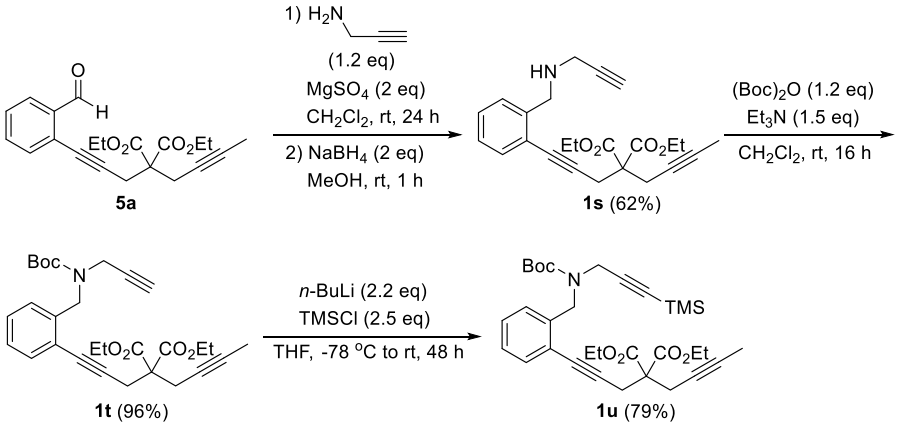
o-Phenylenetriynes **1n**–**p** bearing *N*-tosyl groups on both side chains were synthesized by the sequence shown in Scheme 8. Diyne-benzylalcohols **6n**–**6p** were prepared by Sonogashira coupling of **4a**–**4c** with **12e**, followed by reduction with $NaBH_4$. Mitsunobu reaction of **6n**–**p** with *N*-tosylbut-2-yn-1-amine gave **1n**–**p** in good yields.

Scheme 8. Synthesis of *o*-phenylenetriynes **1n**–**1p**



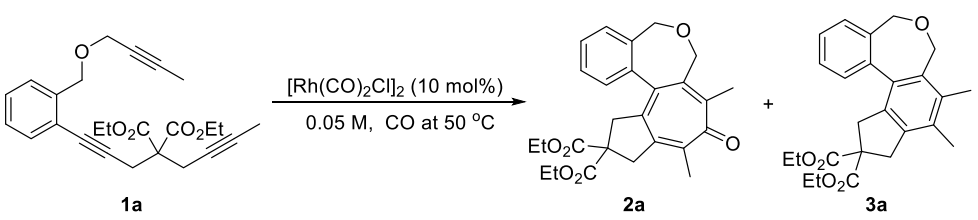
o-Phenylenetriynes **1s**–**u** bearing a nitrogen atom on the side chain were synthesized as shown in Scheme 9. Reductive amination of diyne-aldehyde **5a** with propargylamine and subsequent reduction with $NaBH_4$ gave **1s**. The secondary amine moiety of **1s** was protected with a *t*-Boc group using di-*tert*-butyl dicarbonate to afford **1t**. Lithium acetylide of **1t** was reacted with TMSCl to yield **1u**.

Scheme 9. Synthesis of *o*-phenylenetriynea **1s**, **1t**, and **1u**



Optimization of the Rh-catalyzed carbonylative [2+2+2+1] cycloaddition reaction conditions. *o*-Phenylenetriyne **1a** was employed to optimize the reaction conditions and the results are summarized in Table 1. The reaction of **1a** in the presence of $[Rh(CO)_2Cl]_2$ (10 mol%) in eight different solvents (entries 1–8) was completed at 50 °C under ambient pressure of CO for 48 h to give **2a** as the predominant product accompanied by a small amount of **3a**. The products **2a** and **3a** are the products of [2+2+2+1] and [2+2+2] cycloaddition processes, respectively. The attempted reactions in DMF (entry 9) and EtOH (entry 10) did not proceed at all. The reaction in a mixed solvent, i.e., dichloroethane (DCE) and 2,2,2-trifluoroethanol (TFE) (1:1), gave a high conversion, the product selectivity was low (**2a**/**3a**, 86:14, entry 8). Among the solvents examined, the highest product selectivity (96:4) was observed in decane (entry 1), toluene (entry 3), and 1,4-dioxane (entry 7), wherein toluene gave the highest conversion (64%). Accordingly, toluene was selected for further optimization. The reactions were carried out under different CO pressures (entries 11−14). Interestingly, CO pressure did not affect the product selectivity but affected the conversion, wherein higher CO pressure was found to slow down the reaction. Thus, best conversion (100%) was achieved under an ambient pressure of CO in 36 h (entry 13). The reaction in a microwave reactor for 3 h gave 70% conversion and 96:4 product selectivity (entry 14). Although some acceleration might have happened, there was no dramatic effect of microwave irradiation.

Table 1. Effects of solvent and CO pressure on the conversion and product selectivity in the reaction of **1a**



1a **2a** **3a**

Entry[a]	Solvent	CO pressure (atm)	Time (h)	Conversion[b] (%)	Product selectivity[b] **2a** : **3a**
1	decane	3	48	43	96 : 4
2	*p*-xylene	3	48	71	95 : 5
3	toluene	3	48	64	96 : 4
4	THF	3	48	8	87 : 13
5	DME	3	48	15	92 : 8
6	DCE	3	48	47	93 : 7
7	1,4-dioxane	3	48	58	96 : 4
8	DCE/TFE (1/1)	3	48	96	86 : 14
9	DMF	3	48	0	nd
10	EtOH	3	48	0	nd
11	toluene	6	48	77	96 : 4
12	toluene	2	48	100	96 : 4
13	toluene	1	36	100	96 : 4
14[c]	toluene	1	3	70	96 : 4

[a]A mixture of **1a** (0.15 mmol) and $[Rh(CO)_2Cl]_2$ (10 mol%) in a solvent (3 mL, 0.05M concentration) was used for each entry.
[b]Conversion and product selectivity were determined by HPLC. Since the reactions appeared to be clean, the selectivity shown would represent HPLC yields or conversion yields when the reaction did not complete.
[c]The reaction was carried out using a microwave reactor.

Next, we examined other reaction variables in toluene under ambient pressure of CO. Results are summarized in Table 2. As entries 1−3 of Table 2 show, the increase in reaction temperature lowered the product selectivity. However, lowering temperature below 50 °C did not show any benefit. At 35° C, product selectivity was not improved, but reaction was slowed as expected (entry 4) and at 20 °C even the product selectivity became worse (entry 5). Therefore, 50 °C was selected as the optimal reaction temperature. Next, the effect of substrate concentration on the reaction was examined (entries 6 and 7). When the reaction of **1a** was performed at higher concentration, the product selectivity was slightly increased (entry 6 vs. entries 3 and 7). Lowering the catalyst amount slowed down the reaction but did not give significant change in the product selectivity (entries 8−10).

At 5 mol% of $[Rh(CO)_2Cl_2]_2$ and 0.1-0.2 M concentration of **1a** (entries 11−14), the increase in the reaction temperature by 10 °C to 60 °C accelerated the reaction considerably without sacrificing the product selectivity (entry 13). Bubbling CO did not show appreciable effect

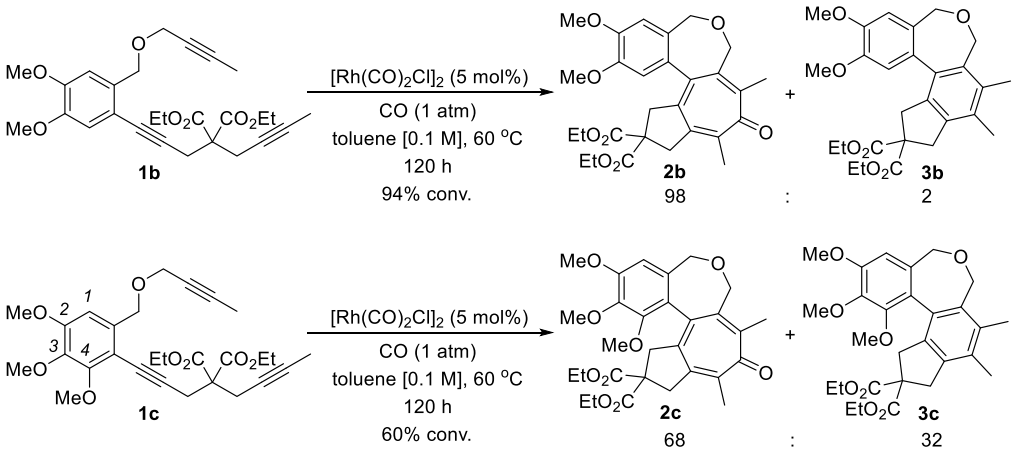
(entry 12). Addition of 1,3-bis(diphenylphosphono)propane (DPPP) (10 mol%) was detrimental to the reaction (entry 14). In this case, it is likely that DPPP blocks the proper coordination of triyne **1a**. Another Rh-catalyst, $[Rh(COD)Cl]_2$ gave similar product selectivity but with lower conversion (entry 15 vs. entry 6). We also examined several catalyst systems for this reaction, including $Rh(acac)(CO)_2$, $Rh(PPh_3)_2(CO)Cl$, $Rh(PPh_3)_3Cl$, $Rh_4(CO)_{12}$, $Rh_2Co_2(CO)_{12}$, $[Rh(COD)_2]SbF_6$, $[Co(CO)_4]_2$, $Ru_3(CO)_{12}$, and $Ir(PPh_3)_2(CO)Cl$. However, none of them showed ability to catalyze the [2+2+2+1] and [2+2+2] cycloaddition reactions.

Table 2. Effects of the temperature, substrate concentration and catalyst concentration on the conversion and product selectivity in the reaction of **1a** under CO

Entry[a]	Temp. (°C)	Conc. (M)	$[Rh(CO)_2Cl_2]_2$ (mol%)	Time (h)	Conversion[b] (%)	Product selectivity[b] **2a** : **3a**
1	110	0.05	10	6	100	71 : 29
2	80	0.05	10	16	100	93 : 7
3	50	0.05	10	36	100	96 : 4
4	35	0.05	10	72	62	96 : 4
5	20	0.05	10	120	58	91 : 9
6	50	0.1	10	24	100	97 : 3
7	50	0.025	10	72	96	96 : 4
8	50	0.1	7.5	48	82	97 : 3
9	50	0.1	5	48	50	97 : 3
10	50	0.1	2.5	48	26	96 : 4
11	50	0.2	5	24	31	96 : 4
12[c]	50	0.1	5	48	49	97 : 3
13[d]	60	0.1	5	48	94	96 : 4
14	50	0.1	5 (10 mol% DPPP)	48	0	nd
15	50	0.1	10 ($[Rh(COD)Cl]_2$)	24	46	96 : 4

[a] 0.15 mmol of **1a** was used for each entry.
[b] Conversion and product selectivity were determined by HPLC. Since the reactions appeared to be clean, the selectivity shown would represent HPLC yields or conversion yields when the reaction did not complete.
[c] The reaction was carried out by bubbling CO.
[d] Isolated yield of **2a** was 80%.

Scheme 10. Reactions of *o*-phenylenetriynes **1b** and **1c** under CO

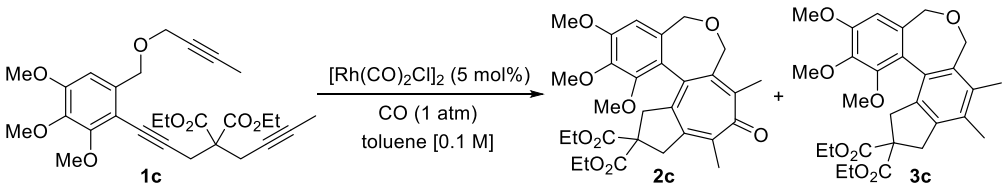


Based on these optimization studies, we selected the reaction conditions of entry 13 in Table 2 as the standard for the subsequent investigation on the synthesis of a variety of colchicinoids **2** and allocolchicinoids **3**. Thus, *o*-phenylenetriynes **1b** and **1c** were subjected to the standard conditions but with longer reaction time (Scheme 10). The reactions of **1b** and **1c** were considerably slower than that of **1a**. The product selectivity for the reaction of **1b** was excellent (**2b**:**3b** = 98:2) and pure **2b** was isolated in 84% yield. In contrast, the reaction of **1c** was sluggish and resulted in only moderate product selectivity (**2c**:**3c** = 68:32).

Since the reaction conditions for **1c**, in particular, were clearly not optimal, we examined the reaction variables and effect of additives on the conversion and product selectivity. The results are summarized in Table 3. The increase in reaction temperature to 80 °C exhibited substantial enhancement in the reaction rate, while the product selectivity was only slightly affected. Thus, 100% conversion in 64 h was achieved with a **2c**:**3c** ratio of 66:34 (entry 1). Next, we examined the effect of additives on the reaction in toluene. In the presence of 4Å molecular sieves, a slightly longer reaction time but similar product selectivity was observed (entry 2). While the addition of Brønsted and Lewis acids drastically shortened the reaction time and afforded 100% conversion

after 24 h, these acids did not improve the product selectivity (entries 3–7). Nevertheless, the addition of a solid Lewis acid, montmorillonite K10 (K10), provided slightly better product selectivity than those of other additives, and more importantly achieved 100% conversion in 32 h at 60 °C with a **2c**:**3c** ratio of 70:30 (entries 8 and 9), wherein **2c** was isolated in 52% yield. Consequently, we used K10 as the additive in the subsequent reactions of various *o*-phenylenetriynes **1d**-**1r**.

Table 3. Effect of additives on the reaction of **1c** under CO



Entry[a]	Additive	Temp. (°C)	Time (h)	Conversion[b] (%)	Product selectivity[b] **2c** : **3c**
Scheme 10	—	60	120	60	68 : 32
1	—	80	60	100	66 : 34
2	4Å MS	80	72	100	65 : 35
3	CSA[c]	80	24	100	66 : 34
4	HOAc[c]	80	24	100	68 : 32
5	TFE[c]	80	24	100	68 : 32
6	$LiClO_4$[c]	80	24	100	65 : 35
7	$BF_3{\cdot}OEt_2$[c]	80	24	100	61 : 39
8	K10	80	24	100	69 : 31
9[d]	K10	60	32	100	70 : 30

[a] 0.15 mmol of **1c** was used for each entry.
[b] Conversion and product selectivity were determined by HPLC. Since the reactions appeared to be clean, the selectivity shown would represent HPLC yields or conversion yields when the reaction did not complete.
[c] 0.2 equiv. of additive was used.
[d] Isolated yield of **2c** was 52%.

Effects of the substituents at the α- and ω-terminal ethyne units on the carbonylative [2+2+2+1] cycloaddition. We have examined the effects of substituents (Y and Z) at the two terminal ethyne moieties of ten *o*-phenylenetriynes **1d-k** on the product selectivity and yield of the [2+2+2+1] cycloaddition with CO. Results are summarized in Table 4.

First, we fixed the Z terminus to a methyl group and introduced a bulky group to the Y terminus. The reaction of **1d**, bearing a *t*-Bu group as Y, gave **2d** almost exclusively (99% by HPLC; isolated yield of **2d** was 83%) in 72 h at 60 ºC (entry 1). However, the same reaction completed in 24 h at 80 ºC without any change in the product selectivity (entry 2). Thus, the subsequent reactions were all carried out at 80 °C. The reaction of **1e**, bearing a 2-triethylsiloxyisopropyl group that is bulkier than a *t*-Bu group as Y at 80 °C, afforded **2e** exclusively (isolated yield of **2e** was 87%), i.e., the formation of **3e** was not detected at all (entry 3). Accordingly, it is clearly shown that a bulky substituent at the Y terminal strongly favors the tropone formation. Next, we fixed the Y terminus to a methyl group and introduced different groups to the Z terminus. The reaction of **1f**, bearing an unsubstituted enyne at the Z terminus (Z = H), gave **2f** with only 56% selectivity although the reaction completed in 24 h (entry 4). The reaction of **1g**, bearing a phenyl group as Z, afforded **2g** with 84% selectivity (entry 5). Since the reaction of **1c**, bearing a methyl group as Z, gave **2c** with 69% selectivity, the introduction of a bulkier substituent as Z appears to favor the tropone formation in a manner similar to the case of Y. Thus, we introduced TMS and dimethylphenylsilyl (DMPS) groups as Z next. These reactions, however, disclosed totally unexpected results.

The reaction of **1h**, bearing a TMS group as Z, gave [2+2+2+1] cycloaddition products with 96% combined yield (HPLC), accompanied by **3h** (4%) (entry 6). However, surprisingly, no anticipated product **2h** was detected, and **2f** (90%) and **2c** (6%) were formed instead. The structures of these products were unambiguously identified (see the Experimental Section). The formation of **2f** in this reaction can be accommodated rather easily by assuming the desilylation of **2h** under the reaction conditions. In contrast, the formation of **2c** requires to hypothesize an unprecedented methyl migration from the TMS group to the Z terminal ethyne carbon, involving C-Si activation.

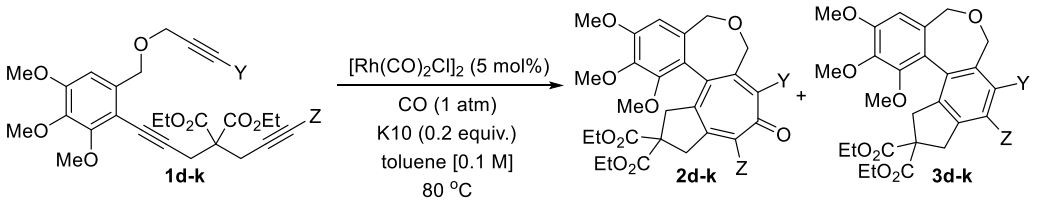
The reaction of **1h** in the absence of K10 under otherwise the same conditions as those for entry 6 afforded the same products **2f** (81%), **2c** (13%) and **3c** (6%) with slightly different ratio at 94% conversion in 120 h (entry 7). Thus, it appears that K10 accelerates the reaction and rather suppresses the methyl migration, but is not responsible for the desilylation process. It is worth mentioning that the desilylation did not occur in the starting **1h** to give **1f**, since the product selectivity and the reaction rate are markedly different between the reactions of **1f** (entry 4) and **1h** (entry 6). Thus, the desilylation should have occurred after the [2+2+2+1] cycloaddition was completed or the carbonylated key intermediate (**B** or **B'** in Scheme 11) leading to the formation of the [2+2+2+1] cycloaddition product **2** was formed. It is also noteworthy that no desilylation took place in the [2+2+2] cycloaddition process, forming **3h**.

