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Graphical Abstract

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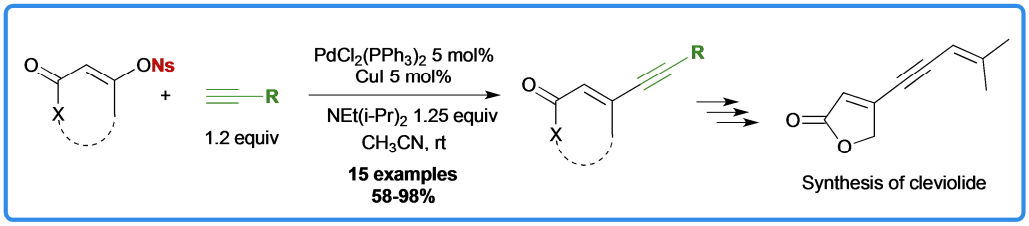

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Dedicated to Prof. Leon Ghosez, for his humanism, his numerous achievements in organic chemistry and in the promotion of organic chemistry

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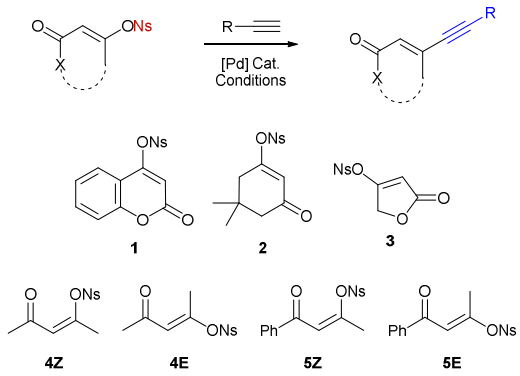
ABSTRACT

Vinyl nosylates, readily obtained from β-dicarbonyl derivatives, could be efficiently engaged in Sonogashira cross-coupling reactions, either cocatalyzed by copper or silver salts. The *para*-nitrobenzenesulfonate (nosylate) group allows this coupling to be performed under very mild conditions (room temperature). These new leaving group and mild conditions could be applied to the synthesis of acetylenic coumarinyl derivatives and to the total synthesis of an acetylenic monoterpene natural product, named cleviolide.

1. Introduction

The Sonogashira reaction is one of the four most well-known palladium-catalyzed cross-coupling reactions beside Mizoroki-Heck, Stille and Suzuki-Miyaura couplings.[1] This reaction has been extensively applied to many areas, from total synthesis[2] to OFET, OLED and related materials synthesis.[3] As a result, a wide panel of substrates has been engaged in this coupling reaction, but most of them are vinyl or aryl halides and triflates. Although quite reactive in such coupling reactions, triflates require specific conditions for their introduction due to the use of the sensitive and expensive triflic anhydride. Therefore, convenient and cheaper alternatives to triflates are highly sought. In this context, various other electrophiles,[4] such as phosphates[5] and a few sulfonates[6] have been investigated. As we recently showed that para-nitrobenzenesulfonate or nosylates (NsO) derivatives are very interesting, cheap and stable electrophilic coupling partners in various palladium-catalyzed cross-coupling reactions,[7] we further explored the behavior of such leaving group in the Sonogashira reaction (Scheme 1). We report here a full account of the results we gained specifically for the Sonogashira reaction with a series of challenging compounds.

In this work, we mostly focused on nosylates derived from 4-hydroxycoumarin **1**, dimedone **2**, and 4-hydroxy-5(*H*)-furan-2-one **3** as models for comparison purposes (Scheme 1). These compounds have indeed been studied with other leaving groups, such as the classical halides and triflate, but also tosylates, mesylates and phosphates.[8] We also investigated the vinyl nosylates **4-5** in connection with various total synthesis projects, including our approach to dienediyne synthesis (Figure 1).[9] To demonstrate the usefulness of nosylates in Sonogashira coupling reaction, we also report here the synthesis of cleviolide, the only naturally occurring acetylenic monoterpene.



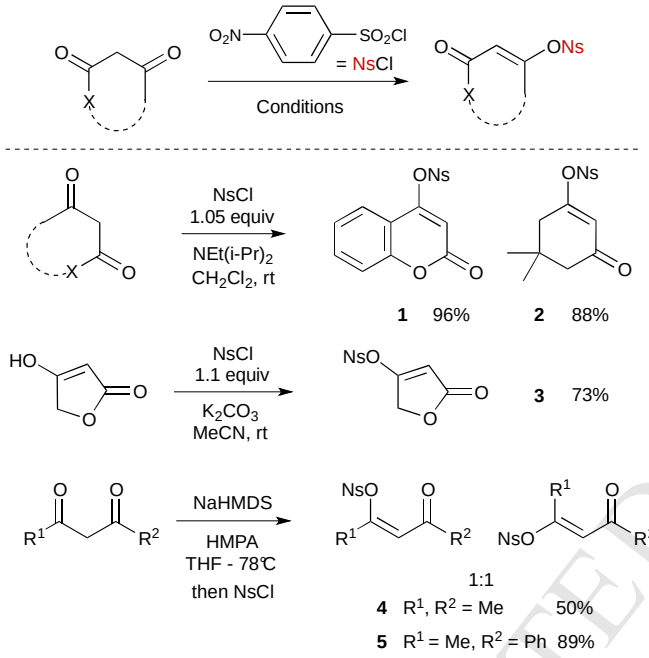
Scheme 1. Sonogashira coupling of vinyl nosylates highlighted in this work (Ns = *para*-nitrobenzenesulfonyl or nosyl)

2. Results and discussion

2.1. Nosylate formations

Vinyl nosylates are readily obtained after treating β-dicarbonyl derivatives with nosyl chloride in the presence of mild bases.[7b] For cyclic compounds **1-2**, the most appropriate base and solvent were diisopropylethylamine and dichloromethane at room temperature (96 and 88 % isolated yields), although potassium carbonate and acetonitrile were as effective. In the case of the more sensitive **3**, potassium carbonate and acetonitrile were required.

With acyclic dicarbonyl derivatives, these conditions could not be applied and only strong bases, such as Na- or K-HMDS, in THF allowed the formation of the corresponding nosylates **4-5**, but the use of HMPA was mandatory. Under such conditions, a 1:1 mixture of *E* and *Z* isomers were always obtained, but they can be readily separated by chromatography (Scheme 2).



Scheme 2. Standard procedures for the preparation of vinyl nosylate derivatives **1-5** using NsCl.