In a manner similar to entry 3 and entry 6, the reaction of **1i**, bearing a bulky DMPS) group as Z, yielded the [2+2+2+1] cycloaddition products **2** exclusively without any trace of the [2+2+2] cycloaddition product **3i**, wherein the product **2** was not **2i**, but a mixture of **2g** (79%) and **2g** (21%) (entry 8). Thus, in the same manner as the entry 6, the desilylation and the phenyl migration took place in this reaction. To the best of our knowledge, this type of the methyl or phenyl group migration from the TMS or DMPS group has not been reported in the literature. Therefore, this novel methyl/phenyl migration reaction involving C-Si activation warrants further investigation.

The reaction of **1j**, bearing a methylsulfanyl group as Z, gave a 1:1 mixture of **2j** and **3j** (entry 9). Thus, it has been shown that the sulfide group does not interfere with this Rh-catalyzed reaction, but it does not favor the tropone formation, either. The introduction of an electron-withdrawing ester group to **1** as Z appears to be unfavorable to the [2+2+2+1] cycloaddition. Thus, the reaction of **1k**, bearing a methoxycarbonyl group as Z, yielded the [2+2+2] cycloaddition product **3k** as the major product (entry 10).

Those results clearly indicate that the introduction of a bulky substituent to either ethyne terminus as Y or Z strongly favor the carbonylative [2+2+2+1] cycloaddition process. Also, it is disclosed that a bulky silyl group used as Z can be eliminated via a desilylation under the reaction conditions. This finding can be further exploited for the design and synthesis of various colchicinoids for structure-activity relationship studies.

Table 4. Substituent effects on the reaction of *o*-phenylenetriynes **1d–k** under CO



Entry[a]	*o*-Phenylenetriyne	Time (h)	Conversion[b] (%)	Product selectivity[b] **2** : **3**
1[c]	**1d** Y = *t*-Bu, Z = Me	72	100	99 : 1
2[d]	**1d** Y = *t*-Bu, Z = Me	24	100	99 : 1
3[e]	**1e** Y = CMe_2OTES, Z = Me	72	100	100 : 0
4	**1f** Y = Me, Z = H	16	100	56 : 44
5[f]	**1g** Y = Me, Z = Ph	36	100	84 : 16
6	**1h** Y = Me, Z = TMS	96	100	90 (**2f**) : 6 (**2c**) : 4 (**3h**)
7[g]	**1h** Y = Me, Z = TMS	120	94	81 (**2f**) : 13 (**2c**) : 6 (**3h**)
8	**1i** Y = Me, Z = DMPS	96	100	79 (**2f**) : 21 (**2g**)
9	**1j** Y = Me, Z = SMe	120	100	50 : 50
10	**1k** Y = Me, Z = CO_2Me	20	100	34 : 66

[a] 0.15 mmol of starting material was used for each entry.
[b] Conversion and product selectivity were determined by HPLC. Since the reactions appeared to be clean, the selectivity shown would represent HPLC yields or conversion yields when the reaction did not complete.
[c] Reaction was carried out at 60 °C.
[d] Isolated yield of **2d** was 83%.
[e] Isolated yield of **2e** was 87%.
[f] Isolated yield of **2g** was 66%.

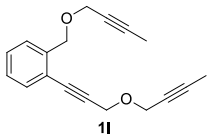
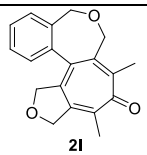
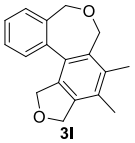
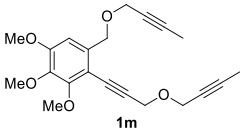
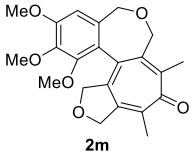
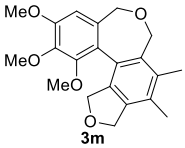
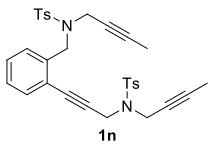
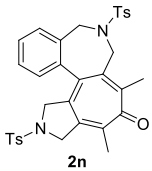
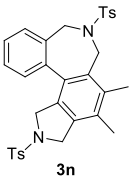
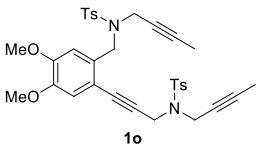
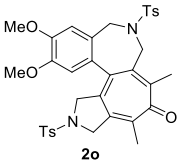
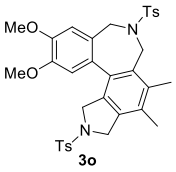
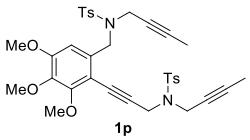
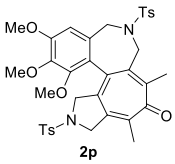
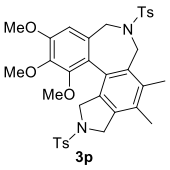
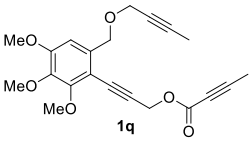
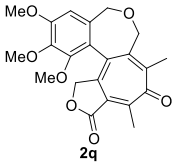
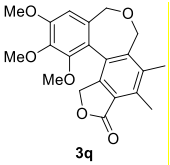
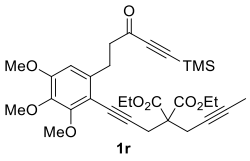
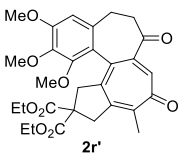
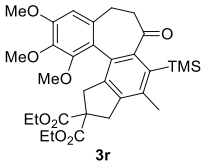
[g] Reaction was carried out without K10 additive.

Effects of the tether groups on the carbonylative [2+2+2+1] cycloaddition. Next, we investigated the effects of the tether groups connecting two ethyne groups as well as the *o*-phenylene and ethyne groups on the product selectivity and yield of the [2+2+2+1] cycloaddition process. Results are summarized in Table 5. The reactions of **1l** and **1m**, wherein the malonate moiety of **1a** and **1c** were replaced with an ether group, gave the corresponding **2l** and **2m** with 98% and 70% selectivity (entries 1 and 2). Replacement of the ether tether and the malonate tether of **1a**, **1b** and **1c** with tosylamino groups gave nitrogen-containing *o*-phenylenetriynes **1n**, **1o** and **1p**, respectively. The reactions of **1n-p** afforded the corresponding mixtures of **2n-p** and **3n-p** with considerably lower product selectivity than that for **2a-c** (entries 3-5).

The reaction of **1q**, wherein the malonate moiety of **1c** was replaced with an ester linkage, yielded the corresponding [2+2+2] cycloaddition product **3q** as the predominant product (87% HPLC yield) (entry 6). Thus, the ester linkage at this tether position appears to be detrimental to the tropone formation. The replacement of the but-2-ynyloxy moiety of **1c** with a trimethylsilylethynylcarbonylmethyl group gave **1r**. The reaction of **1r** afforded the corresponding **2r'** (58%) and **3r** (42%), wherein the originally expected product **2r** was not yielded, but its desilylated product **2r'** was obtained. The formation of **2r'** can be explained in the same manner as that for the cases of the reactions of **1h** and **1i** discussed above (Table 4), but no methyl migration was observed in this reaction.

Table 5. Reaction of *o*-phenylenetriynes **1l–r**[a]

Entry[b]	*o*-Phenylenetriyne	Temp. (°C)	Time (h)	Conversion[c] (%)	Product selectivity[c] **2** : **3**

1[d]	 1l	60	48	100	 2l  3l 98 : 2
2	 1m	80	48	100	 2m  3m 70 : 30
3[e]	 1n	60	30	100	 2n  3n 81 : 19
4	 1o	70	24	100	 2o  3o 66 : 34
5	 1p	80	48	100	 2p  3p 45 : 55
6[f]	 1q	80	120	96	 2q  3q 13 : 87
7	 1r	80	24	100	 2r'  3r 58 : 42

[a] The same conditions as shown in Table 4 were used.
[b] 0.15 mmol of starting material was used for each entry.
[c] Conversion and product selectivity were determined by HPLC. Since the reactions appeared to be clean, the selectivity shown would represent HPLC yields or conversion yields when the reaction did not complete.
[d] Isolated yield of **2l** was 80%.
[e] Isolated yield of **2n** was 62%.
[f] **2q** was identified based on HRMS due to minute quantity.

Proposed mechanism for the Rh-catalyzed [2+2+2+1] and [2+2+2] cycloaddition reactions of 1. The proposed mechanism of the [2+2+2+1] and [2+2+2] cycloaddition reactions of *ortho*-phenylenetriynes **1** is illustrated in Scheme 11. The carbonylative [2+2+2+1] cycloaddition reaction proceeds through (i) selective coordination of the diyne side chain of **1** to the active Rh-catalyst species to give rhodacycle **A** or **A'** ([2+2+M]); (ii) migratory insertion of CO into the Rh–C bond to form rhodacyclohexadienone **B** or **B'**; (iii) insertion of the alkyne side chain of **B** or **B'** into the Rh–C bond to generate 6-7-8-5 fused-tetracyclic rhodacyclooctatrienone **C** or **C'**; and (iv) reductive elimination to give [2+2+2+1] cycloaddition product **2** and regenerate the active Rh-catalyst species.

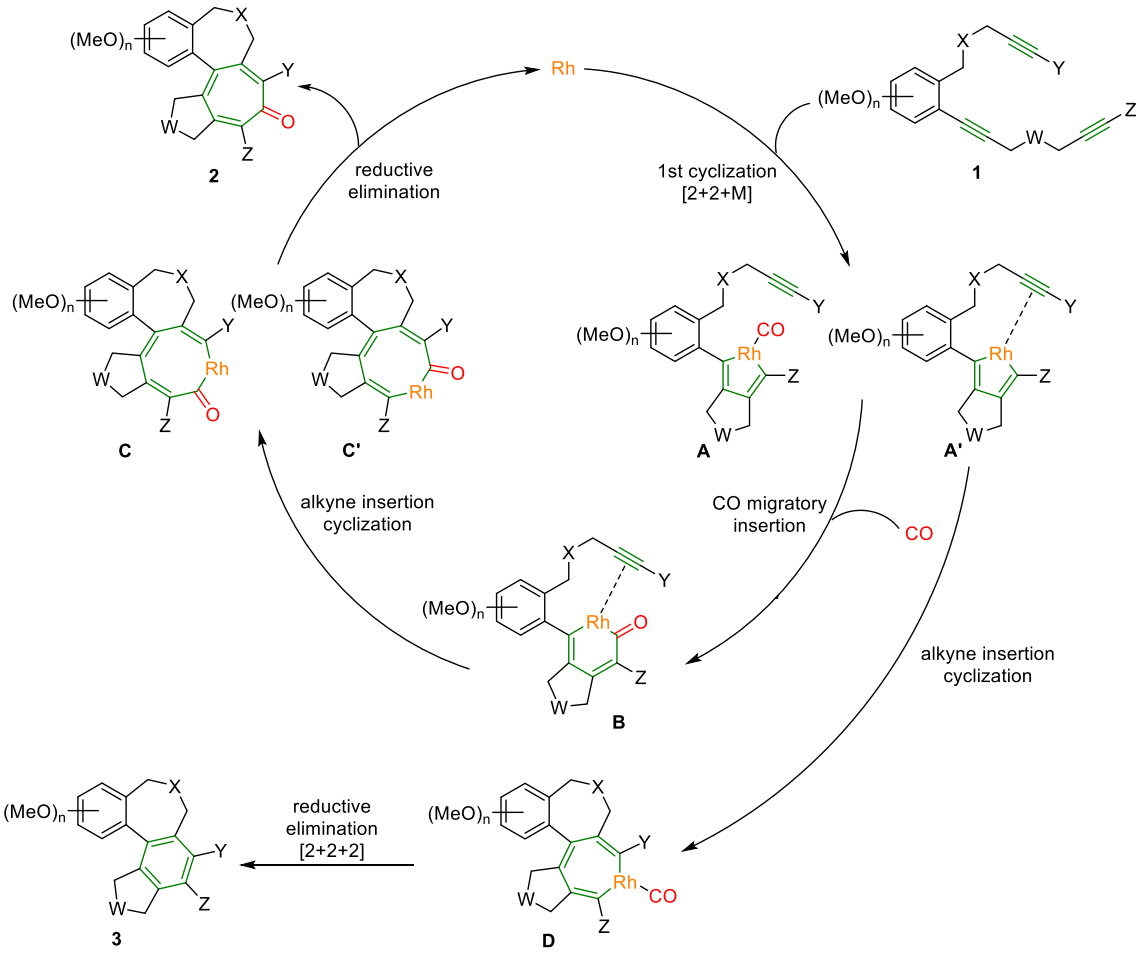
The [2+2+2] cycloaddition reaction also involves rhodacyclopentadine **A** or **A'**. In this reaction pathway, however, the alkyne side chain of **A** or **A'** inserts into the Rh–C bond, instead of CO migratory insertion, leading to the formation of 6-7-7-5 fused-tetracyclic rhodacycloheptatriene **D**, which undergoes reductive elimination to afford [2+2+2] cycloaddition product **3**. The [2+2+2] cycloaddition or cyclotrimerization of triynes and its applications is well precedented.[42]

The proposed mechanism can nicely accommodate the observed remarkable effect of bulky substituents at either terminal ethyne moiety (Y or Z), favoring the formation of the carbonylative [2+2+2+1] cycloaddion product **2**. The bulky terminal groups, i.e., *t*-Bu, TMS, and DMPS, would interfere with the approach of the alkyne side chain to the Rh metal of **A** or **A'** and block or slow down the alkyne insertion, which allows the CO migratory insertion to occur predominantly or exclusively, pushing the catalytic cycle to produce the carbonylative [2+2+2+1] cycloaddition product **2**.

As described above, no desilylation took place in the [2+2+2] cycloaddition process,

forming **3**. Accordingly, it is strongly suggested that the rhodacyclooctatrienone C' intermediate would be responsible for the desilylation and the methyl/phenyl migration observed in this reaction.

Scheme 11. Proposed mechanism for the Rh-catalyzed [2+2+2+1] and [2+2+2] cycloaddition reactions of triyne **1**

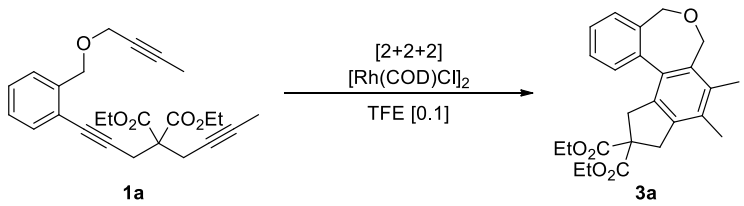


Comparison of the results obtained for the reactions of **1a**–**c** and other *o*-phenylenetriynes, it is obvious that the introduction of additional methoxy group to the C4-position of the o-phenylene moiety significantly affects the formation of the fused tropone products. The electronic effect of the methoxy group can be ruled out for this phenomenon since there is no apparent difference in product selectivity between non-substituted *o*-phenylenetriynes such as **1a** and

dimethoxy-*o*-phenylenetriynes such as **1b**. The unfavorable effect of the 4-methoxyl group in **1** on the carbonylative [2+2+2+1] cycloaddition would be explained as follows: (i) The 4-methoxy group of the o-phenylene moiety restricts the free rotation of the rhodacyclopentadiene moiety of **A** or **A'**; (ii) The lack of the free rotation places the alkyne side chain at a very good position to coordinate to the Rh metal; (iii) The coordination of the alkyne moiety to the Rh metal facilitates the alkyne insertion over CO migratory insertion to generate the rhodacycle **D**, leading to the formation of the [2+2+2] cycloaddition product **3**.

Rh-catalyzed [2+2+2] cycloaddition. In addition to the Rh-catalyzed carbonylative [2+2+2+1] cycloaddition to synthesize colchicinoids, we also investigated the Rh-catalyzed [2+2+2] cycloaddition of o-phenylenetriynes **1** as an efficient approach to allocolchicinoids. We examined reaction variables in the reaction of **1a** to optimize this process, as shown in Table 6. As described above, under the carbonylative [2+2+2+1] cycloaddition conditions, only $[Rh(CO)_2Cl]_2$ and $[Rh(COD)Cl]_2$ showed catalytic activity and the addition of 2,2,2-trifluoroethanol (TFE) as a co-solvent appears to have favored the formation of [2+2+2] cycloaddition product **3a** (Table 1, entry 8). Accordingly, a combination of $[Rh(COD)Cl]_2$ and TFE was chosen as the initial reaction conditions for optimization.

Table 6. Optimization of the [2+2+2] cycloaddition of **1a**



1a **3a**

Entry[a]	$[Rh(COD)Cl]_2$ (mol%)	Ligand	Temp. (°C)	Time (h)	Conversion[b] (%)	Isolated Yield (%)
1	5	none	80	48	62	51
2	5	DPPP (10 mol%)	80	16	100	86
3	5	DPPP (10 mol%)	80 (μw)	1	100	92
4	2.5	DPPP (5 mol%)	80 (μw)	2	100	94
5	2.5	DPPP (5 mol%)	100 (μw)	0.5	100	92

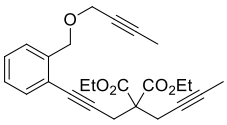
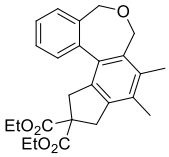
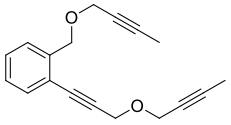
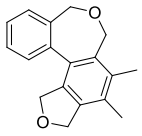
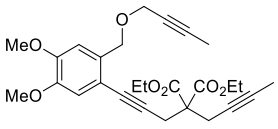
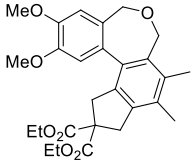
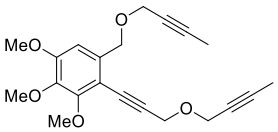
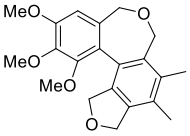
[a] 0.15 mmol of **1a** was used for each entry.
[b] Conversion was determined by HPLC.

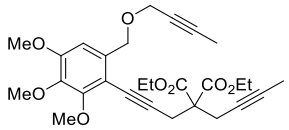
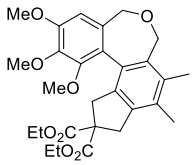
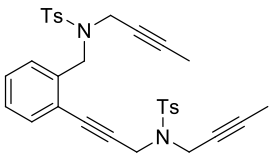
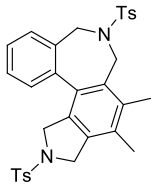
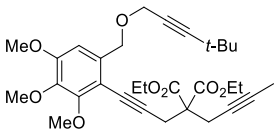
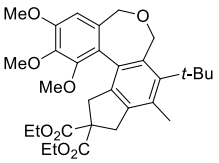
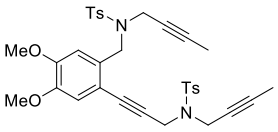
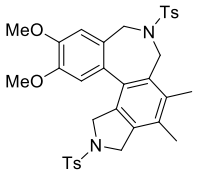
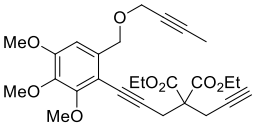
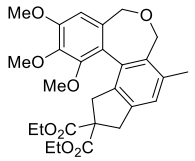
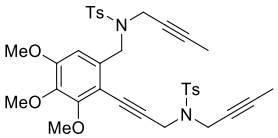
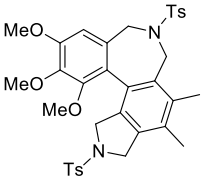
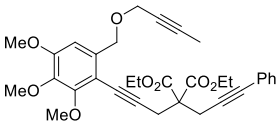
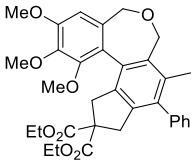
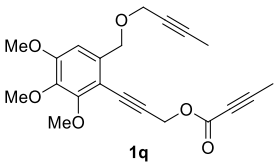
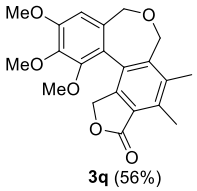
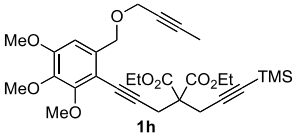
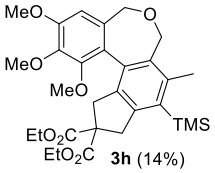
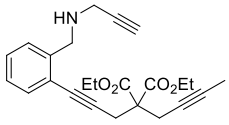
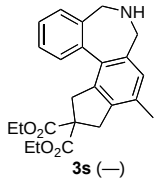
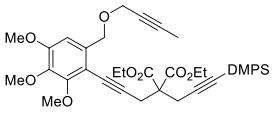
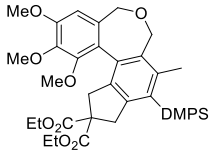
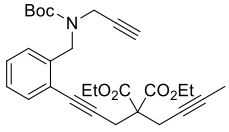
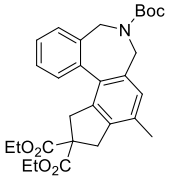
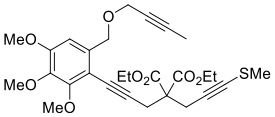
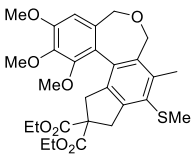
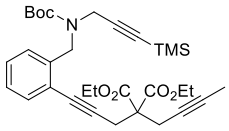
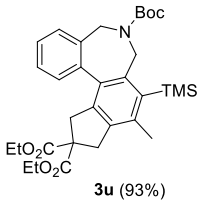
When the reaction of **1a** was carried out in the presence of $[Rh(COD)Cl]_2$ (5 mol%) in TFE at 80 °C for 48 h, only 62% of the starting material **1a** was consumed to afford the desired cycloadduct **3a** in 51% isolated yield (entry 1). Addition of 1,3-bis(diphenylphosphino)propane (DPPP) (10 mol%) drastically accelerated the reaction to complete in 16 h, giving **3a** in 86% isolated yield (entry 2). Next, we carried out the reaction using a microwave reactor. The reaction of **1a** in the presence of $[Rh(COD)Cl]_2$ (5 mol%) and DPPP (10 mol%) in TFE under microwave irradiation at 80 °C for 1 h, **3a** was obtained in 92% isolated yield (entry 3). When the amounts of the catalyst and the ligand were reduced to 2.5 and 5 mol%, respectively, the reaction needed 2 h to complete, but gave **3a** in 94% isolated yield (entry 4). The reaction of **1a** under the same conditions, except for the elevated temperature at 100 °C, completed in 30 min, giving **3a** in 92% isolated yield (entry 5).

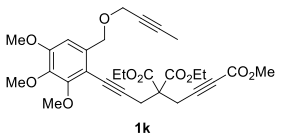
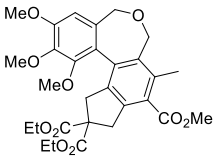
Consequently, we selected the reaction variables under microwave irradiation in the entry

5 as the standard conditions for the subsequent investigation of the scope and limitations of this reaction process using a variety of *o*-phenylenetriynes **1**. As Table 7 shows, various functional groups and heteroatoms are well tolerated under the microwave irradiation conditions to give the corresponding fused 6-7-6-5 tetracyclic allocolchicinoids **3** in moderate to excellent isolated yields. Except for the reactions of **1d** and **1i** which required 1 h and 1.5 h irradiation to reach full conversion (entries 4 and 8), all other o-phenylenetriynes completed the reaction within 30 min. It was found that a free secondary amino group was not tolerated. Thus, the reaction of **1s**, bearing a free secondary amino group, gave a messy mixture with no trace of **3s** (entry 17). On the other hand, *N*-protected secondary amino groups were well tolerated in this reaction. Thus, the reactions of **1n**–**p** and **1t**–**u**, bearing sulfonamide and carbamate groups, respectively, gave the corresponding allocolchicinoids, **3n**–**p** and **3t**–**u**, in high to excellent yields (entries 13–15 and 18–19).

Table 7. [2+2+2] cycloaddition of o-phenylenetriynes **1a–u**

Entry[a]	*o*-Phenylenetriyne	Product (isolated yield)	Entry[a]	*o*-Phenylenetriyne	Product (isolated yield)
1	 **1a**	 **3a** (92%)	11	 **1l**	 **3l** (58%)
2	 **1b**	 **3b** (82%)	12	 **1m**	 **3m** (79%)

3	 **1c**	 **3c** (83%)	13	 **1n**	 **3n** (82%)
4[b]	 **1d**	 **3d** (73%)	14	 **1o**	 **3o** (100%)
5	 **1f**	 **3f** (75%)	15	 **1p**	 **3p** (86%)
6	 **1g**	 **3g** (90%)	16	 **1q**	 **3q** (56%)
7	 **1h**	 **3h** (14%)	17	 **1s**	 **3s** (—)
8[c]	 **1i**	 **3i** (43%)	18	 **1t**	 **3t** (91%)
9	 **1j**	 **3j** (55%)	19	 **1u**	 **3u** (93%)

10	 **1k**	 **3k** (46%)			

[a] Reaction of **1** (0.15 mmol) was carried out in the presence of $[Rh(COD)Cl]_2$ (3.75 μmol) and DPPP (7.5 μmol) in TFE at 100 °C under microwave irradiation (250 W) for 0.5 h.
[b] 1 h irradiation.
[c] 1.5 h irradiation.

■ CONCLUSIONS

The [2+2+2+1] cycloaddition of *o*-phenylenetriynes with CO catalyzed by Rh complexes was investigated as a new and efficient approach to the rapid construction of various colchicinoids. Various o-phenylenetriynes **1** were designed and synthesized to examine the feasibility as well as the scope and limitation of this novel reaction process. The novel carbonylative [2+2+2+1] cycloaddition of **1** proceeded as designed with broad functional group tolerance to afford the corresponding colchicinoids **2** in moderate to excellent yields, accompanied by [2+2+2] cycloaddition by-products **3**. It has been found that the introduction of bulky substituents to the terminal ethyne moieties can markedly promote the carbonylation process to give colchicinoids **2** exclusively. When silyl groups were introduced to the terminal ethyne moieties, desilylation took place along with the formation of **2** under the reaction conditions, and an unprecedented methyl/phenyl migration via C-Si activation was observed as a minor process. Besides the carbonylative [2+2+2+1] cycloaddition, Rh-catalyzed [2+2+2] cycloaddition of **1** was also investigated, which provided a rapid access to a variety of allocolchicinoids. This process was found to be effectively promoted by microwave irradiation.

These two processes have a high synthetic potential to provide efficient routes to various polycyclic skeletons of biological interest. Further studies on the expansion of these catalytic processes for the synthesis of colchicinoids and allocolchicinoids, as well as their biological

evaluations are actively underway in our laboratory.

■ EXPERIMENTAL SECTION

General Methods. Microwave-assisted reactions were carried out with CEM Discover S series microwave reactor. ^{1}H and ^{13}C NMR spectra were measured on Bruker Avance III HD-Nanobay 400 (400 MHz ^{1}H; 100 MHz ^{13}C) spectrometer in a deuterated solvent using residual protons ($CHCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.00 ppm. $CHDCl_2$: ^{1}H, 5.32 ppm; ^{13}C, 54.00 ppm. CD_3COCHD_2: ^{1}H, 2.05 ppm; ^{13}C, 29.92 ppm) as the internal standard. Melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter. TLC was performed on Merck DC-Alufolien Kieselgel 60F 254 and flash column chromatography was carried out on Silicyle Silia*Flash*P60®. Analytical HPLC was carried out with a Shimadzu LC-2010A HPLC system. High resolution mass spectrometry analysis was carried out on an Agilent LC-UV-TOF (ESI/APCI) mass spectrometer at the Institute of Chemical Biology and Drug Discovery, Stony Brook University. The X-ray crystallographic structures were obtained on Oxford Gemini A diffractometer. Unless otherwise noted, all reactions were carried out under nitrogen atmosphere in oven-dried glassware using standard Schlenck technique.

Materials. All solvents used as reaction media were purified using the Solvent Purification System 400-4 from Innovative Technology, Inc. or distilled under nitrogen immediately before use. Ether and THF were distilled from Na/benzophenone ketyl. Toluene and CH_2Cl_2 were distilled from CaH_2. Solvents for extraction and chromatography were reagent grade and used as received. All chemicals were purchased from Alfa Aesar, Aldrich, or Acros Chemical Co., and were used without further purification unless otherwise noted. 2-Iodobenzaldehyde (**4a**)

was commercially available. 2-Iodo-4,5-dimethoxybenzaldehyde (**4b**)[43], 2-iodo-3,4,5-trimethoxybenzaldehyde (**4c**)[29] 2-[3-(but-2-ynyloxy)prop-1-ynyl]benzaldehyde (**5l**)[44] and *N*-(but-2-yn-1-yl)-*N*-[3-(2-formylphenyl)prop-2-yn-1-yl]-4-methylbenzenesulfonamide (**5n**)[44] were prepared by the literature methods.

Experimental Procedures. *Diethyl 2-(but-2-ynyl)-2-[3-(2-formylphenyl)prop-2-ynyl]malonate (**5a**).* A solution of 2-iodobenzaldehyde (**4a**) (2.32 g, 10.0 mmol) and diethyl 2-(but-2-ynyl)-2-(prop-2-ynyl)malonate (**12a**)[36] (3.75 g, 15.0 mmol) in THF (40 mL) was added to a mixture of $Pd(PPh_3)_2Cl_2$ (0.14 g, 0.20 mmol), CuI (76 mg, 0.40 mmol), and K_2CO_3 (4.15 g, 30.0 mmol) in THF (40 mL). After addition, the reaction mixture was refluxed for 24 h and then cooled to room temperature. The reaction was filtered through Celite®, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 9:1) to give **5a** (3.18 g, 90% yield) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.45 (d, J = 0.9 Hz, 1H), 7.90–7.87 (m, 1H), 7.55–7.38 (m, 3H), 4.24 (q, J = 7.2 Hz, 4H), 3.27 (s, 2H), 2.97 (q, J = 2.4 Hz, 2H), 1.77 (t, J = 2.4 Hz, 3H), 1.25 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 169.2, 136.4, 133.9, 133.8, 128.6, 127.2, 127.1, 92.2, 79.6, 79.4, 73.1, 62.2, 57.1, 24.0, 23.6, 14.3, 3.7; HRMS (TOF) calcd for $C_{21}H_{23}O_5$ $[M + H]^+$ 355.1545, found 355.1545 (Δ = 0.0 ppm).

In the same manner, **5b**–**c**, **5f**, **5h**, **5m**, **5o** and **5p** were synthesized using corresponding diynes or alkyne.

*Diethyl 2-(but-2-ynyl)-2-(3-(2-formyl-4,5-dimethoxyphenyl)prop-2-ynyl)malonate (**5b**).* The titled compound **5b** was obtained as a light yellow oil (1.28 g, 90% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.28 (s, 1H), 7.36 (s, 1H), 6.90 (s, 1H), 4.24 (q, J = 7.2 Hz, 4H), 3.94 (s, 3H), 3.93 (s, 3H), 3.25 (s, 2H), 2.97 (q, J = 2.4 Hz, 2H), 1.77 (t, J = 2.4 Hz, 3H), 1.26 (t, J = 7.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.1, 169.6, 149.5, 148.2, 131.5, 115.1, 113.9, 111.5,

87.5, 81.5, 79.5, 73.2, 62.2, 57.2, 56.3, 56.1, 24.1, 23.5, 14.3, 3.7; HRMS (TOF) calcd for $C_{23}H_{27}O_7$ $[M + H]^+$ 415.1757, found 415.1758 (Δ = +0.2 ppm).

*Diethyl 2-(but-2-ynyl)-2-(3-(6-formyl-2,3,4-trimethoxyphenyl)prop-2-ynyl)malonate (**5c**).* The titled compound **5c** was obtained as a light yellow oil (0.98 g, 71% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.33 (s, 1H), 7.21 (s, 1H), 4.23 (q, *J* = 7.2 Hz, 4H), 3.95 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H), 3.30 (s, 2H), 2.99 (q, *J* = 2.4 Hz, 2H), 1.77 (t, *J* = 2.4 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.1, 169.2, 155.2, 154.0, 147.8, 132.5, 116.0, 105.2, 94.8, 79.5, 74.8, 73.2, 62.2, 61.6, 61.4, 57.0, 56.4, 24.3, 23.5, 14.3, 3.7; HRMS (TOF) calcd for $C_{24}H_{29}O_8$ $[M + H]^+$ 445.1862, found 445.1861 (Δ = –0.2 ppm).

*Diethyl 2-[3-(6-formyl-2,3,4-trimethoxyphenyl)prop-2-ynyl]-2-(prop-2-ynyl)malonate (**5f**).* The titled compound **5f** (1.30 g, 69% yield) was obtained as a pale yellow solid: mp 95.0–96.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.20 (s, 1H), 4.28–4.19 (m, 4H), 3.93 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H), 3.32 (s, 2H), 3.06 (d, *J* = 2.6 Hz, 2H), 2.05 (t, *J* = 2.6 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 168.6, 154.9, 153.8, 147.5, 132.2, 115.6, 104.50, 94.0, 78.4, 74.8, 71.8, 62.1, 61.4, 61.1, 56.4, 56.2, 24.0, 22.8, 14.0; HRMS (TOF) calcd for $C_{23}H_{27}O_8$ $[M + H]^+$ 431.1706, found 431.1706 (Δ = 0.0 ppm).

*Diethyl 2-[3-(6-formyl-2,3,4-trimethoxyphenyl)prop-2-ynyl]-2-[3-(trimethylsilyl)prop-2-ynyl]malonate (**5h**).* The titled compound **5h** (1.84 g, 73% yield) was obtained as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (s, 1H), 7.18 (s, 1H), 4.26–4.16 (m, 4H), 3.91 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.28 (s, 2H), 3.05 (s, 2H), 1.24 (t, *J* = 7.1 Hz, 6H), 0.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 168.6, 154.9, 153.7, 147.5, 132.1, 115.6, 104.9, 100.7, 94.2, 88.5, 74.7, 61.9, 61.3, 61.06, 56.6, 56.1, 24.2, 23.9, 14.0, –0.18; HRMS (TOF) calcd for $C_{26}H_{35}O_8Si$ $[M + H]^+$ 503.2101, found 503.2100 (Δ = –0.2 ppm).

*2-[3-(But-2-ynyloxy)prop-1-ynyl]-3,4,5-trimethoxybenzaldehyde (**5m**).* The titled compound **5m** (0.89 g, 68% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 7.25 (s, 1H), 4.56 (s, 2H), 4.31 (q, J = 2.3 Hz, 2H), 3.97 (s, 3H), 3.96 (s, 3H), 3.92 (s, 3H), 1.88 (t, J = 2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 154.9, 154.2, 147.5, 132.2, 114.9, 105.2, 94.5, 83.5, 77.9, 74.2, 61.5, 61.2, 57.3, 57.1, 56.2, 3.6; HRMS (TOF) calcd for $C_{17}H_{19}O_5$ $[M + H]^+$ 303.1232, found 303.1232 (Δ = 0.0 ppm).

*N-(but-2-yn-1-yl)-N-[3-(2-formyl-4,5-dimethoxyphenyl)prop-2-yn-1-yl]-4-methylbenzenesulfonamide (**5o**).* The titled compound **5o** (1.09 g, 85% yield) was obtained as a pale yellow oil: ^{1}H NMR (400 MHz, acetone-d_6) δ 9.92 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.29 (s, 1H), 6.96 (s, 1H), 4.49 (s, 2H), 4.19 (q, J = 2.4 Hz, 2H), 3.94 (s, 3H), 3.90 (s, 3H), 2.32 (s, 3H), 1.69 (t, J = 2.4 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8, 153.5, 149.9, 143.9, 135.4, 130.4, 129.5, 127.9, 120.4, 114.1, 108.0, 87.8, 82.3, 81.1, 71.4, 56.3, 56.1, 37.4, 37.2, 21.5, 3.4; HRMS (TOF) calcd for $C_{23}H_{24}NO_5S$ $[M + H]^+$ 426.1370, found 426.1381 (Δ = +2.6 ppm).

*N-(but-2-yn-1-yl)-N-[3-(6-formyl-2,3,4-trimethoxyphenyl)prop-2-yn-1-yl]-4-methylbenzenesulfonamide (**5p**).* The titled compound **5p** (1.83 g, 80% yield) was obtained as a red oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.18 (s, 1H), 4.47 (s, 2H), 4.17 (q, J = 2.4 Hz, 2H), 3.94 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 2.31 (s, 3H), 1.67 (t, J = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 154.9, 154.1, 147.4, 143.8, 135.3, 132.0, 129.4, 127.8, 114.6, 105.0, 91.7, 82.1, 71.4, 61.4, 61.1, 56.2, 37.3, 37.1, 21.4, 3.4; HRMS (TOF) calcd for $C_{24}H_{26}NO_6S$ $[M + H]^+$ 456.1475, found 456.1484 (Δ = +2.0 ppm).

*3,4,5-Trimethoxy-2-hydroxymethyl-3-[(tetrahydro-2H-pyran-2-yloxy)prop-1-yn-1-yl]benzene (**8**).* The title compound **8** was prepared (60% yield) by the Sonogashira coupling of

iodinated benzyl alcohol **7**[39] with propargyl-O-THP as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (s, 1H), 4.93 (t, *J* = 3.4 Hz, 1H), 4.73 (br s, 2H), 4.56 (s, 2H), 3.95 (s, 3H), 3.93–3.87 (m, 4H), 3.85 (s, 3H), 3.60–3.53 (m, 1H), 2.42 (br s, 1H), 1.90–1.71 (m, 2H), 1.68–1.52 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 154.1, 141.2, 139.7, 108.0, 106.8, 97.1, 92.8, 79.4, 63.9, 62.3, 61.3, 61.1, 56.0, 55.2, 30.4, 25.3, 19.2; HRMS (TOF) calcd for $C_{18}H_{24}NaO_6$ $[M + Na]^+$ 359.1465, found 359.1465 (Δ = 0.0 ppm).