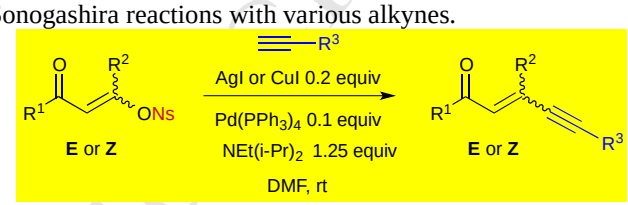
2.2. Silver vs copper co-catalyzed Sonogashira coupling with vinyl nosylates

Some years ago, our group developed a variant of the Sonogashira coupling based on silver salts as co-catalyst, silver iodide in DMF being the best, starting from triflate derivatives.[9,10] The purpose of this variant was to suppress alkyne homocoupling, a common side-reaction of the classical Sonogashira reaction, but also to limit self-addition of certain substrates.[11] The former side-reaction results from the well-known Glaser reaction,[12] while the latter is due to the nucleophilic character of the *in situ* formed copper acetylide.[13] As silver acetylides are less prone to oxidative coupling and less nucleophilic than their copper analogs[14] but can still transmetalate to palladium,[15] the corresponding side-products become totally absent or negligible in the silver version of the Sonogashira coupling.

Within this frame, we decided to explore the behavior of vinyl nosylates in our silver-cocatalyzed Sonogashira coupling. For comparison purposes, both silver and copper-cocatalyzed versions were evaluated with the nosylates **4** (Table 1).

Under the conditions previously set for silver-cocatalyzed Sonogashira coupling,[9,10] the *E*-nosylate **4** derived from acetylacetone readily reacted with various alkynes, functionalized or not, and provided the corresponding *E*-enynones **6-8** in reasonable to high yields, depending on the sensitivity of the compound (entries 3, 7 and 11). With copper iodide as co-catalyst, the *E*-enynones **6-8** were obtained in good to high yields (entries 4, 8 and 12). As expected from the lower reactivity of silver acetylides,[14] reaction times were longer, and yields were thus often lower with the silver Sonogashira reaction as compared to the classical copper version (entries 3 vs 4, 7 vs 8 and 11 vs 12). More surprising was the lack of reaction starting from the corresponding *Z* isomer of **4**, even after prolonged reaction time (entries 1-2, 5-6). It nevertheless reacted with the silyl protected *Z*-pent-3-en-4-yn-1-ol, but after prolonged reaction time, whatever the copper or silver conditions applied. The yields were modest, with a large difference between those achieved starting from the *E* isomer (entries 9-10 vs 11-12).

Table 1. *E* or *Z* Vinyl nosylate in Ag- vs Cu-cocatalyzed Sonogashira reactions with various alkynes.

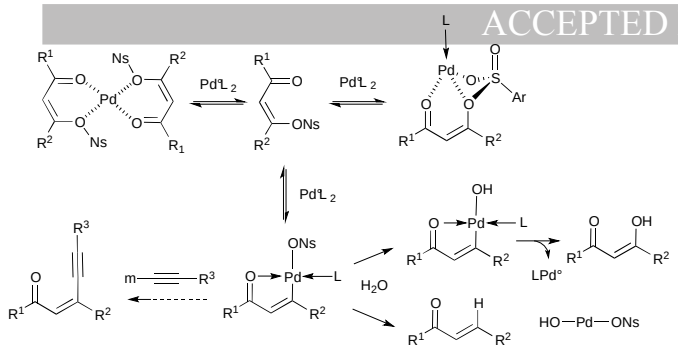


Entry	Nosylate	Alkyne	Co-Cat.	Product	Time (h)	Yield[a] (%)
1	4Z	*n*Bu	AgI	-	24	0[b]
2			CuI		24	0[b]
3	4E	*n*Bu	AgI	6E	4	50
4			CuI		2	58
5	4Z	OH	AgI	-	24	0[b]
6			CuI		24	0[b]
7	4E	OH	AgI	7E	4	68
8			CuI		1	84
9	4Z	TBDPSO	AgI	8Z	24	38
10			CuI		24	45
11	4E	TBDPSO	AgI	8E	4	57
12			CuI		4	77

[a] Yields of isolated pure products unless otherwise stated.

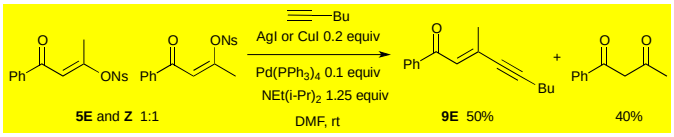
[b] No reaction.

As the oxidative addition of palladium species to the carbon-nosylate bond obviously occurred for the *E* isomer, the problems observed for the other isomer clearly imply specific phenomenon. The lack of reaction or the very slow reaction for the *Z* isomer could be due to either competitive chelation or special stability of the insertion complex. The *Z* starting material could act as a kind of acac ligand, strongly chelating palladium and thus inhibiting further transformation (Scheme 3, top left). It is worth noting that, due to the sulfonate structure, such β-keto nosylate could also act as a tridentate ligand nicely complementing the Pd^0 coordination sphere (Scheme 3, top right). Furthermore, the complex formed upon oxidative addition could be stabilized by chelation with the adjacent carbonyl group (Scheme 3, bottom). Upon work-up, this complex could be simply hydrolyzed, leading to the corresponding enone, or converted to a new hydroxo complex,[16] which could provide back the diketone.



Scheme 3. Possible explanations for the lack or poor reactivity of *Z*-β-keto nosylates.

To check these possibilities, we engaged a 1:1 mixture of **5E** and **5Z** in copper or silver Sonogashira coupling reactions with 1-hexyne (Scheme 4). Whatever the conditions and as expected from the above results, only the *E* coupling product **9E** coming from the *E* isomer **5E** could be isolated. Interestingly, the corresponding diketone was also isolated. The presence of this compound thus tends to support the second hypothesis, involving a stable insertion complex and the hydroxo complex mechanism with the starting *Z* isomer **4** or **5**.



Scheme 4. Competitive experiment set to decipher the possible reasons for the non-coupling of *Z*-β-keto nosylates.

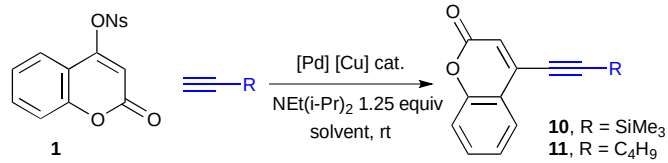
With these surprising results, we then mostly focused on the classical Sonogashira reaction, trying to adjust conditions to nosylate derivatives as substrates.

2.3. Copper co-catalyzed Sonogashira reaction with vinyl nosylates

We selected the nosylate **1** derived from coumarin as our first but challenging starting material. Indeed, the analog triflate is known to be unstable,[17] except when α-substituted,[18] and phosphates have been reported as unreactive.[19] Since the halide and tosylate derived from coumarin have been described and engaged in cross-coupling reactions, Sonogashira reaction with **1** would serve as benchmark to qualify nosylate as effective partner in such coupling reaction.