3-{6-[(But-2-yn-1-yloxy)methyl]-2,3,4-trimethoxyphenyl}prop-2-yn-1-ol ***(9)***. Etherification of **8** (1.14 g, 3.38 mmol) followed the same procedure as synthesis of **1a**. The obtained crude orange oil was dissolved in MeOH (6.6 mL) and added *p*-toluenesulfonic acid (64 mg, 0.34 mmol). The reaction mixture was stirred at room temperature for 24 h. The mixture was then diluted with water (20 mL) and extracted with Et_2O (20 mL × 3). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 6:4) to give **9** (0.47 g, 45% yield) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 1H), 4.63 (s, 2H), 4.53 (d, *J* = 5.9 Hz, 2H), 4.18 (q, *J* = 2.3 Hz, 2H), 3.93 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 2.39 (t, *J* = 5.9 Hz, 1H), 1.86 (t, *J* = 2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 154.0, 141.2, 136.3, 108.5, 107.1, 94.7, 82.8, 78.9, 75.1, 69.5, 61.3, 61.0, 58.3, 56.0, 51.7, 3.6; HRMS (TOF) calcd for $C_{17}H_{21}O_5$ $[M + H]^+$ 305.1384, found 305.1378 (Δ = –2.0 ppm).

Diethyl 2-(but-2-yn-1-yl)-2-[3-(2,3,4-trimethoxy-6-{3-[methoxy(methyl)-amino]-3-oxopropyl}phenyl)prop-2-yn-1-yl]malonate ***(11)***. Diethyl 2-(but-2-ynyl)-2-(prop-2-ynyl)malonate (**12a**)[36], (0.55 g, 2.2 mmol), **10**[40, 41] (0.82 g, 2.0 mmol), $Pd(PPh_3)_2Cl_2$ (28 mg, 0.04 mmol), and CuI (15 mg, 0.09 mmol) were introduced to a 10 mL microwave reaction vessel. The reaction vessel was evacuated and refilled with nitrogen three times and placed under a nitrogen

atmosphere. Diethylamine (3.3 mL) and DMF (1.1 mL) were added to the reaction vessel and the reaction mixture was stirred at 120 ºC for 40 min under microwave radiation (250 W). The mixture was then poured into 1 M aqueous HCl solution (10 mL) and extracted with Et_2O (10 mL × 3). The combined organic layers were washed with saturated $NaHCO_3$ solution (10 mL), water (50 mL), and brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 6:4) to give **11** (0.99 g, 93% yield) as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (s, 1H), 4.26–4.17 (m, 4H), 3.89 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.61 (s, 3H), 3.26 (s, 2H), 3.16 (s, 3H), 3.02–2.95 (m, 4H), 2.73 (t, *J* = 7.2 Hz, 2H), 1.74 (t, *J* = 2.5 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 155.1, 153.3, 140.3, 140.1, 109.9, 108.4, 90.6, 78.9, 77.6, 73.2, 61.8, 61.1, 61.0, 56.9, 56.0, 29.7, 23.9, 23.1, 14.0, 3.5; HRMS (TOF) calcd for $C_{28}H_{38}NO_9$ $[M + H]^+$ 532.2541, found 532.2545 (Δ = +0.8 ppm).

*Diethyl 2-(but-2-ynyl)-2-{3-[2-(hydroxymethyl)phenyl]prop-2-ynyl}malonate (**6a**).* To a solution of **5a** (3.00 g, 8.47 mmol) in MeOH (85 mL) was added sodium borohydride (0.64 g, 16.9 mmol) in one portion, and the reaction mixture was stirred for 1 h until gas evolution stopped. The reaction was quenched with 1 M aqueous HCl solution (50 mL), and the solvent was removed in vacuo. The residue was extracted with Et_2O (50 mL × 3). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 7:3) to give **6a** (2.77 g, 92% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.19 (m, 4H), 4.73 (s, 2H), 4.24 (q, *J* = 7.2 Hz, 4H), 3.22 (s, 2H), 2.97 (q, *J* = 2.4 Hz, 2H), 1.77 (t, *J* = 2.4 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 142.9, 132.7, 128.6, 128.0, 127.6, 121.9, 89.2, 81.5, 79.5, 73.2, 64.2, 62.2, 57.2, 24.1, 23.5, 14.3,

3.7; HRMS (TOF) calcd for $C_{21}H_{25}O_5$ $[M + H]^+$ 357.1702, found 357.1702 (Δ = 0.0 ppm).

In the same manner, **6b**–**c**, **6f**, **6h**, and **6l**–**p** were synthesized.

*Diethyl 2-(but-2-ynyl)-2-(3-(2-(hydroxymethyl)-4,5-dimethoxyphenyl)prop-2-ynyl)malonate (**6b**).* The titled compound **6b** was obtained as a light yellow oil (1.02 g, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.89 (s, 1H), 4.67 (s, 2H), 4.25 (q, *J* = 7.2 Hz, 4H), 3.89 (s, 3H), 3.86 (s, 3H), 3.20 (s, 2H), 2.97 (q, *J* = 2.4 Hz, 2H), 1.77 (t, *J* = 2.4 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 149.5, 148.2, 136.5, 115.1, 113.9, 111.5, 87.5, 81.5, 79.5, 73.2, 64.0, 62.2, 57.2, 56.3, 56.2, 24.1, 23.5, 14.3, 3.7; HRMS (TOF) calcd for $C_{23}H_{29}O_7$ $[M + H]^+$ 417.1913, found 417.1914 (Δ = +0.2 ppm).

*Diethyl 2-(but-2-ynyl)-2-(3-(6-(hydroxymethyl)-2,3,4-trimethoxyphenyl)-prop-2-ynyl)malonate (**6c**).* The titled compound **6c** was obtained as a light yellow oil (0.868 g, 88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (s, 1H), 4.61 (s, 2H), 4.25 (q, *J* = 7.2 Hz, 4H), 3.94 (s, 3H), 3.92 (s, 3H), 3.90 (s, 3H), 3.20 (s, 2H), 2.97 (q, *J* = 2.4 Hz, 2H), 1.77 (t, *J* = 2.4 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 155.4, 153.9, 141.6, 139.5, 109.1, 107.5, 91.8, 79.5, 73.2, 64.2, 62.2, 61.5, 61.3, 57.2, 56.3, 24.3, 23.5, 14.2, 3.7; HRMS (TOF) calcd for $C_{24}H_{34}NO_8$ $[M + NH_4]^+$ 464.2284, found 464.2280 (Δ = –0.9 ppm).

*Diethyl 2-{3-[6-(hydroxymethyl)-2,3,4-trimethoxyphenyl]prop-2-ynyl}-2-(prop-2-ynyl)malonate (**6f**).* The titled compound **6f** (1.20 g, 96% yield) was obtained as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (s, 1H), 4.65 (d, *J* = 6.5 Hz, 2H), 4.29–4.20 (m, 4H), 3.91 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.28 (s, 2H), 3.06 (d, *J* = 2.6 Hz, 2H), 2.50 (t, *J* = 6.5 Hz, 1H), 2.05 (t, *J* = 2.6 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 155.1, 153.7, 141.3, 139.3, 108.5, 107.0, 91.1, 78.4, 77.2, 71.8, 63.9, 62.1, 61.2, 61.0, 56.5, 56.0, 24.0, 22.8, 14.0; HRMS (TOF) calcd for $C_{23}H_{32}NO_8$ $[M + NH_4]^+$ 450.2128, found 450.2128 (Δ = 0.0

ppm).

*Diethyl 2-{3-[6-(hydroxymethyl)-2,3,4-trimethoxyphenyl]prop-2-ynyl}-2-[3-(trimethylsilyl)prop-2-ynyl]malonate (**6h**).* The titled compound **6h** (1.90 g, 87% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (s, 1H), 4.65 (d, *J* = 6.5 Hz, 2H), 4.28–4.18 (m, 4H), 3.91 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.26 (s, 2H), 3.06 (s, 2H), 2.54 (t, *J* = 6.5 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 6H), 0.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 155.1, 153.6, 141.3, 139.3, 108.7, 107.1, 100.8, 91.3, 88.5, 77.1, 63.9, 62.0, 61.2, 61.0, 56.8, 56.0, 24.2, 24.1, 14.0, –0.12; HRMS (TOF) calcd for $C_{26}H_{37}O_8Si$ $[M + H]^+$ 505.2258, found 505.2258 (Δ = 0.0 ppm).

*{2-[3-(But-2-ynyloxy)prop-1-ynyl]phenyl}methanol (**6l**).* The titled compound **6l** (0.77 g, 87% yield) was obtained as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.43 (m, 2H), 7.37–7.33 (m, 1H), 7.27–7.23 (m, 1H), 4.83 (s, 2H), 4.50 (s, 2H), 4.28 (q, *J* = 2.3 Hz, 2H), 1.90 (br s, 1H), 1.88 (t, *J* = 2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 132.5, 129.0, 127.4, 127.3, 120.7, 89.4, 84.1, 83.4, 74.3, 63.9, 57.3, 57.1, 3.7; HRMS (TOF) calcd for $C_{14}H_{18}NO_2$ $[M + NH_4]^+$ 232.1338, found 232.1335 (Δ = –1.3 ppm).

*{2-[3-(But-2-ynyloxy)prop-1-ynyl]-3,4,5-trimethoxyphenyl}methanol (**6m**).* The titled compound **6m** (0.39 g, 81% yield) was obtained as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 1H), 4.75 (s, 2H), 4.52 (s, 2H), 4.29 (q, *J* = 2.2 Hz, 2H), 3.95 (s, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 1.87 (t, *J* = 2.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 154.2, 141.2, 139.5, 107.6, 106.5, 92.0, 83.2, 80.1, 74.4, 63.8, 61.3, 61.1, 57.3, 57.1, 56.0, 3.6; HRMS (TOF) calcd for $C_{17}H_{24}NO_5$ $[M + NH_4]^+$ 322.1654, found 322.1653 (Δ = –0.3 ppm).

N-(but-2-yn-1-yl)-N-{3-[2-(hydroxymethyl)phenyl]prop-2-yn-1-yl}-4-

*methylbenzenesulfonamide (**6n**).* The titled compound **6n** (0.76 g, 89% yield) was obtained as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.33–7.27 (m, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.21–7.16 (m, 2H), 4.61 (s, 2H), 4.39 (s, 2H), 4.13 (q, *J* = 2.4 Hz, 2H), 2.33 (s, 4H), 1.67 (t, *J* = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 142.7, 135.1, 132.2, 129.4, 128.8, 127.8, 127.08, 127.05, 120.3, 86.5, 83.1, 82.1, 71.4, 63.4, 37.1, 37.0, 21.3, 3.3; HRMS (TOF) calcd for $C_{21}H_{21}NNaO_3S$ $[M + Na]^+$ 390.1134, found 390.1142 (Δ = +2.1 ppm).

*N-(but-2-yn-1-yl)-N-{3-[2-(hydroxymethyl)-4,5-dimethoxyphenyl]prop-2-yn-1-yl}-4-methylbenzenesulfonamide (**6o**).* The titled compound **6o** (0.90 g, 85% yield) was obtained as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 6.91 (s, 1H), 6.75 (s, 1H), 4.58 (s, 2H), 4.37 (s, 2H), 4.14 (q, *J* = 2.4 Hz, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 2.35 (s, 3H), 2.09 (br s, 1H), 1.66 (t, *J* = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 147.8, 143.7, 136.5, 135.3, 129.4, 127.9, 114.7, 112.3, 110.6, 85.1, 83.1, 82.0, 71.5, 63.4, 56.0, 55.9, 37.1, 37.0, 21.4, 3.4; HRMS (TOF) calcd for $C_{23}H_{29}N_2O_5S$ $[M + NH_4]^+$ 445.1792, found 445.1801 (Δ = +2.0 ppm).

*N-(but-2-yn-1-yl)-N-{3-[6-(hydroxymethyl)-2,3,4-trimethoxyphenyl]prop-2-yn-1-yl}-4-methylbenzenesulfonamide (**6p**).* The titled compound **6p** (0.79 g, 85% yield) was obtained as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 6.76 (s, 1H), 4.58 (d, *J* = 6.1 Hz, 2H), 4.41 (s, 2H), 4.18 (q, *J* = 2.4 Hz, 2H), 3.88 (s, 6H), 3.84 (s, 3H), 2.36 (s, 3H), 2.07 (t, *J* = 6.1 Hz, 1H), 1.66 (t, *J* = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 153.8, 143.6, 140.4, 139.5, 134.8, 129.2, 127.5, 106.7, 105.8, 88.9, 81.7, 79.0, 71.1, 62.7, 60.9, 60.7, 55.7, 37.1, 36.6, 21.1, 3.0; HRMS (TOF) calcd for $C_{24}H_{31}N_2O_6S$ $[M + NH_4]^+$ 475.1897, found 475.1913 (Δ = +3.4 ppm).

*Diethyl 2-(but-2-ynyl)-2-(3-{2-[(but-2-ynyloxy)methyl]phenyl}prop-2-ynyl)malonate (**1a**).* A solution of **6a** (0.71 g, 2.00 mmol) in THF (20 mL) was cooled to –78 ºC. To the solution, LiHMDS (1 M in hexanes) (2.20 mL, 2.20 mmol) was added dropwise. Then, hexamethylphosphoramide (HMPA) (1.79 g, 10.0 mmol) was added dropwise to the reaction mixture. After addition, the reaction was stirred at –78 ºC for 1 h. 1-Bromo-2-butyne (0.40 g, 6.4 mmol) was added dropwise to the reaction mixture. The mixture was stirred at –78 ºC for 2 h and then stirred at room temperature for 48 h. The reaction was quenched with saturated NH_4Cl solution (20 mL) and extracted with Et_2O (20 mL × 3). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 9:1) to give **1a** (0.60 g, 73% yield) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 7.6 Hz, 1H), 7.34 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.27 (td, *J* = 7.6, 1.4 Hz, 1H), 7.17 (td, *J* = 7.6, 1.3 Hz, 1H), 4.66 (s, 2H), 4.26–4.17 (m, 6H), 3.21 (s, 2H), 2.97 (q, *J* = 2.3 Hz, 2H), 1.86 (t, *J* = 2.3 Hz, 3H), 1.75 (t, *J* = 2.5 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 139.5, 132.1, 128.1, 127.3, 127.1, 121.6, 88.8, 82.4, 80.9, 79.0, 75.1, 73.1, 69.6, 61.7, 58.2, 56.8, 23.6, 23.0, 14.0, 3.5, 3.4; HRMS (TOF) calcd for $C_{25}H_{29}O_5$ $[M + H]^+$ 409.2015, found 409.2018 (Δ = +0.7 ppm).

In the same manner, **1b**–**d**, **1f**, **1h**, **1l**, **1m**, and **1v** were synthesized using corresponding bromoalkynes.

*Diethyl 2-(but-2-ynyl)-2-[3-(2-(but-2-ynyloxy)methyl)]-4,5-dimethoxy-phenyl)prop-2-ynyl)malonate (**1b**).* The titled compound **1b** was obtained as a light yellow oil (0.393g, 64%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.84 (s, 1H), 4.62 (s, 2H), 4.21 (q, *J* = 7.2 Hz, 4H), 4.18 (q, *J* = 2.4 Hz, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 3.21 (s, 2H), 2.98 (q, *J* = 2.4 Hz, 2H), 1.88 (t,

J = 2.4 Hz, 3H), 1.77 (t, *J* = 2.4 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 149.6, 148.1, 133.3, 114.8, 114.2, 111.0, 87.4, 82.7, 81.3, 79.3, 75.5, 73.4, 69.8, 62.1, 58.4, 57.2, 56.2, 56.1, 23.9, 23.4, 14.3, 3.9, 3.7; HRMS (TOF) m/z calcd for $C_{27}H_{32}NaO_7$ $[M + Na]^+$: 491.2046, found 491.2047 (Δ 0.2 ppm).

*Diethyl 2-(but-2-ynyl)-2-(3-(6-((but-2-ynyloxy)methyl)-2,3,4-trimethoxy-phenyl)prop-2-ynyl)malonate (**1c**).*

The titled compound **1c** was obtained as a light yellow oil (0.347g, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (s, 1H), 4.61 (s, 2H), 4.28–4.20 (m, 6H), 3.90 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.27 (s, 2H), 3.00 (q, *J* = 2.4 Hz, 2H), 1.88 (t, *J* = 2.4 Hz, 3H), 1.76 (t, *J* = 2.4 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 155.0, 153.9, 141.4, 136.6, 109.2, 106.8, 91.8, 82.9, 79.2, 75.4, 73.5, 69.9, 62.0, 61.4, 61.3, 58.7, 27.2, 26.3, 24.2, 23.3, 14.3, 3.9, 3.7; HRMS (TOF) m/z calcd for $C_{28}H_{35}O_8$ $[M + H]^+$: 499.2332, found 499.2334 (Δ 0.4 ppm).

*Diethyl 2-(but-2-ynyl)-2-(3-{6-[(4,4-dimethylpent-2-ynyloxy)methyl]-2,3,4-trimethoxyphenyl)}prop-2-ynyl)malonate (**1d**).* The titled compound **1d** (0.34 g, 62% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H), 4.59 (s, 2H), 4.26–4.15 (m, 6H), 3.88 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.24 (s, 2H), 2.98 (q, *J* = 2.5 Hz, 2H), 1.73 (t, *J* = 2.5 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 6H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 154.7, 153.5, 141.1, 136.3, 108.9, 106.6, 95.3, 91.4, 78.9, 76.6, 74.3, 73.2, 69.4, 61.7, 61.1, 60.9, 58.3, 56.8, 55.9, 30.9, 27.4, 23.9, 23.0, 14.0, 3.4; HRMS (TOF) calcd for $C_{31}H_{44}NO_8$ $[M + NH_4]^+$ 558.3067, found 558.3067 (Δ = 0.0 ppm).

*Diethyl 2-(3-{6-[(but-2-ynyloxy)methyl]-2,3,4-trimethoxyphenyl}prop-2-ynyl)-2-(prop-2- ynyl)malonate (**1f**).* The titled compound **1f** (0.77 g, 66% yield) was obtained as a white solid: mp 65.0–67.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 1H), 4.60 (s, 2H), 4.29–4.21 (m,

4H), 4.20 (q, *J* = 2.3 Hz, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.29 (s, 2H), 3.08 (d, *J* = 2.7 Hz, 2H), 2.04 (t, *J* = 2.7 Hz, 1H), 1.88 (t, *J* = 2.3 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 154.8, 153.7, 141.1, 136.3, 108.8, 106.5, 91.1, 82.6, 78.7, 77.0, 75.1, 71.6, 69.6, 62.0, 61.2, 61.0, 58.4, 56.5, 56.0, 23.9, 22.7, 14.0, 3.7; HRMS (TOF) calcd for $C_{27}H_{36}NO_8$ $[M + NH_4]^+$ 502.2441, found 502.2435 (Δ = –1.2 ppm).