We first studied the Sonogashira coupling of **1** with 1-hexyne and trimethylsilylacetylene, and diisopropylethylamine as base (Table 2). Under the classical conditions (10 mol% of $Pd(PPh_3)_4$ and 20 mol% of CuI) with trimethylsilylacetylene, only traces of the expected product **10** could be detected by ^{1}H NMR of the crude (entry 1). The use of silver salt instead of copper led to similar results (entry 2). Assuming that the product was sensitive, we switched to 1-hexyne as alkyne. However, the same problem occurred, with the product **11** detected in the crude but not much after work-up and purification (entry 3). We then turned to $PdCl_2(MeCN)_2$ as catalyst while lowering the catalyst loading to 2 mol%, but both modifications led to degradation in THF (entry 4), and to an even more complex crude in DMF (entry 5). In sharp contrast, switching to $PdCl_2(dppf)$[7] with CuI as catalysts were not effective, only leaving unchanged the starting material even after prolonged reaction time (entry 6).

Table 2. Optimization of the Sonogashira coupling conditions.



1

Entry	R	[Pd] (mol%)	[Cu] (mol%)	Solvent	Time (h)	Yield[a] (%)
1	$SiMe_3$	$Pd(PPh_3)_4$ (10)	CuI (20)	DMF	6	-[b]
2	$SiMe_3$	$Pd(PPh_3)_4$ (10)	AgI (20)	DMF	6	-[b]
3	n-C_4H_9	$Pd(PPh_3)_4$ (10)	CuI (20)	DMF	6	-[b]
4	n-C_4H_9	$PdCl_2(MeCN)_2$ (2)	CuI (4)	THF	1	-[c]
5	n-C_4H_9	$PdCl_2(MeCN)_2$ (2)	CuI (4)	DMF	1	-[c]
6	n-C_4H_9	$PdCl_2(dppf)$ (2)	CuI (4)	THF	24	-[d]
7	n-C_4H_9	$PdCl_2(PPh_3)_2$ (5)	CuI (5)	CH_3CN	1	91
8	$SiMe_3$	$PdCl_2(PPh_3)_2$ (5)	CuI (5)	CH_3CN	1	98
9	$SiMe_3$	$PdCl_2(MeCN)_2$ (2)	CuI (4)	CH_3CN	2	-[c]

[a] Yields of isolated pure products unless otherwise stated.

[b] Trace of the product was observed on the crude ^{1}H NMR spectrum.

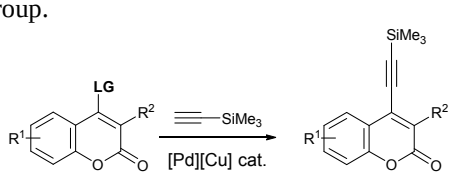
[c] Degradation occurs leading to unidentified by-products.

[d] Starting material was recovered untouched.

Acetonitrile was the key to success, because in this solvent, the coupling with $PdCl_2(PPh_3)_2$ together with CuI as catalysts afforded the expected product **11** in only 2 hours at room temperature in high yields (91%; entry 7). Under the same conditions, trimethylsilylacetylene quantitatively afforded the corresponding product **10** in 1 hour (98%; entry 8). However, triphenylphosphine proved essential as ligand, as a phosphine-free catalyst led to a messy reaction (entry 9).

It is worth mentioning here that these results are highly competitive regarding the few examples of Sonogashira reaction involving coumarinyl derivatives (Table 3). Triflates derived from activated methoxylated coumarins readily reacted with trimethylsilylacetylene within two hours giving the expected coupling product in good to high yields (77-85%).[20] In sharp contrast, the tosylate of coumarin required a very long reaction time (48h) to react with trimethylsilylacetylene producing the coupling product in good yields (68%).[19] It has been reported that the 4-chloro-3-nitrocoumarin also required long reaction times (24h) to provide coupling products in good yields (73%).[8c]

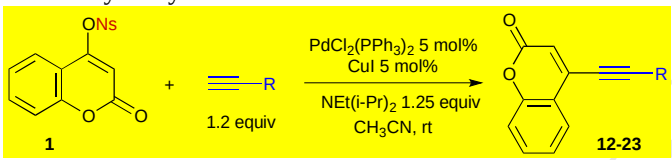
Table 3. Comparison of Sonogashira coupling reactions performed with coumarinyl derivatives carrying different leaving group.



Entry	LG	R^1	R^2	Yield (%)	Ref.
1	**ONs**	**H**	**H**	**98**	**this work**
2	OTf	H	H	deg.	17
3	OTf	OMe	H	77-89	20
4	OTs	H	H	68	19
5	Cl	H	NO_2	73	8c
6	OP(O)(OEt)$_2$	H	H	0	19

With optimal reaction conditions identified, the scope and limitations of this coupling reaction were investigated through the coupling of various alkynes first with the same coumarinyl nosylate **1** (Table 4). Simple linear and cyclic aliphatic alkynes, even the gaseous propyne, were efficiently coupled, leading to the desired products **12-14** in good to high yields (54-92%, entries 1-3). More functionalized alkynes could also be engaged in coupling reaction with nosylate **1**, with usually good results. 1-Ethynylcyclohex-1-ene yielded the dienynone **15** in 87% yield (entry 4), whereas the coupling product with 2-methylbut-1-en-3-yne **16** could not be isolated, presumably due to its fragility (entry 5). Not so surprisingly, propargyl alcohol led to the isolation of the coupling product **17** only in low yield, due to its instability (entry 6). It is worth mentioning that the same issue was observed on a similar substrate by Fairlamb et al..[21] Upon protection of the hydroxy group, the expected product **18** could be isolated in good yield (entry 7). Upon substitution at the propargylic position with two methyl or an isopropyl group, protection of the alcohol was no longer required to isolate the corresponding products **19** and **20** with 89% and 77% yield respectively (entries 8-9). With longer alkyl chain between the hydroxy group and the alkyne, the coupling product was readily produced, again without the requirement for a protecting group and **21** could be isolated in good yield (entry 10). Not unexpectedly, amino-substituted alkynes required a protecting group, as shown with but-3-ynamine for which its *N*-but-1-ynyl phtalimide derivative yielded the expected coupling product **22** in 69% yield (entry 11).

Table 4. Alkyne scope in Sonogashira coupling with coumarinyl nosylate **1**.



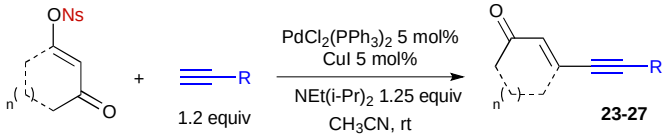
Entry	R	Product	Time (h)	Yield[a] (%)
1	n-C_3H_7	**12**	5	70
2	CH_3	**13**	2	54
3		**14**	1	92
4		**15**	2	87
5		**16**	6	-[b]
6	CH_2OH	**17**	14	10
7	$CH_2OTBDPS$	**18**	14	67
8	$C(CH_3)_2OH$	**19**	4	89
9	CH(OH)*i*Pr	**20**	6	77
10	$(CH_2)_4OH$	**21**	6	71
11	$(CH_2)_2NPht$	**22**	6	69

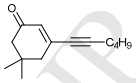
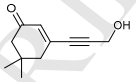
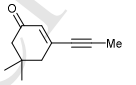
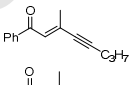
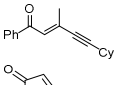
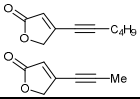
[a] Isolated yields.