*Diethyl 2-(3-{6-[(but-2-ynyloxy)methyl]-2,3,4-trimethoxyphenyl}prop-2-ynyl)-2-[3-(trimethylsilyl)prop-2-ynyl]malonate (**1h**).* The titled compound **1h** (0.20 g, 37% yield) was obtained as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 1H), 4.60 (s, 2H), 4.30–4.15 (m, 6H), 3.90 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.27 (s, 2H), 3.09 (s, 2H), 1.88 (t, *J* = 2.3 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 6H), 0.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 154.8, 153.6, 141.2, 136.3, 108.9, 106.5, 101.1, 91.4, 88.2, 82.6, 76.8, 75.1, 69.6, 61.9, 61.2, 61.0, 58.4, 56.8, 56.0, 24.1, 23.9, 14.0, 3.7, –0.08; HRMS (TOF) calcd for $C_{30}H_{44}NO_8Si$ $[M + NH_4]^+$ 574.2836, found 574.2836 (Δ = 0.0 ppm).

*1-[(But-2-ynyloxy)methyl]-2-[3-(but-2-ynyloxy)prop-1-ynyl]benzene (**1l**).* The titled compound **1l** (0.15 g, 55% yield) was obtained as a pale yellow oil: (400 MHz, $CDCl_3$) δ 7.48–7.43 (m, 2H), 7.35–7.31 (m, 1H), 7.25–7.21 (m, 1H), 4.73 (s, 2H), 4.50 (s, 2H), 4.29 (q, *J* = 2.4 Hz, 2H), 4.20 (q, *J* = 2.4 Hz, 3H), 1.88 (t, *J* = 2.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 132.3, 128.7, 127.8, 127.4, 121.3, 89.1, 84.2, 83.2, 82.7, 75.1, 74.4, 69.6, 58.4, 57.2, 57.1, 3.64, 3.63; HRMS (TOF) calcd for $C_{18}H_{22}NO_2$ $[M + NH_4]^+$ 284.1651, found 284.1646 (Δ = –1.8 ppm).

*1-[(But-2-ynyloxy)methyl]-2-[3-(but-2-ynyloxy)prop-1-ynyl]-3,4,5-trimethoxybenzene (**1m**).* The titled compound **1m** (0.28 g, 77% yield) was obtained as a pale yellow oil: (400 MHz, $CDCl_3$) δ 6.81 (s, 1H), 4.66 (s, 2H), 4.53 (s, 2H), 4.31 (q, *J* = 2.3 Hz, 2H), 4.20 (q, *J* = 2.3 Hz, 2H), 3.94 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 1.88 (t, *J* = 2.3 Hz, 3H), 1.87 (t,

J = 2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 154.1, 141.2, 136.5, 108.4, 106.8, 91.8, 83.0, 82.8, 80.1, 75.0, 74.5, 69.6, 61.3, 61.1, 58.5, 57.3, 56.9, 56.1, 3.64, 3.62; HRMS (TOF) calcd for $C_{21}H_{25}O_5$ $[M + H]^+$ 357.1702, found 357.1702 (Δ = 0.0 ppm).

*Diethyl 2-(but-2-yn-1-yl)-2-(3-{2,3,4-trimethoxy-6-[(prop-2-yn-1-yloxy)methyl]-phenyl}prop-2-yn-1-yl)malonate (**1v**).* The titled compound **1v** (0.76 g, 78% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1H), 4.62 (s, 2H), 4.24–4.19 (m, 6H), 3.89 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.25 (s, 2H), 2.99 (q, *J* = 2.4 Hz, 2H), 2.48 (t, *J* = 2.4 Hz, 1H), 1.74 (t, *J* = 2.5 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 154.8, 153.6, 141.3, 135.8, 109.1, 106.6, 91.5, 79.7, 79.0, 76.6, 74.6, 73.2, 69.7, 61.7, 61.1, 61.0, 57.7, 56.8, 56.0, 23.9, 23.1, 14.0, 3.4; HRMS (TOF) calcd for $C_{27}H_{36}NO_8$ $[M + NH_4]^+$ 502.2435, found 502.2444 (Δ = +1.8 ppm).

*Diethyl 2-(but-2-yn-1-yl)-2-[3-(6-{[(4-hydroxy-4-methylpent-2-yn-1-yl)oxy]-methyl}-2,3,4-trimethoxyphenyl)prop-2-yn-1-yl]malonate (**1w**).* A solution of **1v** (0.97 g, 2.00 mmol) in THF (20 mL) was cooled to –78 °C. To the solution, LiHMDS (1.0 M in hexanes) (3.0 mL, 3.00 mmol) was added dropwise. After addition, the reaction was stirred at –78 °C for 2 h. Acetone (0.22 mL, 3.00 mmol) was added dropwise to the reaction mixture. Then, the mixture was stirred at room temperature for 16 h. The reaction was quenched with 1 M aqueous HCl solution (20 mL) and extracted with Et_2O (20 mL × 3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 6:4) to give **1w** (0.64 g, 59% yield) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (s, 1H), 4.59 (s, 2H), 4.25 (s, 2H), 4.24–4.16 (m, 4H), 3.88 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.24 (s, 2H), 2.98 (q, *J* = 2.5 Hz, 2H), 2.63 (br s, 1H), 1.73 (t, *J* = 2.5 Hz, 3H), 1.49 (s, 6H), 1.22 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 169.1, 154.7, 153.6, 141.0, 136.1, 108.7, 106.2, 91.6, 91.4, 79.1, 77.6, 76.6, 73.1, 69.5, 64.8, 61.8, 61.1, 60.9, 58.0, 56.8, 56.0, 31.2, 23.9, 23.1, 13.9, 3.4; HRMS (TOF) calcd for $C_{30}H_{42}NO_9$ $[M + NH_4]^+$ 560.2854, found 560.2861 (Δ = +1.2 ppm).

*Diethyl 2-(but-2-yn-1-yl)-2-(3-{2,3,4-trimethoxy-6-[({4-methyl-4-[(triethylsilyl)-oxy]pent-2-yn-1-yl}oxy)methyl]phenyl}prop-2-yn-1-yl)malonate (**1e**).* A solution of **1w** (0.38 g, 0.70 mmol) in THF (6 mL) was added dropwise to a suspension of NaH (60% dispersion in mineral oil) (98 mg, 2.44 mmol) in THF (3 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 30 min. To the reaction mixture, chlorotriethylsilane (0.23 g, 1.54 mmol) was then added dropwise at 0 ºC. After addition, the reaction mixture was stirred at room temperature for 72 h. The reaction was quenched with water (10 mL) and extracted with Et_2O (10 mL × 3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 8:2) to give **1e** (0.24 g, 54% yield) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1H), 4.59 (s, 2H), 4.25 (s, 2H), 4.24–4.16 (m, 4H), 3.88 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.24 (s, 2H), 2.98 (q, *J* = 2.5 Hz, 2H), 1.73 (t, *J* = 2.5 Hz, 3H), 1.47 (s, 6H), 1.23 (t, *J* = 7.1 Hz, 6H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.64 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 154.8, 153.6, 141.1, 136.1, 108.9, 106.4, 91.7, 91.5, 78.9, 78.2, 76.6, 73.1, 69.7, 66.1, 61.7, 61.1, 60.9, 58.2, 56.8, 55.9, 32.9, 23.8, 23.0, 14.0, 6.9, 6.0, 3.4; HRMS (TOF) calcd for $C_{36}H_{56}NO_9Si$ $[M + NH_4]^+$ 674.3719, found 674.3726 (Δ = +1.0 ppm).

*Diethyl 2-(3-{6-[(but-2-yn-1-yloxy)methyl]-2,3,4-trimethoxyphenyl}prop-2-yn-1-yl)-2-(3-phenylprop-2-yn-1-yl)malonate (**1g**).* In the same manner as synthesis of **5a**, triyne **1g** was prepared using **1v** (0.40 g, 0.82 mmol) and iodobenzene (0.25 g, 1.24 mmol). The reaction was carried out at room temperature for 48 h. The titled compound **1g** (0.22 g, 48% yield) was obtained

as a dark yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.34 (m, 2H), 7.29–7.24 (m, 3H), 6.80 (s, 1H), 4.62 (s, 2H), 4.30–4.22 (m, 4H), 4.20 (q, J = 2.3 Hz, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.35 (s, 2H), 3.30 (s, 2H), 1.86 (t, J = 2.3 Hz, 3H), 1.27 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 154.8, 153.7, 141.1, 136.3, 131.6, 128.1, 127.9, 123.1, 108.9, 106.5, 91.3, 84.1, 83.6, 82.6, 76.9, 75.1, 69.6, 61.9, 61.2, 61.0, 58.4, 56.9, 56.0, 24.1, 23.6, 14.0, 3.6; HRMS (TOF) calcd for $C_{33}H_{40}NO_8$ $[M + NH_4]^+$ 578.2748, found 578.2753 (Δ = +0.9 ppm).

*Diethyl 2-(3-{6-[(but-2-yn-1-yloxy)methyl]-2,3,4-trimethoxyphenyl}prop-2-yn-1-yl)-2-{3-[dimethyl(phenyl)silyl]prop-2-yn-1-yl}malonate (**1i**).* A solution of **1f** (0.48 g, 1.00 mmol) in THF (10 mL) was cooled to –78 °C. To the solution, *n*-BuLi (1.6 M in hexanes) (0.94 mL, 1.50 mmol) was added dropwise. After addition, the reaction mixture was stirred at –78 °C for 2 h. Then, after chloro(dimethyl)phenylsilane (0.26 g, 1.50 mmol) was added dropwise to the reaction mixture at –78 °C, the mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated NH_4Cl solution (10 mL) and extracted with Et_2O (10 mL × 3). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 8:2) to give **1i** (0.41 g, 68% yield) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.56 (m, 2H), 7.39–7.32 (m, 3H), 6.79 (s, 1H), 4.60 (s, 2H), 4.26–4.17 (m, 6H), 3.89 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.30 (s, 2H), 3.17 (s, 2H), 1.86 (t, J = 2.3 Hz, 3H), 1.24 (t, J = 7.1 Hz, 6H), 0.37 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 154.8, 153.7, 141.1, 137.0, 136.3, 133.6, 129.3, 127.8, 108.9, 106.5, 103.0, 91.3, 86.3, 82.6, 76.9, 75.1, 69.6, 62.0, 61.2, 61.0, 58.4, 56.8, 56.0, 24.2, 24.0, 14.0, 3.6, –0.87; HRMS (TOF) calcd for $C_{35}H_{46}NO_8Si$ $[M + NH_4]^+$ 636.2987, found 636.2994 (Δ = +1.1 ppm).

In the same manner, **1j** and **1k** were synthesized using dimethyl disulfide and methyl

chloroformate as the electrophiles, respectively.

*Diethyl 2-(3-{6-[(but-2-yn-1-yloxy)methyl]-2,3,4-trimethoxyphenyl}prop-2-yn-1-yl)-2-[3-(methylthio)prop-2-yn-1-yl]malonate (**1j**).* The titled compound **1j** (0.30 g, 46% yield) was obtained as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H), 4.58 (s, 2H), 4.27–4.16 (m, 6H), 3.88 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.25 (s, 2H), 3.16 (s, 2H), 2.32 (s, 3H), 1.87 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 154.8, 153.6, 141.1, 136.3, 108.8, 106.5, 91.2, 87.2, 82.6, 76.9, 75.1, 74.1, 69.5, 61.8, 61.1, 61.0, 58.4, 56.8, 56.0, 24.3, 24.0, 19.1, 14.0, 3.6; HRMS (TOF) calcd for $C_{28}H_{38}NO_8S$ $[M + NH_4]^+$ 548.2313, found 548.2317 (Δ = +0.7 ppm).

*4,4-Diethyl 1-methyl 7-{6-[(but-2-yn-1-yloxy)methyl]-2,3,4-trimethoxyphenyl}-hepta-1,6-diyne-1,4,4-tricarboxylate (**1k**).* The titled compound **1k** (0.31 g, 64% yield) was obtained as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 1H), 4.59 (s, 2H), 4.30–4.22 (m, 4H), 4.20 (q, *J* = 2.3 Hz, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.74 (s, 3H), 3.29 (s, 2H), 3.25 (s, 2H), 1.88 (t, *J* = 2.3 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 154.9, 153.8, 153.6, 141.2, 136.3, 108.7, 106.6, 90.5, 83.6, 82.7, 77.5, 75.4, 75.1, 69.6, 62.3, 61.2, 61.0, 58.4, 56.3, 56.1, 52.6, 24.3, 23.0, 14.0, 3.7; HRMS (TOF) calcd for $C_{29}H_{38}NO_{10}$ $[M + NH_4]^+$ 560.2490, found 560.2497 (Δ = +1.2 ppm).

*N-(but-2-yn-1-yl)-N-[3-(2-{[N-(but-2-yn-1-yl)-4-methylphenylsulfonamido]-methyl}phenyl)prop-2-yn-1-yl]-4-methylbenzenesulfonamide (**1n**).* To a solution of *N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide[45] (0.42 g, 1.90 mmol) and triphenylphosphine (0.57 g, 2.17 mmol) in CH_2Cl_2 (7 mL) was added diisopropyl azodicarboxylate (0.44 g, 2.17 mmol) dropwise, and the mixture was stirred for 30 min. Then, after a solution of **6n** (0.50 g, 5.1 mmol) in CH_2Cl_2 (10 mL) was added to the mixture, the mixture was stirred at room temperature for 3 h.

The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (hexanes:EtOAc = 8:2) to give **1n** (0.81 g, 78% yield) as a colorless gummy oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.33–7.28 (m, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.21–7.13 (m, 2H), 4.40 (s, 2H), 4.37 (s, 2H), 4.08 (q, *J* = 2.3 Hz, 2H), 3.89 (q, *J* = 2.3 Hz, 2H), 2.46 (s, 3H), 2.32 (s, 3H), 1.63 (t, *J* = 2.3 Hz, 3H), 1.53 (t, *J* = 2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 143.4, 137.4, 136.2, 135.3, 132.4, 129.4, 129.3, 128.9, 128.4, 127.9, 127.9, 127.4, 121.8, 87.0, 83.0, 82.0, 81.9, 71.6, 71.5, 48.1, 37.2, 37.02, 36.95, 21.5, 21.4, 3.4, 3.2; HRMS (TOF) calcd for $C_{32}H_{33}N_2O_4S_2$ $[M + H]^+$ 573.1876, found 573.1882 (Δ = +1.0 ppm).

In the same manner, **1o** and **1p** were synthesized

*N-(but-2-yn-1-yl)-N-[3-(2-{[N-(but-2-yn-1-yl)-4-methylphenylsulfonamido]-methyl}-4,5-dimethoxyphenyl)prop-2-yn-1-yl]-4-methylbenzenesulfonamide (**1o**).* The titled compound **1o** (0.67 g, 56% yield) was obtained as a white solid: mp 118.0–119.0 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.00 (s, 1H), 6.68 (s, 1H), 4.34 (s, 2H), 4.32 (s, 2H), 4.08 (d, *J* = 2.3 Hz, 2H), 3.88 (d, *J* = 2.4 Hz, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 2.46 (s, 3H), 2.35 (s, 3H), 1.60 (t, *J* = 2.4 Hz, 3H), 1.55 (t, *J* = 2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 148.1, 143.6, 143.4, 136.2, 135.4, 130.8, 129.3, 129.2, 127.9, 127.8, 114.3, 113.9, 111.2, 85.2, 83.0, 81.8, 81.7, 71.8, 71.4, 56.0, 55.9, 47.8, 37.2, 36.9, 36.8, 21.5, 21.4, 3.3, 3.2; HRMS (TOF) calcd for $C_{34}H_{37}N_2O_6S_2$ $[M + H]^+$ 633.2088, found 633.2097 (Δ = +1.4 ppm).

*N-(but-2-yn-1-yl)-N-[3-(6-{[N-(but-2-yn-1-yl)-4-methylphenylsulfonamido]-methyl}-2,3,4-trimethoxyphenyl)prop-2-yn-1-yl]-4-methylbenzenesulfonamide (**1p**).* The titled compound **1p** (0.71 g, 62% yield) was obtained as a colorless gummy oil: ^{1}H NMR (400 MHz,

acetone-d_6) δ 7.83 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 6.84 (s, 1H), 4.40 (s, 2H), 4.32 (s, 2H), 4.11 (q, J = 2.3 Hz, 2H), 3.94 (q, J = 2.3 Hz, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 2.48 (s, 3H), 2.32 (s, 3H), 1.64 (t, J = 2.3 Hz, 3H), 1.58 (t, J = 2.3 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 155.9, 155.5, 144.8, 144.7, 142.5, 137.5, 136.6, 135.0, 130.5, 130.4, 128.9, 128.8, 110.1, 108.5, 90.5, 82.8, 82.7, 80.1, 72.9, 72.5, 61.6, 61.2, 56.5, 49.1, 38.1, 37.9, 37.6, 21.6, 21.5, 3.3, 3.2; HRMS (TOF) calcd for $C_{35}H_{39}N_2O_7S_2$ $[M + H]^+$ 663.2193, found 663.2202 (Δ = +1.4 ppm).

*3-{6-[(But-2-yn-1-yloxy)methyl]-2,3,4-trimethoxyphenyl}prop-2-yn-1-yl but-2-ynoate (**1q**).* A solution of **9** (0.45 g, 1.47 mmol) and 4-dimethylaminopyridine (9 mg, 0.07 mmol) in CH_2Cl_2 (5 mL) was added to a solution of 2-butynoic acid (0.15 g, 1.77 mmol) in CH_2Cl_2 (1 mL) at 0 °C. *N*,*N*'- Dicyclohexylcarbodiimide (0.36 g, 1.77 mmol) was then added to the reaction mixture. After addition, the reaction mixture was stirred at 0 °C for 2 h and then, at room temperature for 16 h. The reaction was quenched with saturated water (15 mL) and extracted with CH_2Cl_2 (15 mL × 3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 8:2) to give **1q** (0.48 g, 89% yield) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1H), 4.98 (s, 2H), 4.58 (s, 2H), 4.15 (q, J = 2.3 Hz, 2H), 3.89 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 1.95 (s, 3H), 1.83 (t, J = 2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 154.3, 152.7, 141.0, 136.8, 107.6, 106.7, 89.2, 86.5, 82.6, 80.6, 74.9, 71.7, 69.3, 61.2, 60.8, 58.3, 55.9, 54.0, 3.6, 3.4; HRMS (TOF) calcd for $C_{21}H_{22}NaO_6$ $[M + Na]^+$ 393.1309, found 393.1317 (Δ = +2.0 ppm).