[b] Degradation occurs leading to unidentified by-products.

We then briefly examined the vinyl nosylate scope with other challenging compounds (Table 5). Vinyl nosylate **2** obtained from dimedone was efficiently coupled under the best conditions set above, and the expected enynone **23** was isolated in high yield (88%; entry 1). Interestingly, in this case, the coupling with propargyl alcohol proceeded efficiently without protection and the resulting product **24** was even obtained quantitatively (entry 2), providing further insights into the instability of **17** (Table 2, entry 6). Gaseous propyne was also efficient in this coupling and provided the enynone **25** in high yield (78%; entry 3). Starting from *E*-β-keto nosylate **5E**, coupling compounds **26** and **27** could be obtained in good yields, even if substantial amount of unidentifiable by-products was also formed during the reactions (entries 4 and 5). The more sensitive nosylate **3** derived from 4-hydroxy-2,5-dihydrofuran-2-one could also be successfully engaged in this procedure and its coupling with 1-hexyne and propyne yielded the corresponding products **28** and **29** in 83% and 58% yield respectively (entries 6 and 7).

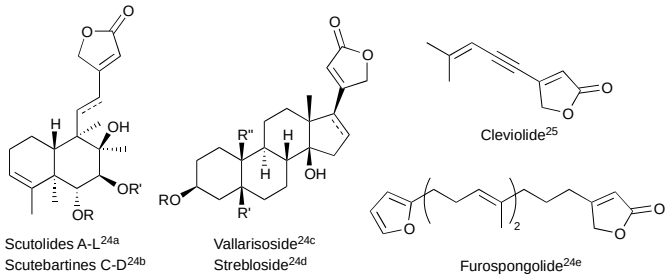
Table 5. Vinyl nosylate scope with various alkynes.



Entry	Vinyl Nosylate	R	Product		Time (h)	Yield[a] (%)
1	**2**	n-C_4H_9		**23**	2	88
2	**2**	CH_2OH		**24**	1	99
3	**2**	CH_3		**25**	2	78
4	**5E**	n-C_3H_7		**26**	2	54
5	**5E**	Cy		**27**	2	63
6	**3**	n-C_4H_9		**28**	4	83
7	**3**	CH_3		**29**	4	58

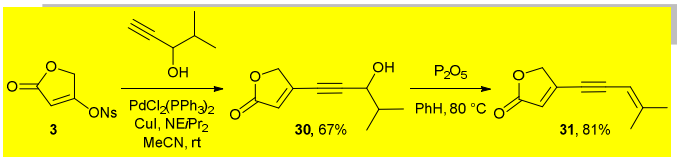
[a] Isolated yields.

The latter was selected, because the 2,5-dihydrofuran-2-one ((5*H*)-furan-2-one) motif can be found in various natural products from different families,[22] but also used as building blocks for the total synthesis of natural products.[23] (5*H*)-Furan-2-one could be found in neoclerodanes, cardenolides as well as simple mono- or diterpenes (Scheme 5), compounds which often exhibit strong and useful biological activities.[24] To illustrate the usefulness of the coupling method described here, we embarked in the total synthesis of one of these monoterpenes, i.e. cleviolide.



Scheme 5. Various natural products containing the 2,5-dihydrofuran-2-one motif.

Cleviolide was isolated as the first acetylenic monoterpene from the plant *Senecio clevelandii*.[25] In contrast to other syntheses,[26] and related works,[27] we used nosylate **3** as starting material and we were able to engage **3** under our coupling conditions directly in the presence of 4-methylpent-1-yn-3-ol as terminal alkyne (Scheme 6).



Scheme 6. Synthesis of cleviolide from vinyl nosylate **3**.

The expected product **30** was isolated in good yield despite its sensitivity (67%). The latter was then very efficiently dehydrated with diphosphorous pentoxide according to the procedure reported by Boukouvalas et al..[26d] The natural product **31** was thus isolated in high yield (81%). This sequence thus offers a three-step synthesis of this naturally occurring acetylenic monoterpene starting from the commercially available 5-hydroxy-(5*H*)-furan-2-one (tetronic acid) with an overall yield of 40%. It is worth to note that the coupling step here was more efficient than those reported from stannyl furanone and 1-iodoalkyne (37%),[26a] from iodofuranone and stannylalkyne (52%)[27d] but similar to the routes from bromofuranone and stannyl alkyne[26c], free alkyne[26d] or potassium alkynyltrifluoroborates[27c].

3. Conclusion

In the present work, we showed that the *para*-nitrobenzenesulfonate (nosylate) group acts as an excellent partner in Sonogashira cross-coupling reaction, whatever the cocatalyst (copper or silver) used. We were also able to set up very mild conditions (room temperature) allowing sensitive compounds and products such as enynes to be engaged or formed under these conditions. We demonstrated that these nosylate leaving group and mild conditions perfectly combine to efficiently produce coumarinyl products. We also applied these new leaving group and mild conditions to the total synthesis of an acetylenic monoterpene natural product.

4. Experimental section

Proton (^{1}H NMR) and Carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on the following 300, 400 or 500 MHz instruments. The chemical shifts are given in part per million on the delta scale. The solvent peak was used as reference values. For ^{1}H NMR: $CHCl_3$ = 7.26 ppm. For ^{13}C NMR: $CDCl_3$ = 77.16 ppm. Data are presented as follow; chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, b = broad), coupling constants (*J*/Hz) and integration. IR spectra were recorded as neat sample on a Brucker Alpha spectrophotometer. High-resolution mass spectra (HRMS) were recorded by Electrospray Ionisation (ESI) on an Agilent 6520 Accurate Mass Q-TOF. Analytical thin layer chromatography (TLC) was carried out on silica gel 60 F_{254} plates with visualization by ultraviolet light, *para*-anisaldehyde or potassium permanganate dip. Flash column chromatography was carried out using silica gel 60 (40–63 μm) and the procedure included the subsequent evaporation of solvents in vacuo. Reagents and solvents were purified using standard means. Tetrahydrofuran was dried using Glasstechnology DryStation ST100 purification system (filtration over alumina) under an argon atmosphere. Acetonitrile and *N*,*N*-diisopropylethylamine (DIPEA) were distilled from CaH_2 and stored under an argon atmosphere. Anhydrous reactions were carried out in flame-dried glassware and under an argon atmosphere. All extractive procedures were performed using non-distilled solvents and all aqueous solutions used were saturated unless details are given. Vinyl nosylate derivatives **1-3** were prepared according reported procedures.[7b]

4.1. General Procedure for Copper Co-Catalyzed Sonogashira Cross-Coupling of Vinyl Nosylates in acetonitrile

$PdCl_2(PPh_3)_2$ (5 mol%), CuI (5 mol%) and the alkyne (1.2 equiv) were successively added at room temperature to a solution of vinyl nosylate (1 equiv, 0.5 mmol) in degassed and anhydrous acetonitrile (5 mL, 10 mL/mmol) under argon. Diisopropylethylamine (DIPEA) (1.25 equiv) was then added dropwise. The reaction mixture was stirred at room temperature until consumption of the starting material (TLC). The suspension was then diluted with Et_2O (9 mL), filtered over a pad of Celite® (elution with Et_2O), then on a silica gel pad. The filtrate was evaporated to dryness and chromatographed over silica gel to afford the product.