*Diethyl 2-(but-2-yn-1-yl)-2-(3-{2,3,4-trimethoxy-6-[3-oxo-5-(trimethylsilyl)pent-4-yn-1-yl]phenyl}prop-2-yn-1-yl)malonate (**1r**).* To a solution of (trimethylsilyl)acetylene (0.15

mL, 1.02 mmol) in THF (2.8 mL) was slowly added *n*-BuLi (0.59 mL, 0.94 mmol, 1.6 M in hexane) at –78 °C. After 30 min, the resulting solution was warmed to 0 °C and then cooled back to –78 °C. The solution of lithiumacetylid obtained was added dropwise through a canula to a solution of **11** (0.45 g, 0.85 mmol) in THF (2.8 mL) at –78 °C. The resulting solution was warmed to –10 °C over 1 h. After 3 h, the reaction mixture was further cooled to –40 °C and then added to a mixture of ice and phosphate-buffer (pH 7, 10 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 8:2) to give **1r** (0.26 g, 53% yield) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (s, 1H), 4.27–4.15 (m, 4H), 3.88 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.25 (s, 2H), 3.01–2.93 (m, 4H), 2.92–2.85 (m, 2H), 1.74 (t, *J* = 2.5 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 6H), 0.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.6, 169.1, 155.1, 153.3, 140.4, 138.9, 109.9, 108.3, 101.9, 97.7, 90.9, 79.0, 77.4, 73.1, 61.7, 61.1, 61.0, 56.8, 55.9, 45.8, 28.7, 23.9, 23.1, 14.0, 3.5, –0.83; HRMS (TOF) calcd for $C_{31}H_{44}NO_8Si$ $[M + NH_4]^+$ 586.2831, found 586.2833 (Δ = +0.3 ppm).

*Diethyl 2-(but-2-ynyl)-2-(3-{2-[(prop-2-ynylamino)methyl]phenyl}prop-2-ynyl)malonate (**1s**).* To a solution of **5a** (0.35 g, 1.00 mmol) and anhydrous $MgSO_4$ (0.24 g, 2.00 mmol) in CH_2Cl_2 (10 mL) was added propargylamine (0.64 g, 16.9 mmol) dropwise, and the reaction mixture was stirred at room temperature for 24 h. The mixture was filtered through Celite®, and the filtrate was concentrated in vacuo. The residue was dissolved in MeOH (10 mL), and $NaBH_4$ (76 mg, 2.00 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with water (10 mL) and extracted with Et_2O (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica

gel (hexanes:EtOAc = 6:4) to give **1s** (0.24 g, 62% yield) as a pale yellow oil: (400 MHz, $CDCl_3$) δ 7.41–7.31 (m, 2H), 7.28–7.22 (m, 1H), 7.19– 7.15 (m, 1H), 4.23 (q, *J* = 7.1 Hz, 4H), 3.95 (s, 2H), 3.43 (d, *J* = 2.4 Hz, 2H), 3.23 (s, 2H), 2.98 (d, *J* = 2.6 Hz, 2H), 2.26 (t, *J* = 2.4 Hz, 1H), 1.81 (s, 1H), 1.76 (t, *J* = 2.6 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 141.2, 132.7, 128.7, 128.2, 126.9, 122.6, 88.7, 82.1, 81.5, 79.2, 73.1, 71.5, 61.9, 56.9, 50.9, 37.5, 23.8, 23.3, 14.1, 3.5; HRMS (TOF) calcd for $C_{24}H_{28}NO_4$ $[M + H]^+$ 394.2018, found 394.2017 (Δ = –0.3 ppm).

*Diethyl 2-(but-2-ynyl)-2-[3-(2-{[tert-butoxycarbonyl(prop-2-ynyl)amino]-methyl}phenyl)prop-2-ynyl]malonate (**1t**).* Di-*tert*-butyl dicarbonate (0.13 mL, 0.55 mmol) was added dropwise to a mixture of **1s** (0.18 g, 0.46 mmol) and triethylamine (0.10 mL, 0.69 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 8:2) to give **1t** (0.22 g, 96% yield) as a colorless oil: (400 MHz, acetone-d_6) δ 7.43–7.30 (m, 2H), 7.27–7.23 (m, 2H), 4.67 (s, 2H), 4.24 (q, *J* = 7.1 Hz, 4H), 4.19–3.97 (m, 2H), 3.22 (s, 2H), 2.96 (q, *J* = 2.6 Hz, 2H), 2.72 (t, *J* = 2.5 Hz, 1H), 1.75 (t, *J* = 2.6 Hz, 3H), 1.55–1.34 (m, 9H), 1.25 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, acetone-d_6) δ 170.0, 156.1, 141.4, 133.7, 129.8, 128.3, 127.5, 123.0, 91.0, 82.3, 81.2, 81.0, 80.5, 74.4, 73.8, 63.0, 58.1, 49.6, 37.5, 29.0, 24.8, 24.3, 14.9, 3.8; HRMS (TOF) calcd for $C_{29}H_{36}NO_6$ $[M + H]^+$ 494.2543, found 494.2543 (Δ = 0.0 ppm).

*Diethyl 2-(but-2-ynyl)-2-{3-[2-({tert-butoxycarbonyl[3-(trimethylsilyl)prop-2-ynyl]amino}methyl)phenyl]prop-2-ynyl}malonate (**1u**).* A solution of **1t** (0.38 g, 0.78 mmol) in

THF (5 mL) was cooled to –78 ºC. To the solution, *n*-BuLi (1.6 M in hexanes) (1.07 mL, 1.71 mmol) was added dropwise. After addition, the reaction mixture was stirred at –78 ºC for 2 h. Then, after chlorotrimethylsilane (0.25 mL, 1.94 mmol) was added dropwise to the mixture, the mixture was stirred at room temperature for 48 h. The reaction was quenched with saturated NH_4Cl solution (5 mL) and extracted with Et_2O (10 mL × 3). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 9:1) to give **1u** (0.35 g, 79% yield) as a pale yellow oil: (400 MHz, acetone-d_6) δ 7.45–7.18 (m, 4H), 4.65 (s, 2H), 4.37–3.90 (m, 6H), 3.22 (s, 2H), 2.96 (q, J = 2.6 Hz, 2H), 1.75 (t, J = 2.6 Hz, 3H), 1.59–1.30 (m, 9H), 1.25 (t, J = 7.1 Hz, 6H), 0.12 (s, 9H); ^{13}C NMR (100 MHz, acetone-d_6) δ 169.5, 155.7, 141.3, 133.1, 129.3, 127.8, 127.2, 122.3, 102.9, 90.4, 82.0, 80.7, 80.0, 73.9, 62.6, 57.7, 49.3, 38.1, 28.5, 24.4, 23.9, 14.5, 3.3, 0.05; HRMS (TOF) calcd for $C_{32}H_{43}NO_6Si$ $[M + H]^+$ 566.2938, found 566.2938 (Δ = 0.0 ppm).

*Rh-catalyzed carbonylative [2+2+2+1] cycloaddition of o-phenylenetriynes **1**.* *o*-Phenylentriyne **1** (0.15 mmol), montmorillonite K10 (equal weight to **1**), and $[Rh(CO)_2Cl]_2$ (2.9 mg, 7.5 μmol) were introduced to a 5 mL round-bottomed flask. The reaction flask was evacuated and refilled with carbon monoxide three times and placed under a carbon monoxide atmosphere (**Caution!! must be done in a well-ventilated fume hood**). Toluene (1.5 mL) was added to the reaction flask and the reaction mixture was stirred at 80 ºC for 48 h unless otherwise noted and then cooled to room temperature. The reaction mixture was filtered through Celite® and concentrated in vacuo. To check the conversion and product selectivity, the crude product was subjected to HPLC analysis using a PFP column (MeOH:H_2O = 7:3, 0.2 mL/min). The reactions were very clean, and thus the product selectivity multiplied by the conversion provided the actual

yields of the products **2** and **3** determined by HPLC. The corresponding product **2** was isolated by column chromatography on silica gel (hexanes:EtOAc = 7:3) together with **3** whenever this side product was formed.

*Diethyl 4,6-dimethyl-5-oxo-3,5,7,9-tetrahydroazuleno[5,4-c]benzo[e]oxepine-2,2(1H)-dicarboxylate (**2a**).* The titled compound **2a** was obtained as an off-white solid (53 mg, 80% yield): mp 142.5–143.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.31 (m, 3H), 7.16–7.11 (m, 1H), 4.70 (bs, 1H), 4.55 (s, 2H), 4.26–4.02 (m, 4H), 3.88 (bs, 1H), 3.49 (s, 2H), 3.37 (bs, 1H), 2.94 (bs, 1H), 2.37 (s, 3H), 2.26 (s, 3H), 1.35–1.12 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 170.8, 145.7, 142.1, 142.0, 141.2, 140.3, 140.0, 138.1, 132.7, 129.2, 129.1, 129.0, 128.8, 68.1, 65.3, 62.1, 58.0, 44.8, 42.4, 19.8, 18.6, 14.1; LR-MS m/z calcd for $C_{26}H_{28}O_6$ $[M]^+$: 436.5, found $[M+1]^+$: 437.1; HRMS (TOF) m/z calcd for $C_{26}H_{29}O_6$ $[M + H]^+$: 437.1964, found 437.1966 (Δ 0.5 ppm).

*Diethyl 11,12-dimethoxy-4,6-dimethyl-5-oxo-3,5,7,9-tetrahydroazuleno[5,4-c]benzo[e]oxepine-2,2(1H)-dicarboxylate (**2b**).* The titled compound **2b** was obtained as a light yellow solid (63 mg, 84% yield): mp 144.0–146.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.67 (s, 1H), 4.70 (bs, 1H), 4.48 (s, 2H), 4.30–4.10 (m, 4 H), 3.95 (s, 3H), 3.87 (bs, 1H), 3.86 (s, 3H), 3.50 (s, 2H), 3.40 (bs, 1H), 3.00 (bs, 1H), 2.37 (s, 3H), 2.25 (s, 3H), 1.24–1.16 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 170.8, 149.3, 148.9, 145.7, 142.3, 141.1, 140.2, 140.1, 138.5, 134.2, 125.4, 112.2, 111.9, 68.0, 65.4, 62.1, 57.9, 56.4, 56.3, 56.2, 44.9, 42.5, 19.9, 19.8, 18.6, 14.2; HRMS (TOF) m/z calcd for $C_{28}H_{33}O_8$ $[M+H]^+$: 497.2175, found 497.2171 (Δ 0.8 ppm).

*Diethyl 11,12,13-trimethoxy-4,6-dimethyl-5-oxo-3,5,7,9-tetrahydroazuleno[5,4-c]benzo[e]oxepine-2,2(1H)-dicarboxylate (**2c**).* Compound **2c** (70% HPLC yield) was isolated as an off-white solid (41 mg, 52%): mp 123.0–125.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (s,

1H), 4.76 (d, *J* = 12.8 Hz, 1H), 4.47 (d, *J* = 11.3 Hz, 1H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.26–3.98 (m, 4H), 3.95 (d, *J* = 13.9 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.62 (dd, *J* = 1.6, 17.8 Hz, 1H), 3.44 (s, 3H), 3.41 (d, *J* = 10.7 Hz, 1H), 3.36 (d, *J* = 10.5 Hz, 1H), 2.93 (d, *J* = 16.6 Hz, 1H), 2.39 (s, 3H), 2.26 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 171.0, 170.5, 153.7, 150.7, 145.5, 142.3, 141.8, 140.1, 137.5, 134.8, 127.9, 127.4, 107.9, 67.9, 65.3, 61.8, 61.7, 61.3, 61.2, 57.4, 56.1, 43.6, 42.3, 19.9, 18.3, 14.0, 13.9; HRMS (TOF) calcd for $C_{29}H_{35}O_9$ $[M+H]^+$ 527.2281, found 527.2285 (Δ = +0.8 ppm).

*Diethyl 6-(tert-butyl)-11,12,13-trimethoxy-4-methyl-5-oxo-3,5,7,9-tetrahydroazuleno[5,4-c]benzo[e]oxepine-2,2(1H)-dicarboxylate (**2d**).* The titled compound **2d** (71 mg, 83% yield) was obtained as an off-white solid: mp 144.0–146.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (s, 1H), 4.93 (d, *J* = 13.3 Hz, 1H), 4.46 (d, *J* = 11.1 Hz, 1H), 4.42 (d, *J* = 11.1 Hz, 1H), 4.22–4.10 (m, 2H), 4.10–4.00 (m, 2H), 3.90 (s, 3H), 3.89 (d, *J* = 13.3 Hz, 1H), 3.85 (s, 3H), 3.45 (dd, *J* = 17.6, 1.4 Hz, 1H), 3.34 (s, 3H), 3.24 (d, *J* = 17.6 Hz, 1H), 3.19 (d, *J* = 16.4 Hz, 1H), 2.77 (dd, *J* = 16.4, 1.4 Hz, 1H), 2.19 (s, 3H), 1.39 (s, 9H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 171.2, 170.6, 153.3, 151.0, 147.6, 142.1, 140.4, 140.3, 134.4, 133.3, 132.2, 127.7, 127.4, 107.6, 67.7, 63.8, 61.7, 61.6, 61.22, 61.16, 57.7, 56.0, 42.8, 39.8, 37.0, 32.9, 16.2, 13.9, 13.9; HRMS (TOF) calcd for $C_{32}H_{41}O_9$ $[M + H]^+$ 569.2751, found 569.2749 (Δ = –0.4 ppm).

*Diethyl 11,12,13-trimethoxy-4-methyl-5-oxo-6-{2-[(triethylsilyl)oxy]propan-2-yl}-3,5,7,9-tetrahydroazuleno[5,4-c]benzo[e]oxepine-2,2(1H)-dicarboxylate (**2e**).* The titled compound **2e** (89 mg, 87% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 1H), 5.56 (d, *J* = 12.5 Hz, 1H), 4.55 (d, *J* = 11.2 Hz, 1H), 4.43 (d, *J* = 11.2 Hz, 1H), 4.21–4.11 (m, 2H), 4.11–4.02 (m, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.83 (d, *J* = 12.5 Hz, 1H), 3.46 (dd, *J*

= 17.6, 1.0 Hz, 1H), 3.33 (s, 3H), 3.26 (d, *J* = 17.6 Hz, 1H), 3.14 (d, *J* = 16.2 Hz, 1H), 2.82 (dd, *J* = 16.2, 1.0 Hz, 1H), 2.20 (s, 3H), 1.69 (s, 3H), 1.55 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H), 0.86 (t, *J* = 7.9 Hz, 9H), 0.61–0.53 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 171.0, 170.6, 153.3, 151.0, 146.1, 142.0, 141.1, 140.6, 135.5, 133.9, 133.7, 128.1, 127.2, 107.5, 76.0, 67.6, 63.0, 61.8, 61.6, 61.3, 61.1, 57.9, 56.0, 42.7, 39.7, 35.0, 32.0, 16.5, 13.9, 13.9, 7.0, 6.4; HRMS (TOF) calcd for $C_{37}H_{52}NaO_{10}Si$ $[M + H]^+$ 707.3222, found 707.3228 (Δ = +0.8ppm).

*Diethyl 11,12,13-trimethoxy-6-methyl-5-oxo-3,5,7,9-tetrahydroazuleno[5,4-c]benzo[e]oxepine-2,2(1H)-dicarboxylate (**2f**).* The titled compound **2f** (56% HPLC yield) was isolated as an off-white solid (27 mg, 34%): mp 136.0–138.0 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.70 (s, 1H), 4.80 (d, *J* = 12.4 Hz, 1H), 4.47 (d, *J* = 11.3 Hz, 1H), 4.37 (d, *J* = 11.3 Hz, 1H), 4.23–4.02 (m, 4H), 3.93 (s, 3H), 3.92 (d, *J* = 12.4 Hz, 1H), 3.90 (s, 3H), 3.70 (dd, *J* = 17.1, 2.0 Hz, 1H), 3.50 (s, 3H), 3.45 (d, *J* = 17.2 Hz, 1H), 3.36 (d, *J* = 17.1 Hz, 1H), 2.93 (d, *J* = 17.2 Hz, 1H), 2.43 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5, 170.7, 170.1, 154.0, 150.5, 149.2, 147.3, 144.5, 142.4, 139.4, 137.9, 131.7, 127.8, 127.1, 108.0, 67.8, 66.0, 61.8, 61.8, 61.4, 61.2, 58.4, 56.1, 43.9, 43.3, 19.4, 13.9, 13.9; HRMS (TOF) calcd for $C_{28}H_{32}O_9$ $[M + H]^+$ 513.2125, found 513.2123 (Δ = –0.4 ppm).

*Diethyl 11,12,13-trimethoxy-6-methyl-5-oxo-4-phenyl-3,5,7,9-tetrahydro-azuleno[5,4-c]benzo[e]oxepine-2,2(1H)-dicarboxylate (**2g**).* The titled compound **2g** (21% HPLC yield) was isolated as an off-white solid (58 mg, 66%): mp 175.5–177.5 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.40 (m, 2H), 7.38–7.35 (m, 1H), 7.35–7.30 (m, 2H), 6.72 (s, 1H), 4.78 (d, *J* = 12.8 Hz, 1H), 4.51 (s, 2H), 4.17–4.01 (m, 4H), 4.00 (d, *J* = 12.8 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.53 (s, 3H), 3.42 (d, *J* = 16.8 Hz, 1H), 3.34 (d, *J* = 17.7 Hz, 1H), 3.14 (dd, *J* = 17.7, 1.5 Hz, 1H), 2.95 (d, *J* = 16.8 Hz, 1H), 2.39 (s, 3H), 1.16 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 189.7, 170.9, 170.4, 153.8, 150.8, 145.6, 143.7, 142.7, 142.4, 141.9, 138.5, 137.4, 136.2, 128.9, 128.4, 127.9, 127.7, 127.3, 108.0, 68.0, 65.5, 61.8, 61.7, 61.4, 61.2, 57.8, 56.1, 43.7, 42.7, 29.7, 19.6, 13.9; HRMS (TOF) calcd for $C_{34}H_{37}O_9$ $[M + H]^+$ 589.2432, found 589.2439 (Δ = +1.2 ppm).