*4.1.1. 4-(Trimethylsilylethynyl)-2H-chromen-2-one (**10**)*

Following the *general procedure*, 2-oxo-2*H*-chromen-4-yl 4-nitrobenzenesulfonate **1** (173 mg, 0.5 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 5 mol%), CuI (4.7 mg, 5 mol%), ethynyltrimethylsilane (92 μL, 0.65 mmol) and DIPEA (109 μL, 0.625 mmol) were stirred at room temperature during 1 h and gave **10** (119 mg, 4.91 mmol, 98 %) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.34 (s, 9H), 6.56 (s, 1H), 7.32 (dd, J = 7.8 and 1.2 Hz, 1H), 7.33 (ddd, *J* = 8.2, 7.8 and 1.2 Hz, 1H), 7.55 (ddd, *J* =8.2, 7.8 and 1.6 Hz, 1H), 7.84 (dd, *J* = 8.2 and 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) -0.2, 97.7, 109.7, 117.2, 118.5, 119.4, 124.7, 126.9, 132.9, 137.1, 153.8, 160.4; consistent with literature data.[19]

*4.1.2. 4-(Hex-1-ynyl)-2H-chromen-2-one (**11**)*

Following the *general procedure*, 2-oxo-2*H*-chromen-4-yl 4-nitrobenzenesulfonate **1** (173 mg, 0.5 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 5 mol%), CuI (4.7 mg, 5 mol%), 1-hexyne (72 μL, 0.63 mmol) and DIPEA (109 μL, 0.625 mmol) were stirred at room temperature during 4h and gave **11** (103 mg, 0.455 mmol, 91 %) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.99 (t, *J* = 7.3 Hz, 3H), 1.53 (m, *J* = 7.3 Hz, 2H), 1.68 (tt, *J* = 7.3 and 7.1 Hz, 2H), 2.57 (t, *J* = 7.1 Hz, 2H), 6.49 (s, 1H), 7.28-7.33 (m, 2H), 7.54 (ddd, *J* = 8.2, 7.5 and 1.6 Hz, 1H), 7.84 (dd, *J* = 8.2 and 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 13.6 19.5, 22.1, 30.3, 74.8, 105.0, 116.9, 118.2, 118.8, 124.3, 126.7, 127.8, 132.0, 138.0, 153.5; consistent with literature data.[27c]

*4.1.3. 4-(Pent-1-ynyl)-2H-chromen-2-one (**12**)*

Following the *general procedure*, 2-oxo-2*H*-chromen-4-yl 4-nitrobenzenesulfonate **1** (173 mg, 0.5 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 5 mol%), CuI (4.7 mg, 5 mol%), 1-pentyne (59 μL, 0.6 mmol) and DIPEA (109 μL, 0.625 mmol) were stirred at room temperature during 5 h and gave **12** (74 mg, 0.35 mmol, 70 %) as a brown solid. TLC Rf 0.23 (Cyclohexane/EtOAc 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.10 (t, *J* = 7.3 Hz, 3H), 1.73 (m, *J* = 7.3 Hz, 2H), 2.55 (t, *J* = 7.3 Hz, 2H), 6.48 (s, 1H), 7.27- 7.33 (m, 2H), 7.53 (ddd, *J* = 7.8, 7.8 and 1.6 Hz, 1H), 7.85 (dd, *J* = 8.1 and 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 13.8, 22.0, 22.0, 75.2, 105.0, 117.1, 118.5, 119.1, 124.5, 126.9, 132.3, 138.3, 153.8, 160.6; HR-MS 235.073 ($C_{14}H_{12}O_2$ + Na^+ calcd 235.073).

*4.1.4. 4-(Prop-1-ynyl)-2H-chromen-2-one (**13**)*

Following the *general procedure*, 2-oxo-2*H*-chromen-4-yl 4-nitrobenzenesulfonate **1** (173 mg, 0.5 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 5 mol%), CuI (4.7 mg, 5 mol%), propyne (1-2 bar, recharged after 1 h) and DIPEA (109 μL, 0.625 mmol) were stirred at room temperature during 2 h and gave **13** (49 mg, 0.27 mmol, 54 %) as a brown solid. TLC Rf 0.19 (Cyclohexane/EtOAc 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.23 (s, 3H), 6.49 (s, 1H), 7.27-7.34 (m, 2H), 7.54 (ddd, *J* = 7.8, 7.8 and 1.6 Hz, 1H), 7.86 (dd, *J* = 8.1 and 1.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 5.2, 74.2,

100.7, 117.1, 118.5, 119.0, 124.5, 127.0, 132.3, 138.3, 153.7, 160.7; HR-MS 207.044 ($C_{12}H_8O_2$ + Na^+ calcd 207.042).

*4.1.5. 4-(Cyclohexylethynyl)-2H-chromen-2-one (**14**)*

Following the *general procedure*, 2-oxo-2*H*-chromen-4-yl 4-nitrobenzenesulfonate **1** (173 mg, 0.5 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 5 mol%), CuI (4.7 mg, 5 mol%), cyclohexylacetylene (79 µL, 0.6 mmol) and DIPEA (109 µL, 0.625 mmol) were stirred at room temperature during 1 h and gave **14** (116 mg, 0.46 mmol, 92 %) as a brown solid. TLC Rf 0.28 (Cyclohexane/EtOAc 9/1); mp 60-61°C; IR ν_{max} 3064, 2933, 2924, 2845, 2221, 2209, 1718, 1603, 1555, 1484, 1460, 1448, 1369, 1323, 1302, 1273, 1251, 1238, 1174, 1152, 1139, 1105, 1030, 980, 950, 922, 887, 871, 843, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.35-1.48 (m, 3H), 1.55-1.68 (m, 3H), 1.73-1.84 (m, 2H), 1.90-2.00 (m, 2H), 2.76 (m, 1H), 6.48 (s, 1H), 7.28-7.33 (m, 2H), 7.53 (ddd, *J* = 8.3, 7.4 and 1.6 Hz, 1H), 7.84 (dd, *J* = 8.3 and 1.6, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 25.0, 25.9, 30.3, 32.4, 75.0, 109.1, 117.1, 118.3, 119.1, 124.5, 126.9, 132.2, 138.3, 153.8, 160.7; HR-MS 253.124 ($C_{17}H_{16}O_2S$ calcd 253.122).