*Diethyl 11,12,13-trimethoxy-6-methyl-4-(methylthio)-5-oxo-3,5,7,9-tetrahydro-azuleno[5,4-c]benzo[e]oxepine-2,2(1H)-dicarboxylate (**2j**).* The titled compound **2j** (50% HPLC yield) was isolated as a light yellow solid (27 mg, 32%): mp 150.0–152.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (s, 1H), 4.71 (d, *J* = 12.9 Hz, 1H), 4.47 (d, *J* = 11.3 Hz, 1H), 4.43 (d, *J* = 11.3 Hz, 1H), 4.23–4.13 (m, 2H), 4.13–4.01 (m, 2H), 3.97 (d, *J* = 12.9 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.64 (dd, *J* = 18.3, 1.0 Hz, 1H), 3.58 (d, *J* = 18.3 Hz, 1H), 3.46 (s, 3H), 3.35 (dd, *J* = 16.3, 1.0 Hz, 1H), 2.94 (d, *J* = 16.3 Hz, 1H), 2.42 (s, 3H), 2.35 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.7, 171.0, 170.3, 153.7, 150.8, 144.6, 142.2, 141.6, 139.6, 137.1, 136.5, 134.1, 128.0, 127.2, 107.9, 68.0, 64.4, 61.8, 61.7, 61.3, 61.2, 58.0, 56.1, 44.0, 42.6, 19.0, 15.8, 14.0, 13.9; HRMS (TOF) calcd for $C_{29}H_{35}O_9S$ $[M + H]^+$ 559.1996, found 559.2003 (Δ = +1.3 ppm).

*2,2-Diethyl 4-methyl 11,12,13-trimethoxy-6-methyl-5-oxo-7,9-dihydroazuleno[5,4-c]benzo[e]oxepine-2,2,4(1H,3H,5H)-tricarboxylate (**2k**).* The titled compound **2k** (34% HPLC yield) was isolated as a light yellow gummy oil (17 mg, 20%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (s, 1H), 4.75 (d, *J* = 12.7 Hz, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 4.40 (d, *J* = 11.4 Hz, 1H), 4.23–4.12 (m, 2H), 4.12–4.01 (m, 2H), 3.95 (d, *J* = 12.7 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 3.86 (d, *J* = 18.3 Hz, 1H), 3.50 (s, 3H), 3.37 (dd, *J* = 16.7, 1.1 Hz, 1H), 3.35 (dd, *J* = 18.3, 1.8 Hz, 1H), 2.90 (d, *J* = 16.7 Hz, 1H), 2.43 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1, 170.6, 169.9, 167.5, 154.2, 150.7, 147.4, 145.9, 143.6,

142.4, 139.2, 138.4, 133.4, 127.7, 126.8, 108.0, 67.9, 65.1, 62.0, 61.9, 61.4, 61.2, 58.1, 56.1, 52.6, 43.4, 41.8, 19.1, 14.0, 13.9; HRMS (TOF) calcd for $C_{30}H_{35}O_{11}$ $[M + H]^+$ 571.2174, found 571.2180 (Δ = +1.1 ppm).

*4,6-Dimethyl-7,9-dihydro-1H-benzo[c]furo[3',4':6,7]cyclohepta[1,2-e]oxepin-5(3H)-one (**2l**).* The titled compound **2l** (35 mg, 80% yield) was obtained as an off-white solid: mp 123.0–125.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.37 (m, 3H), 7.18–7.13 (m, 1H), 4.99 (s, 3H), 4.80 (br s, 1H), 4.55 (s, 2H), 4.35 (br s, 1H), 3.92 (br s, 1H), 2.47 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.1, 145.2, 144.7, 140.6, 140.2, 138.7, 138.3, 138.1, 132.4, 129.6, 129.3, 128.6, 127.8, 76.2, 74.8, 67.8, 65.6, 20.1, 17.4; HRMS (TOF) calcd for $C_{19}H_{19}O_3$ $[M + H]^+$ 295.1329, found 295.1344 (Δ = +5.1 ppm).

*11,12,13-Trimethoxy-4,6-dimethyl-7,9-dihydro-1H-benzo[c]furo-[3',4':6,7]cyclohepta[1,2-e]oxepin-5(3H)-one (**2m**).* The titled compound **2m** (70% HPLC yield) was isolated as an off-white solid (23 mg, 40%): mp 161.0–163.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (s, 1H), 5.08–4.96 (m, 3H), 4.83 (d, J = 12.5 Hz, 1H), 4.47 (d, J = 11.4 Hz, 1H), 4.37 (d, J = 11.4 Hz, 1H), 4.33 (d, J = 14.0 Hz, 1H), 3.97 (d, J = 12.5 Hz, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.51 (s, 3H), 2.48 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3, 154.0, 150.5, 145.1, 144.2, 142.5, 141.8, 139.5, 138.4, 137.9, 133.2, 128.0, 126.3, 108.2, 76.3, 75.0, 67.9, 65.8, 61.4, 61.3, 56.1, 20.3, 17.4; HRMS (TOF) calcd for $C_{22}H_{25}O_6$ $[M + H]^+$ 385.1646, found 385.1657 (Δ = +2.9 ppm).

*4,6-Dimethyl-2,8-ditosyl-2,3,8,9-tetrahydro-1H-benzo[c]pyrrolo-[3',4':6,7]cyclohepta[1,2-e]azepin-5(7H)-one (**2n**).* The titled compound **2n** (81% HPLC yield) was isolated as a white solid (56 mg, 62%): mp 162.0–164.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.30–7.23 (m, 2H),

7.20 (d, *J* = 8.0 Hz, 2H), 7.03 (dd, *J* = 7.2, 1.4 Hz, 1H), 6.87 (dd, *J* = 7.2, 1.5 Hz, 1H), 4.89 (d, *J* = 14.2 Hz, 1H), 4.54 (d, *J* = 13.5 Hz, 1H), 4.42 (d, *J* = 15.2 Hz, 1H), 4.23 (d, *J* = 15.2 Hz, 1H), 4.15 (d, *J* = 14.8 Hz, 1H), 3.96 (d, *J* = 13.5 Hz, 1H), 3.74 (d, *J* = 14.8 Hz, 1H), 3.23 (d, *J* = 14.2 Hz, 1H), 2.43 (s, 3H), 2.40 (s, 6H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.5, 144.4, 143.6, 143.3, 140.9, 140.0, 139.0, 138.5, 136.6, 136.0, 135.9, 132.3, 130.1, 130.0, 129.5, 129.2, 128.8, 128.0, 127.6, 127.2, 55.8, 54.3, 48.9, 46.8, 21.6, 21.5, 19.4, 17.9; HRMS (TOF) calcd for $C_{33}H_{33}N_2O_5S_2$ $[M + H]^+$ 601.1825, found 601.1835 (Δ = +1.7 ppm).

*11,12-dimethoxy-4,6-dimethyl-2,8-ditosyl-2,3,8,9-tetrahydro-1H-benzo[c]pyrrolo[3',4':6,7]cyclohepta[1,2-e]azepin-5(7H)-one (**2o**).* The titled compound **2o** (66% HPLC yield) was isolated as a light yellow solid (46 mg, 46%): mp 170.0–172.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.42 (s, 1H), 6.35 (s, 1H), 4.90 (d, *J* = 13.8 Hz, 1H), 4.46 (d, *J* = 14.2 Hz, 2H), 4.25 (d, *J* = 15.2 Hz, 1H), 4.18 (d, *J* = 14.9 Hz, 1H), 3.91 (d, *J* = 13.9 Hz, 1H), 3.81 (d, *J* = 15.2 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.23 (d, *J* = 13.8 Hz, 1H), 2.43 (s, 3H), 2.40 (s, 3H), 2.40 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.1, 149.3, 148.7, 144.5, 143.8, 143.5, 141.1, 139.1, 138.7, 136.6, 136.3, 136.2, 132.3, 132.1, 129.9, 129.6, 127.7, 127.2, 122.7, 111.8, 111.0, 56.1, 56.0, 55.9, 54.5, 48.7, 47.1, 21.5, 21.5, 19.6, 17.9; HRMS (TOF) calcd for $C_{35}H_{37}N_2O_7S_2$ $[M + H]^+$ 661.2037, found 661.2063 (Δ = +3.9 ppm).

*11,12,13-Trimethoxy-4,6-dimethyl-2,8-ditosyl-2,3,8,9-tetrahydro-1H-benzo[c]pyrrolo[3',4':6,7]cyclohepta[1,2-e]azepin-5(7H)-one (**2p**).* The titled compound **2p** (45% HPLC yield) was isolated as a white solid (34 mg, 33%): mp 172.0–174.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.1 Hz, 4H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 6.26 (s, 1H), 4.92 (d, *J* = 13.6 Hz, 1H), 4.50 (d, *J* = 15.2 Hz, 1H), 4.47 (d, *J* = 13.7 Hz, 1H), 4.26 (d, *J*

= 15.2 Hz, 1H), 4.24 (d, *J* = 15.0 Hz, 1H), 3.85 (d, *J* = 15.0 Hz, 1H), 3.85 (s, 3H), 3.81–3.78 (m, 4H), 3.36 (s, 3H), 3.27 (d, *J* = 13.6 Hz, 1H), 2.44 (s, 3H), 2.41 (s, 3H), 2.40 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.1, 154.0, 150.3, 144.3, 143.6, 143.5, 142.3, 141.0, 139.1, 138.6, 136.2, 135.9, 133.5, 132.5, 129.9, 129.6, 127.7, 127.3, 125.7, 125.6, 108.0, 61.3, 61.1, 55.9, 55.8, 54.7, 48.9, 47.2, 21.5, 21.5, 19.7, 17.9; HRMS (TOF) calcd for $C_{36}H_{39}N_2O_8S_2$ $[M + H]^+$ 691.2142, found 691.2150 (Δ = +1.6 ppm).

*Diethyl 11,12,13-trimethoxy-4-methyl-5,7-dioxo-5,7,8,9-tetrahydro-1H-benzo-[a]cyclopenta[j]heptalene-2,2(3H)-dicarboxylate (**2r'**).* The titled compound **2r'** (58 % HPLC yield) was isolated as a yellow oil (28 mg, 36%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.57 (s, 1H), 4.26–4.05 (m, 4H), 3.89 (s, 3H), 3.84 (s, 3H), 3.69 (dd, *J* = 17.8, 1.2 Hz, 1H), 3.48 (d, *J* = 17.8 Hz, 1H), 3.47 (s, 3H), 3.35 (d, *J* = 17.2 Hz, 1H), 3.14 (td, *J* = 12.9, 6.3 Hz, 1H), 3.04 (dd, *J* = 17.2, 1.2 Hz, 1H), 2.88–2.75 (m, 2H), 2.69–2.64 (m, 1H), 2.28 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 185.8, 170.9, 170.1, 154.1, 152.3, 148.4, 148.1, 147.9, 145.8, 141.2, 134.6, 133.3, 131.8, 123.3, 106.8, 62.0, 61.9, 61.7, 61.2, 56.9, 56.0, 46.8, 43.5, 43.2, 29.1, 18.1, 13.94, 13.91; HRMS (TOF) calcd for $C_{29}H_{33}O_9$ $[M + H]^+$ 525.2125, found 525.2124 (Δ = -0.2 ppm).

*Rh-catalyzed [2+2+2] cycloaddition of o-phenylenetriynes **1** under microwave irradiation.* *o*-Phenylenetriyne **1** (0.15 mmol), 1,3-bis(diphenylphosphino)propane (DPPP) (3.1 mg, 7.5 μmol) and $[Rh(COD)Cl]_2$ (1.8 mg, 3.75 μmol) were introduced to a 10 mL microwave reaction vessel. The reaction vessel was evacuated and refilled with nitrogen three times and placed under a nitrogen atmosphere. 2,2,2-Trifluoroethanol (TFE) (1.5 mL) was added to the reaction vessel and the reaction mixture was stirred at 80 ºC for 30 min with microwave radiation (250 W). The reaction mixture was concentrated in vacuo. The corresponding product **3** was isolated by

column chromatography on silica gel (hexanes:EtOAc = 9:1).

*Diethyl 8,9-dimethyl-10,12-dihydro-5H-benzo[c]indeno[4,5-e]oxepine-11,11(7H)-dicarboxylate (**3a**).* The titled compound **3a** (57 mg, 92% yield) was obtained as a white solid: mp 125.0–126.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.36 (m, 4H), 4.82 (d, *J* = 11.7 Hz, 1H), 4.45 (d, *J* = 11.1 Hz, 1H), 4.30–4.02 (m, 6H), 3.83 (d, *J* = 11.7 Hz, 1H), 3.71 (d, *J* = 16.5 Hz, 1H), 3.57 (d, *J* = 16.2 Hz, 1H), 3.32 (d, *J* = 16.5 Hz, 1H), 2.38 (s, 3H), 2.29 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 171.8, 140.3, 140.0, 135.4, 134.8, 134.5, 134.3, 132.7, 132.6, 129.7, 128.3, 128.2, 128.1, 67.5, 62.9, 62.0, 61.9, 60.1, 40.7, 40.5, 17.1, 15.7, 14.3, 14.2; LR-MS m/z calcd for $C_{25}H_{28}O_5$ $[M]^+$ 408.5, found $[M + 1]^+$: 409.2; HRMS (TOF) m/z calcd for $C_{25}H_{29}O_5$ $[M+H]^+$: 409.2015, found 409.2015 (Δ 0.0 ppm).

*Diethyl 2,3-dimethoxy-8,9-dimethyl-10,12-dihydro-5H-benzo[c]indeno[4,5-e]oxepine-11,11(7H)-dicarboxylate (**3b**).* The titled compound **3b** (58 mg, 82% yield) was obtained as an off-white solid; mp 124.0–126.0 °C; mp 124-126 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 1 H), 6.94 (s, 1H), 4.83 (d, *J* = 11.8 Hz, 1H), 4.40 (d, *J* = 11.2 Hz, 1H), 4.25 (m, 1H), 4.15–3.99 (m, 5H), 3.95 (s, 6H), 3.82 (d, *J* = 11.9 Hz, 1H), 3.73 (d, *J* = 16.5 Hz, 1H), 3.59 (d, *J* = 16.5 Hz, 1H), 3.36 (d, *J* = 16.5 Hz, 1H), 2.37 (s, 3H), 2.28 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 171.6, 148.5, 148.4, 139.9, 134.8, 134.3, 134.0, 132.6, 132.6, 132.2, 128.2, 112.5, 111.4, 67.2, 62.8, 61.9, 61.8, 60.0, 56.2, 56.1, 40.7, 40.4, 17.0, 15.7, 14.2, 14.1; HRMS (TOF) m/z calcd for $C_{27}H_{33}O_7$ $(M + H)^+$: 469.2221, found 469.2222 (Δ 0.3 ppm).

*Diethyl 11,12,13-trimethoxy-4,6-dimethyl-5-oxo-3,5,7,9-tetrahydroazuleno[5,4-c]benzo[e]oxepine-2,2(1H)-dicarboxylate (**3c**).* The titled compound **3c** (62 mg, 83% yield) was obtained as a white solid; mp 153.5–155.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (s, 1H),

4.84 (d, *J* = 11.7 Hz, 1H), 4.33–4.27 (m, 5H), 3.96–3.91 (m, 8H), 3.86 (d, *J* = 6 Hz, 2H), 3.71 (d, *J* = 16.5 Hz, 1H), 3.51 (d, *J* = 16.5 Hz, 1H), 3.47, (s, 3H), 3.22 (d, *J* = 17.1 Hz, 1H), 2.36 (s, 3H), 2.28 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 172.2, 153.2, 150.8, 142.5, 139.5, 136.6, 133.4, 132.4, 132.1, 131.5, 131.1, 125.8, 108.4, 67.6, 63.2, 61.8, 61.7, 61.0, 59.8, 56.3, 40.9, 40.6, 17.2, 15.7, 14.3; HRMS (TOF) m/z calcd for $C_{28}H_{35}O_8$ $[M + H]^+$: 499.2332, found 499.2328 (Δ 0.8 ppm).

*Diethyl 8-(tert-butyl)-1,2,3-trimethoxy-9-methyl-10,12-dihydro-5H-benzo[c]indeno[4,5-e]oxepine-11,11(7H)-dicarboxylate (**3d**).* The titled compound **3d** (59 mg, 73% yield) was obtained as a white solid: mp 128.0–130.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (s, 1H), 5.14 (d, *J* = 12.2 Hz, 1H), 4.34 (d, *J* = 11.1 Hz, 1H), 4.27–4.19 (m, 2H), 4.16–4.06 (m, 2H), 4.07 (d, *J* = 11.1 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.83 (d, *J* = 12.2 Hz, 1H), 3.83 (d, *J* = 16.6 Hz, 1H), 3.71 (d, *J* = 16.5 Hz, 1H), 3.42 (d, *J* = 16.5 Hz, 1H), 3.38 (s, 3H), 3.20 (d, *J* = 16.6 Hz, 1H), 2.45 (s, 3H), 1.60 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 171.9, 153.0, 150.5, 147.1, 142.2, 140.8, 136.1, 132.8, 132.7, 132.3, 130.5, 125.4, 107.5, 67.1, 64.5, 61.44, 61.36, 61.3, 60.7, 59.1, 56.0, 41.1, 40.5, 38.4, 34.5, 21.6, 14.0, 13.9; HRMS (TOF) calcd for $C_{31}H_{44}NO_8$ $[M + NH_4]^+$ 558.3067, found 558.3066 (Δ = –0.2 ppm).

*Diethyl 1,2,3-trimethoxy-8-methyl-10,12-dihydro-5H-benzo[c]indeno[4,5-e]oxepine-11,11(7H)-dicarboxylate (**3f**).* The titled compound **3f** (55 mg, 75% yield) was obtained as a pale yellow gummy oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 1H), 6.73 (s, 1H), 4.77 (d, *J* = 11.6 Hz, 1H), 4.31 (d, *J* = 11.2 Hz, 1H), 4.28–4.18 (m, 2H), 4.12–4.07 (m, 2H), 3.96 (s, 3H), 3.92 (s, 3H), 3.91–3.86 (m, 2H), 3.83 (d, *J* = 16.8 Hz, 1H), 3.72 (d, *J* = 16.4 Hz, 1H), 3.49 (d, *J* = 16.4 Hz, 1H), 3.47 (s, 3H), 3.19 (d, *J* = 16.8 Hz, 1H), 2.44 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H),

1.15 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 153.1, 150.7, 142.3, 140.1, 137.3, 134.8, 133.9, 131.5, 131.1, 125.7, 125.2, 108.2, 67.3, 62.4, 61.5, 61.41, 61.36, 60.8, 60.3, 56.0, 40.6, 40.4, 19.8, 14.0, 13.9; HRMS (TOF) calcd for $C_{27}H_{33}O_8$ $[M + H]^+$ 485.2170, found 485.2179 (Δ = +1.9 ppm).