*4.1.6. 4-(Cyclohex-1-enylethynyl)-2H-chromen-2-one (**15**)*

Following the *general procedure*, 2-oxo-2*H*-chromen-4-yl 4-nitrobenzenesulfonate **1** (173 mg, 0.5 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 5 mol%), CuI (4.7 mg, 5 mol%), 1-ethynylcyclohexene (76 µL, 0.65 mmol) and DIPEA (109 µL, 0.625 mmol) were stirred at room temperature during 2 h and gave **15** (109 mg, 0.43 mmol, 87 %) as a brown solid. mp 92-93°C; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.64-1.70 (m, 2H), 1.70-1.76 (m, 2H), 2.19-2.26 (m, 2H), 2.27-2.33 (m, 2H), 6.47 (tt, *J* = 4.2 and 1.9 Hz, 1H), 6.50 (s, 1H), 7.31 (ddd, *J* = 8.4, 7.3 and 1.6 Hz, 1H), 7.32 (dd, *J* = 7.7 and 1.6 Hz, 1H), 7.54 (ddd, *J* = 8.4, 7.3 and 1.6 Hz, 1H), 7.84 (dd, *J* = 7.7 and 1.6 Hz, 1H) ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 21.5, 22.3, 26.3, 29.0, 80.9, 117.2, 118.8, 120.1, 124.5, 126.9, 132.3, 138.0, 140.3; HR-MS 273.090 ($C_{17}H_{14}O_2$ + Na^+ calcd 273.089).

*4.1.7. 4-(3-Hydroxyprop-1-ynyl)-2H-chromen-2-one (**17**)*

Following the *general procedure*, 2-oxo-2*H*-chromen-4-yl 4-nitrobenzenesulfonate **1** (173 mg, 0.5 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 5 mol%), CuI (4.7 mg, 5 mol%), propargyl alcohol (38 µL, 0.65 mmol) and DIPEA (109 µL, 0.625 mmol) were stirred at room temperature during 14 h and gave **17** (10 mg, 0.05 mmol, 10 %) as a yellow powder. TLC R*f* 0.23 (Cyclohexane/Et_2O 7/3); mp 89-91°C; IR ν_{max} 3265, 2924, 2851, 1671, 1604, 1557, 1530, 1442, 1372, 1349, 1278, 1260, 1229, 1191, 1138, 1100, 1016, 970, 950, 914, 877, 856, 811 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 4.64 (s, 2H), 6.56 (s, 1H), 7.32 (ddd, *J* = 8.3, 7.7 and 1.3 Hz, 1H), 7.33 (dd, *J* = 7.2 and 1.3 Hz, 1H), 7.56 (ddd, *J* = 8.3, 7.2 and 1.3 Hz, 1H), 7.85(dd, *J* = 7.7 and 1.3 Hz, 1H); HR-MS 223.036 ($C_{12}H_8O_3$ + Na^+ calcd 223.037).

*4.1.8. 4-(3-(tert-Butyldiphenylsilyloxy)prop-1-ynyl)-2H-chromen-2-one (**18**)*

Following the *general procedure*, 2-oxo-2*H*-chromen-4-yl 4-nitrobenzenesulfonate **1** (173 mg, 0.5 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 5 mol%), CuI (4.7 mg, 5 mol%), tert-butyldiphenyl(prop-2-yn-1-yloxy)silane (191 mg, 0.65 mmol) and DIPEA (109 µL, 0.625 mmol) were stirred at room temperature during 14 h and gave **18** (147 mg, 3.3 mmol, 67 %) as a brown oil. TLC R*f* 0.20 (Cyclohexane/Et_2O 8/2); IR ν_{max} 3070, 2929, 2856, 1721, 1605, 1557, 1488, 1471, 1450, 1427, 1369, 1323, 1274, 1253, 1230, 1178, 1137, 1105, 1075, 1031, 997, 932, 860, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.10 (s, 9H), 4.67 (s, 2H), 6.40 (s, 1H), 7.26 (ddd, *J* = 7.9, 7.3 and 1.2 Hz, 1H), 7.31 (dd, *J* = 8.3 and 1.2 Hz, 1H), 7.38-7.48 (m, 6H), 7.54 (ddd, *J* = 8.3, 7.3 and 1.4 Hz, 1H), 7.70 (dd, *J* = 7.9 and 1.4 Hz, 1H), 7.72-7.77 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.4, 26.9, 53.3, 79.0, 101.1, 117.1, 118.5, 119.1, 124.6, 126.9, 128.1, 130.3, 132.4, 132.9, 135.9, 137.1, 153.7, 160.3; HR-MS 461.154 ($C_{28}H_{26}O_3Si$ + Na^+ calcd 461.154).

*4.1.9. 4-(3-Hydroxy-3-methylbut-1-ynyl)-2H-chromen-2-one (**19**)*

Following the *general procedure*, 2-oxo-2*H*-chromen-4-yl 4-nitrobenzenesulfonate **1** (173 mg, 0.5 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 5 mol%), CuI (4.7 mg, 5 mol%), 2-methyl-3-butyn-2-ol (63 µL, 0.65 mmol) and DIPEA (109 µL, 0.625 mmol) %) were stirred at room temperature during 4 h and gave **19** (102 mg, 4.45 mmol, 89 %) as a yellow powder. TLC R*f* 0.25 (Cyclohexane/Et_2O 7/3); mp 93-94°C; IR ν_{max} 3422, 3199, 2983, 1690, 1600, 1554, 1487, 1445, 1396, 1364, 1326, 1273, 1245,1210, 1169, 1128, 1029, 964, 947, 894, 858, 843 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.70 (s, 6H), 1.94 (bs, 1H), 6.53 (s, 1H), 7.32 (ddd, *J* = 7.4, 7.1 and 1.6 Hz, 1H), 7.32 (dd, *J* = 7.1 and 1.6 Hz, 1H), 7.55 (ddd, *J* = 8.1, 7.4 and 1.6 Hz, 1H), 7.80 (dd, *J* = 8.1 and 1.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 31.3, 76.1, 84.2, 107.0, 117.2, 118.5, 119.1, 124.7, 126.8, 132.6, 137.0, 153.8, 160.3; HR-MS 251.067 ($C_{14}H_{12}O_2$ + Na^+ calcd 251.068).