*Diethyl 1,2,3-trimethoxy-8-methyl-9-phenyl-10,12-dihydro-5H-benzo[c]indeno-[4,5-e]oxepine-11,11(7H)-dicarboxylate (**3g**).* The titled compound **3g** (76 mg, 90% yield) was obtained as a colorless gummy oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.42 (m, 2H), 7.38–7.32 (m, 1H), 7.27–7.22 (m, 2H), 6.75 (s, 1H), 4.85 (d, J = 11.6 Hz, 1H), 4.36 (d, J = 11.2 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 4.06 (q, J = 7.1 Hz, 2H), 4.00–3.91 (m, 9H), 3.56 (s, 3H), 3.40 (d, J = 16.7 Hz, 1H), 3.24 (d, J = 16.8 Hz, 1H), 3.23 (d, J = 16.7 Hz, 1H), 2.20 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 171.7, 153.2, 150.7, 142.3, 140.5, 139.1, 138.4, 136.6, 132.9, 132.4, 132.2, 131.0, 129.2, 129.0, 128.4, 126.8, 125.3, 108.2, 67.4, 62.9, 61.4, 61.34, 61.32, 60.9, 60.0, 56.0, 40.8, 40.7, 16.7, 14.0, 13.9; HRMS (TOF) calcd for $C_{33}H_{37}O_8$ $[M + H]^+$ 561.2483, found 561.2489 (Δ = +1.1 ppm).

*Diethyl 1,2,3-trimethoxy-8-methyl-9-(trimethylsilyl)-10,12-dihydro-5H-benzo-[c]indeno[4,5-e]oxepine-11,11(7H)-dicarboxylate (**3h**).* The titled compound **3h** (12 mg, 14% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 1H), 4.83 (d, J = 11.7 Hz, 1H), 4.32 (d, J = 11.2 Hz, 1H), 4.28–4.18 (m, 2H), 4.07 (q, J = 7.1 Hz, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 3.89 (d, J = 11.2 Hz, 1H), 3.87 (d, J = 11.7 Hz, 1H), 3.77 (d, J = 16.0 Hz, 1H), 3.73 (d, J = 16.5 Hz, 1H), 3.61 (d, J = 16.0 Hz, 1H), 3.50 (s, 3H), 3.11 (d, J = 16.5 Hz, 1H), 2.54 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H), 0.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 171.8, 153.3, 150.8, 145.8, 142.2, 140.5, 136.5, 134.8, 134.6, 131.6, 131.0, 125.4, 108.2, 67.4, 62.9, 61.5, 61.4, 61.3, 60.9, 60.3, 56.1, 43.3, 39.6, 21.0, 14.03, 13.95, 2.8; HRMS (TOF)

calcd for $C_{30}H_{41}O_8Si$ $[M + H]^+$ 557.2565, found 557.2572 (Δ = +1.3 ppm).

*Diethyl 9-[dimethyl(phenyl)silyl]-1,2,3-trimethoxy-8-methyl-10,12-dihydro-5H-benzo[c]indeno[4,5-e]oxepine-11,11(7H)-dicarboxylate (**3i**).* The titled compound **3i** (39 mg, 43% yield) was obtained as a colorless gummy oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.47 (m, 2H), 7.36–7.30 (m, 3H), 6.73 (s, 1H), 4.79 (d, *J* = 11.7 Hz, 1H), 4.32 (d, *J* = 11.2 Hz, 1H), 4.24–4.14 (m, 2H), 4.07–3.98 (m, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 3.91 (d, *J* = 11.2 Hz, 1H), 3.87 (d, *J* = 11.7 Hz, 1H), 3.73 (d, *J* = 16.5 Hz, 1H), 3.64 (d, *J* = 16.2 Hz, 1H), 3.53 (s, 3H), 3.50 (d, *J* = 16.2 Hz, 1H), 3.11 (d, *J* = 16.5 Hz, 1H), 2.38 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.08 (t, *J* = 7.1 Hz, 3H), 0.68 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 153.3, 150.8, 146.8, 142.2, 141.2, 140.5, 136.7, 135.3, 133.5, 132.3, 131.8, 131.0, 128.8, 127.9, 125.3, 108.2, 67.4, 62.8, 61.5, 61.4, 61.3, 61.0, 60.2, 56.1, 43.5, 39.6, 21.4, 14.0, 13.9, 2.1, 2.0; HRMS (TOF) calcd for $C_{35}H_{43}O_8Si$ $[M + H]^+$ 619.2722, found 619.2726 (Δ = +0.6 ppm).

*Diethyl 1,2,3-trimethoxy-8-methyl-9-(methylthio)-10,12-dihydro-5H-benzo-[c]indeno[4,5-e]oxepine-11,11(7H)-dicarboxylate (**3j**).* The titled compound **3j** (44 mg, 55% yield) was obtained as a colorless gummy oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 1H), 4.82 (d, *J* = 11.7 Hz, 1H), 4.32 (d, *J* = 11.3 Hz, 1H), 4.28–4.19 (m, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 3.90–3.86 (m, 4H), 3.75 (d, *J* = 17.0 Hz, 1H), 3.49 (s, 3H), 3.22 (d, *J* = 16.8 Hz, 1H), 2.68 (s, 3H), 2.31 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.73, 171.70, 153.4, 150.6, 145.3, 142.3, 138.6, 137.2, 134.2, 132.8, 131.8, 130.9, 124.9, 108.3, 67.3, 63.4, 61.5, 61.4, 61.3, 60.9, 59.4, 56.0, 41.8, 41.0, 18.7, 17.0, 14.0, 13.9; HRMS (TOF) calcd for $C_{28}H_{35}O_8S$ $[M + H]^+$ 531.2047, found 531.2052 (Δ = +0.9 ppm).

*11,11-Diethyl 9-methyl 1,2,3-trimethoxy-8-methyl-5H-benzo[c]indeno[4,5-e]oxepine-9,11,11(7H,10H,12H)-tricarboxylate (**3k**).* The titled compound **3k** (38 mg, 46%

yield) was obtained as a white solid: mp 114.5–115.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 1H), 4.82 (d, *J* = 11.8 Hz, 1H), 4.32 (d, *J* = 11.4 Hz, 1H), 4.26–4.17 (m, 2H), 4.13–4.05 (m, 2H), 3.94 (s, 3H), 3.94 (s, 3H), 3.91 (s, 3H), 3.86 (d, *J* = 11.5 Hz, 2H), 3.84 (d, *J* = 16.9 Hz, 1H), 3.77 (d, *J* = 17.0 Hz, 1H), 3.61 (d, *J* = 17.0 Hz, 1H), 3.46 (s, 3H), 3.19 (d, *J* = 16.9 Hz, 1H), 2.47 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 169.4, 153.6, 150.7, 142.4, 139.2, 137.9, 136.1, 133.3, 132.8, 130.9, 129.2, 124.5, 108.4, 67.2, 62.2, 61.6, 61.5, 61.3, 61.0, 59.7, 56.0, 52.0, 40.6, 40.2, 16.7, 14.0, 13.9; HRMS (TOF) calcd for $C_{29}H_{38}NO_{10}$ $[M + NH_4]^+$ 560.2490, found 560.2499 (Δ = +1.6 ppm).

*4,5-Dimethyl-1,3,6,8-tetrahydrobenzo[e]isobenzofuro[5,4-c]oxepine (**3l**).* The titled compound **3l** (23 mg, 58% yield) was obtained as a white solid: mp 125.0–127.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.36 (m, 4H), 5.57 (d, *J* = 11.2 Hz, 1H), 5.19 (d, *J* = 10.3 Hz, 2H), 4.93 (d, *J* = 11.6 Hz, 1H), 4.87 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 9.9 Hz, 1H), 4.06 (d, *J* = 9.9 Hz, 1H), 3.91 (d, *J* = 11.2 Hz, 1H), 2.42 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 139.1, 135.1, 134.7, 133.6, 132.9, 132.7, 129.9, 129.8, 128.4, 128.2, 126.8, 74.2, 73.8, 67.3, 62.5, 17.0, 15.2; HRMS (TOF) calcd for $C_{18}H_{19}O_2$ $[M + H]^+$ 267.1380, found 267.1383 (Δ = +1.1 ppm).

*10,11,12-Trimethoxy-4,5-dimethyl-1,3,6,8-tetrahydrobenzo[e]isobenzofuro-[5,4-c]oxepine (**3m**).* The titled compound **3m** (42 mg, 79% yield) was obtained as a white solid: mp 159.5–161.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (s, 1H), 5.42 (d, *J* = 12.5 Hz, 1H), 5.19 (d, *J* = 12.0 Hz, 1H), 5.12 (d, *J* = 12.0 Hz, 1H), 4.88 (d, *J* = 11.7 Hz, 1H), 4.71 (d, *J* = 12.5 Hz, 1H), 4.34 (d, *J* = 11.2 Hz, 1H), 3.94 (s, 3H), 3.94 (d, *J* = 11.7 Hz, 1H), 3.92 (s, 3H), 3.89 (d, *J* = 11.2 Hz, 1H), 3.52 (s, 3H), 2.40 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 150.5, 142.3, 138.7, 135.5, 133.7, 132.4, 130.9, 129.5, 128.9, 125.1, 108.4, 74.9, 73.6, 67.3, 62.8, 61.3, 60.8, 56.0, 16.9, 15.2; HRMS (TOF) calcd for $C_{21}H_{25}O_5$ $[M + H]^+$ 357.1702, found 357.1699 (Δ =

–0.8 ppm).

*4,5-Dimethyl-2,7-ditosyl-1,2,3,6,7,8-hexahydrobenzo[5,6]azepino[4,3-e]isoindole (**3n**).* The titled compound **3n** (70 mg, 82% yield) was obtained as a white solid: mp 149.0–151.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.37–7.28 (m, 3H), 7.26–7.23 (m, 3H), 7.16 (td, *J* = 7.5, 1.2 Hz, 1H), 6.95 (dd, *J* = 7.5, 0.8 Hz, 1H), 4.96–4.89 (m, 3H), 4.66 (d, *J* = 13.2 Hz, 1H), 4.60 (dd, *J* = 13.2, 1.7 Hz, 1H), 4.51 (d, *J* = 14.0 Hz, 1H), 4.27 (d, *J* = 13.4 Hz, 1H), 3.59 (d, *J* = 14.0 Hz, 1H), 3.15 (d, *J* = 12.4 Hz, 1H), 2.39 (s, 6H), 2.35 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 143.3, 138.1, 136.6, 136.2, 135.5, 133.6, 132.9, 131.9, 131.5, 130.78, 130.77, 129.8, 129.6, 129.5, 128.4, 128.1, 127.5, 127.23, 127.19, 53.9, 53.7, 48.6, 44.3, 21.4, 21.4, 16.7, 15.3; HRMS (TOF) calcd for $C_{32}H_{33}N_2O_4S_2$ [M + H]$^+$ 573.1876, found 573.1882 (Δ = +1.0 ppm).

*10,11-Dimethoxy-4,5-dimethyl-2,7-ditosyl-1,2,3,6,7,8-hexahydrobenzo[5,6]-azepino[4,3-e]isoindole (**3o**).* The titled compound **3o** (95 mg, 100% yield) was obtained as a white solid: mp 220.0–221.0 °C; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.70 (d, *J* = 8.3 Hz, 4H), 7.31–7.28 (m, 4H), 6.72 (s, 1H), 6.36 (s, 1H), 4.90 (d, *J* = 12.2 Hz, 2H), 4.66 (d, *J* = 13.6 Hz, 1H), 4.61 (d, *J* = 13.6 Hz, 1H), 4.42 (d, *J* = 14.3 Hz, 1H), 4.27 (d, *J* = 13.5 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.51 (d, *J* = 14.3 Hz, 1H), 3.12 (d, *J* = 12.2 Hz, 1H), 2.39 (s, 3H), 2.38 (s, 3H), 2.35 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 149.2, 149.1, 144.5, 144.1, 137.5, 136.8, 136.0, 134.1, 133.7, 131.8, 131.3, 131.2, 131.2, 130.3, 130.2, 128.1, 127.8, 125.3, 113.2, 111.2, 56.4, 56.2, 54.7, 54.4, 49.0, 45.2, 21.8, 17.1, 15.7; HRMS (TOF) calcd for $C_{34}H_{37}N_2O_6S_2$ [M + H]$^+$ 633.2088, found 633.2098 (Δ = +1.6 ppm).

*10,11,12-trimethoxy-4,5-dimethyl-2,7-ditosyl-1,2,3,6,7,8-hexahydrobenzo-[5,6]azepino[4,3-e]isoindole (**3p**).* The titled compound **3p** (86 mg, 86% yield) was obtained

as a white solid: mp 206.0–208.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.20 (s, 1H), 4.91 (d, *J* = 12.1 Hz, 2H), 4.67–4.55 (m, 2H), 4.40 (d, *J* = 14.1 Hz, 1H), 4.15 (d, *J* = 13.8 Hz, 1H), 3.90 (s, 3H), 3.73 (s, 3H), 3.41 (d, *J* = 14.1 Hz, 1H), 3.37 (s, 3H), 3.20 (d, *J* = 12.2 Hz, 1H), 2.40 (s, 3H), 2.39 (s, 3H), 2.30 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 150.3, 143.4, 143.3, 142.1, 137.0, 135.7, 134.6, 133.9, 133.0, 131.2, 130.6, 129.6, 129.6, 129.4, 127.9, 127.6, 127.3, 123.9, 108.2, 61.3, 60.7, 55.8, 54.5, 53.9, 48.7, 44.6, 21.5, 16.7, 15.3; HRMS (TOF) calcd for $C_{35}H_{39}N_2O_7S_2$ $[M + H]^+$ 663.2193, found 663.2198 (Δ = +0.8 ppm).

*10,11,12-Trimethoxy-4,5-dimethyl-6,8-dihydrobenzo[5,6]oxepino[4,3-e]isobenzofuran-3(1H)-one (**3q**).* The titled compound **3q** (31 mg, 56% yield) was obtained as an off-white solid: mp 184.0–186.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H), 5.64 (d, *J* = 15.7 Hz, 1H), 4.94 (d, *J* = 11.7 Hz, 1H), 4.81 (d, *J* = 15.7 Hz, 1H), 4.39 (d, *J* = 11.4 Hz, 1H), 3.99 (d, *J* = 11.7 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 3.86 (d, *J* = 11.4 Hz, 1H), 3.53 (s, 3H), 2.76 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 153.9, 150.3, 143.5, 142.5, 138.6, 138.1, 136.7, 130.9, 129.7, 123.04, 123.03, 109.0, 69.4, 67.5, 62.7, 61.4, 61.2, 56.1, 15.2, 13.8; HRMS (TOF) calcd for $C_{21}H_{23}O_6$ $[M + H]^+$ 371.1489, found 371.1497 (Δ = +2.2 ppm).

*Diethyl 10,11,12-trimethoxy-4-methyl-6-oxo-5-(trimethylsilyl)-3,6,7,8-tetrahydrobenzo[6,7]cyclohepta[1,2-e]indene-2,2(1H)-dicarboxylate (**3r**).* The titled compound **3r** (42% HPLC yield) formed in the reaction of **1r** under the [2+2+2+1] conditions as a minor product (Table 5, entry 7) was isolated as yellow oil (30 mg, 35%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (s, 1H), 4.27–4.13 (m, 4H), 3.87 (s, 3H), 3.78 (s, 3H), 3.65–3.58 (m, 4H), 3.53 (dt, *J* = 18.3, 1.8 Hz, 1H), 3.30 (dd, *J* = 18.3, 1.5 Hz, 1H), 3.18 (dt, *J* = 16.7, 1.9 Hz, 1H), 2.82–2.64 (m, 2H), 2.48–2.36 (m, 2H), 2.22 (s, 3H), 1.24 (td, *J* = 7.1, 2.2 Hz, 6H), 0.14 (s, 9H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 197.0, 171.5, 171.3, 153.3, 151.5, 150.8, 141.0, 137.1, 134.7, 133.1, 119.5, 118.4, 107.3, 104.5, 101.7, 61.51, 61.46, 61.2, 60.6, 56.3, 56.0, 46.8, 41.0, 28.7, 28.4, 27.8, 14.1, 14.0, –0.21; HRMS (TOF) calcd for $C_{31}H_{41}O_8Si$ $[M + H]^+$ 569.2565, found 569.2572 (Δ = +1.2 ppm).

*6-tert-Butyl 11,11-diethyl 9-methyl-10,12-dihydrobenzo[e]indeno[5,4-c]azepine-6,11,11(5H,7H)-tricarboxylate (**3t**)*. The titled compound **3t** (67 mg, 91% yield) was obtained as an off-white solid: mp 102.0–104.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53–7.48 (m, 1H), 7.47–7.31 (m, 3H), 7.16–6.95 (m, 1H), 4.81 (d, *J* = 13.4 Hz, 1H), 4.66 (d, *J* = 13.4 Hz, 1H), 4.31–4.22 (m, 2H), 4.20–4.06 (m, 2H), 4.02 (d, *J* = 16.7 Hz, 1H), 3.70–3.43 (m, 4H), 3.33 (d, *J* = 16.7 Hz, 1H), 2.31 (s, 3H), 1.50 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 171.4, 154.1, 139.5, 138.7, 137.5, 134.8, 133.7, 133.5, 129.8, 129.5, 128.4, 127.81, 127.75, 79.7, 61.8, 61.6, 60.2, 48.0, 47.6, 47.2, 46.8, 40.3, 39.3, 28.5, 18.8, 14.0, 13.9; HRMS (TOF) calcd for $C_{29}H_{36}NO_6$ $[M + H]^+$ 494.2543, found 494.2541 (Δ = –0.4 ppm).

*6-tert-Butyl 11,11-diethyl 9-methyl-8-(trimethylsilyl)-10,12-dihydrobenzo-[e]indeno[5,4-c]azepine-6,11,11(5H,7H)-tricarboxylate (**3u**)*. The titled compound **3u** (79 mg, 93% yield) was obtained as a white solid: mp 157.5–158.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.49 (m, 1H), 7.47–7.28 (m, 3H), 5.16–4.68 (m, 2H), 4.33–4.20 (m, 2H), 4.20–4.05 (m, 2H), 4.02 (d, *J* = 16.9 Hz, 1H), 3.71–3.32 (m, 4H), 3.24 (d, *J* = 16.9 Hz, 1H), 2.43 (s, 3H), 1.49 (br s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 171.5, 154.0, 139.6, 139.0, 138.8, 138.4, 137.9, 135.3, 134.9, 128.7, 128.3, 128.1, 127.5, 127.5, 80.0, 79.7, 61.8, 61.6, 59.5, 47.3, 46.7, 46.4, 46.1, 40.9, 40.5, 28.4, 21.3, 14.0, 13.9, 3.7, 3.4; HRMS (TOF) calcd for $C_{32}H_{44}NO_6Si$ $[M + H]^+$ 566.2938, found 566.2939 (Δ = +0.2 ppm).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:xxxxxxxxxxxxxxxx. ^{1}H and ^{13}C NMR spectra of all new compounds synthesized in this work.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: iwao.ojima@stonybrook.edu

ORCID

Iwao Ojima: 0000-0002-3628-1161

Notes

The authors declare no competing financial interest.

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