*4.1.10. 4-(3-Hydroxy-4-methylpent-1-ynyl)-2H-chromen-2-one (**20**)*

Following the *general procedure*, 2-oxo-2*H*-chromen-4-yl 4-nitrobenzenesulfonate **1** (173 mg, 0.5 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 5 mol%), CuI (4.7 mg, 5 mol%), 4-methylpent-1-yn-3-ol (64 µL, 0.6 mmol) and DIPEA (109 µL, 0.625 mmol) were stirred at room temperature during 6h and gave **20** (94 mg, 0.39 mmol, 77 %) as a yellow powder. TLC Rf 0.23 (Cyclohexane/EtOAc 7/3); mp 83-84°C; IR ν_{max} 3505, 3071, 2967, 2932, 2872, 2225, 1710, 1606, 1556, 1487, 1472, 1452, 1373, 1326, 1275, 1253, 1235, 1182, 1144, 1113, 1100, 1032, 959, 940, 896, 860, 836, 808 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.11 (d, *J* = 6.8 Hz, 3H), 1.13 (d, *J* = 6.8 Hz, 3H), 2.08 (dm, *J* = 6.8 and 5.6 Hz, 1H), 2.17 (bs, 1H), 4.53 (d, *J* = 5.6 Hz, 1H), 6.55 (s, 1H), 7.31 (ddd, *J* = 7.6, 7.5 and 1.6 Hz, 1H), 7.32 (dd, *J* = 7.5 and 1.6 Hz, 1H), 7.55 (ddd, *J* = 8.0, 7.6 and 1.6 Hz, 1H), 7.82 (dd, *J* = 8.0 and 1.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 17.9, 18.4, 34.8, 68.6, 79.3, 102.6, 117.3, 118.5, 119.3, 124.7, 126.8, 132.6, 137.1, 153.8, 160.3; HR-MS 265.084 ($C_{15}H_{14}O_3$ calcd + Na^+ 265.084).

*4.1.11. 4-(6-Hydroxyhex-1-ynyl)-2H-chromen-2-one (**21**)*

Following the *general procedure*, 2-oxo-2*H*-chromen-4-yl 4-nitrobenzenesulfonate **1** (173 mg, 0.5 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 5 mol%), CuI (4.7 mg, 5 mol%), 5-hexyn-1-ol (72 µL, 0.65 mmol) and DIPEA (109 µL, 0.625 mmol) were stirred at room temperature during 6 h and gave **21** (86 mg, 0.36 mmol, 71 %) as a white solid. TLC R*f* 0.13 (Cyclohexane/EtOAc 7/3); mp 50-51°C; IR ν_{max} 3321, 3068, 2940, 2223, 1711, 1682, 1603, 1555, 1485, 1449, 1420, 1373, 1329, 1273, 1256, 1179, 1136, 1103, 1049, 1031, 984, 936, 858, 813 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.74- 1.84 (m, 4H), 2.62 (t, *J* = 6.8 Hz, 2H), 3.74 (t, *J* = 5.7 Hz, 2H), 6.48 (s, 1H), 7.27-7.33 (m, 2H), 7.53 (ddd, *J* = 8.3, 7.4 and 2.0 Hz, 1H), 7.83 (dd, *J* = 8.1 and 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.9, 24.9, 32.1, 62.4, 75.3, 104.7, 117.1, 118.5, 118.9, 124.6, 126.9, 132.3, 138.2, 153.7, 160.6; HR-MS 265.084 ($C_{15}H_{14}O_3$ + Na^+ calcd 265.084).

*4.1.12. 2-(4-(2-Oxo-2H-chromen-4-yl)but-3-ynyl)isoindoline-1,3-dione (**22**)*

Following the *general procedure*, 2-oxo-2*H*-chromen-4-yl 4-nitrobenzenesulfonate **1** (173 mg, 0.5 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 5 mol%), CuI (4.7 mg, 5 mol%), *N*-(3-butynyl)phthalimide (129 mg, 0.65 mmol) and DIPEA (109 µL, 0.625 mmol) were stirred at room temperature during 6 h and gave **22** (119 mg, 3.45 mmol, 69 %) as a white solid. TLC R*f* 0.13 (Cyclohexane/EtOAc 7/3); mp 169-170°C; IR ν_{max} 3035, 2227, 1767, 1701, 1608, 1558, 1487, 1463, 1397, 1374, 1359, 1346, 1298, 1277, 1252, 1233, 1159, 1115, 1089, 1072, 1032, 1020, 986, 963, 934, 884, 852 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 3.01 (t, *J* = 6.8 Hz, 2H), 4.05 (t, *J* = 6.8 Hz, 2H), 6.44 (s, 1H), 7.23 (ddd, *J* = 8.1, 7.4 and 1.2 Hz, 1H), 7.28 (dd, *J* = 8.1 and 1.2 Hz, 1H), 7.52 (ddd, *J* = 8.2, 7.4 and 1.7 Hz, 1H), 7.73-7.76 (m, 3H), 7.86-7.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 20.1, 36.3, 76.6, 100.0, 117.1, 118.7, 119.2, 123.7, 124.5, 127.0, 132.1, 132.4, 137.5, 153.7, 160.4, 168.0; HR-MS 366.075 ($C_{21}H_{13}NO_4 + Na^+$ calcd 366.074).

*4.1.13. 3-(Hex-1-ynyl)-5,5-dimethylcyclohex-2-enone (**23**)*

Following the *general procedure*, 5,5-dimethyl-3-oxocyclohex-1-en-1-yl 4-nitrobenzenesulfonate **2** (162 mg, 0.5 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 5 mol%), CuI (4.7 mg, 5 mol%), 1-hexyne (72 µL, 0.63 mmol) and DIPEA (109 µL, 0.625 mmol) were stirred at room temperature during 2 h and gave **23** (90 mg, 0.44 mmol, 88 %) as a brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.93 (t, *J* = 7.3 Hz, 3H), 1.05 (s, 6H), 1.43 (m, *J* = 7.3 Hz, 2H), 1.55 (tt, J = 7.3 and 7.1 Hz, 2H), 2.23 (s, 2H), 2.29 (d, J = 1.6 Hz, 2H), 2.40 (t, *J* = 7.1 Hz, 2H), 6.13 (t, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 13.8, 19.7, 22.2, 28.3, 30.6, 33.9, 45.0, 51.3, 80.9, 102.2, 131.0, 142.6, 190.4, 199.4; consistent with literature data.[28]

*4.1.14. 3-(3-Hydroxyprop-1-ynyl)-5,5-dimethylcyclohex-2-enone (**24**)*

Following the *general procedure*, 5,5-dimethyl-3-oxocyclohex-1-en-1-yl 4-nitrobenzenesulfonate **2** (162 mg, 0.5 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 5 mol%), CuI (4.7 mg, 5 mol%), propargyl alcohol (38 µL, 0.65 mmol), and DIPEA (109 µL, 0.625 mmol) were stirred at room temperature during 1 h and gave **24** (88 mg, 0.494 mmol, 99 %) as a clear oil. TLC R*f* 0.21 (Cyclohexane/EtOAc 7/3); IR ν_{max} 3407, 2958, 2218, 1657, 1594, 1470, 1355, 1278, 1243, 1213, 1164, 1143, 1120, 1034, 997, 967, 901, 870, 849 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.05 (s, 6H), 2.26 (s, 2H), 2.32 (d, *J* = 1.6 Hz, 2H), 2.68 (bs, 1H), 4.47 (d, *J* = 5.8 Hz , 2H), 6.21 (t, *J* = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 28.3, 34.0, 44.4, 51.1, 51.5, 84.8, 98.3, 131.7, 141.3, 199.7; HR-MS 201.088 ($C_{11}H_{14}O_2 + Na^+$ calcd 201.089).

*4.1.15. 3-(Prop-1-ynyl)-5,5-dimethylcyclohex-2-enone (**25**)*

Following the *general procedure*, 5,5-dimethyl-3-oxocyclohex-1-en-1-yl 4-nitrobenzenesulfonate **2** (162 mg, 0.5 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 5 mol%), CuI (4.7 mg, 5 mol%), propyne (1-2 bar) and DIPEA (109 µL, 0.625 mmol) were stirred at room temperature during 2 h and gave **25** (63 mg, 0.39 mmol, 78 %) as a yellow liquid. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.04 (s, 6H), 2.05 (s, 3H), 2.23 (s, 2H), 2.23 (d, *J* = 1.8 Hz, 2H), 6.13 (t, *J* = 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 5.1, 28.3, 33.9, 44.8, 51.2, 80.0, 97.7, 131.1, 142.6, 199.6; HR-MS 185.094 ($C_{11}H_{14}O + Na^+$ calcd 185.094).

*4.1.16. (E)-3-Methyl-1-phenyloct-2-en-4-ynone (**26**)*

Following the *general procedure*, (*E*)-4-oxo-4-phenylbut-2-en-2-yl 4-nitrobenzenesulfonate **5E** (27 mg, 77.7 µmol), $PdCl_2(PPh_3)_2$ (2.8 mg, 5 mol%), CuI (0.8 mg, 5 mol%), pentyne (10 µL, 93.3 µmol) and DIPEA (17 µL, 97.2 µmol) were stirred at room temperature during 2 h and gave **26** (8.9 mg, 42.0 µmol, 54 %) as brown oil. TLC R*f* 0.48 (Cyclohexane/EtOAc 8/2); IR ν_{max} ;^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.03 (t, *J* = 7.3 Hz, 3H), 1.62 (p, *J* = 7.3 Hz, 2H), 2.33 (d, *J* = 1.4 Hz, 3H), 2.38 (t, *J* = 7.0 Hz, 2H), 7.08 (d, *J* = 1.7 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.90-7.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 13.7, 21.3, 21.8, 22.1, 84.3, 96.7, 127.3, 128.3 (x2), 128.7 (x2), 132.8, 138.9, 139.1, 190.9. HR-MS 213.1289 ($C_{15}H_{16}O + H^+$ calcd 213.1274).

*4.1.17. (E)-5-Cyclohexyl-3-methyl-1-phenylpent-2-en-4-ynone (**27**)*

Following the *general procedure*, (*E*)-4-oxo-4-phenylbut-2-en-2-yl 4-nitrobenzenesulfonate **5E** (37 mg, 106.5 µmol), $PdCl_2(PPh_3)_2$ (3.9 mg, 5 mol%), CuI (1.1 mg, 5 mol%), cyclohexylacetylene (18 µL, 128 µmol) and DIPEA (25 µL, 133 µmol) were stirred at room temperature during 2 h and gave **27** (17.5 mg, 69 µmol, 63 %) as brown oil. TLC Rf 0.47 (Cyclohexane/EtOAc 8/2); IR ν_{max} ; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.34 (td, *J* = 10.3 and 4.1 Hz, 4H), 1.51 (tdd, *J* = 12.5, 5.2 and 3.0 Hz, 2H), 1.73 (dtd, *J* = 11.5, 7.7, 6.6 and 3.5 Hz, 2H), 1.85 (dq, *J* = 12.6 and 3.5 Hz, 2H), 2.34 (d, *J* = 1.4 Hz, 3H), 2.57 (tt, *J* = 8.3 and 3.5 Hz, 1H), 7.07 (q, *J* = 1.5 Hz, 1H), 7.43-7.48 (m, 2H), 7.50-7.57 (m, 1H), 7.92- 7.96 (m, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 21.5, 25.0, 25.9, 29.9, 30.0, 32.5, 84.1, 100.9, 127.2, 128.3 (x2), 128.7 (x2), 132.7, 139.0, 139.3, 190.9. HR-MS 253.1580 ($C_{18}H_{20}O + H^+$ calcd 253.1587).

*4.1.18. 4-(Hex-1-ynyl)-2(5H)-furanone (**28**)*

Following the *general procedure*, 5-oxo-2,5-dihydrofuran-3-yl 4-nitrobenzenesulfonate **3** (142 mg, 0.5 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 5 mol%), CuI (4.7 mg, 5 mol%), 1-hexyne (75 µL, 0.65 mmol), and DIPEA (109 µL, 0.625 mmol) were stirred at room temperature during 2 h and gave **28** (68 mg, 0.415 mmol, 83 %) as a brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.94 (t, *J* = 7.3 Hz, 3H), 1.43 (m, *J* = 7.3 Hz, 2H), 1.58 (tt, *J* = 7.3 and 7.1 Hz, 2H), 2.45 (t, *J* = 7.1 Hz, 2H), 4.76 (d, *J* =1.9 Hz, 2H), 6.08 (t, *J* = 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 13.7, 19.8, 22.2, 30.2, 71.7, 73.5, 108.4, 121.6, 148.4, 158.8; consistent with literature data.[27a]

*4.1.19. 4-(Prop-1-ynyl)-2(5H)-furanone (**29**)*

Following the *general procedure*, 5-oxo-2,5-dihydrofuran-3-yl 4-nitrobenzenesulfonate **3** (142 mg, 0.5 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 5 mol%), CuI (4.7 mg, 5 mol%), propyne (1-2 bar), and DIPEA (109 µL, 0.625 mmol) were stirred at room temperature during 4 h and gave **29** (65 mg, 0.265 mmol, 58 %) as a brown oil. TLC R*f* 0.27 (Cyclohexane/EtOAc 8/2); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.12 (s, 3H), 4.76 (d, *J* = 2.0 Hz, 2H), 6.09 (t, *J* = 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 5.2, 71.0, 73.4, 104.0, 121.7, 148.4, 173.9; HR-MS 145.026 ($C_7H_6O_2 + Na^+$ calcd 145.026).

*4.1.20. 4-(3-Hydroxy-4-methylpent-1-ynyl)-2(5H)-furanone (**30**)*

Following the *general procedure*, 5-oxo-2,5-dihydrofuran-3-yl 4- nitrobenzenesulfonate **3** (142 mg, 0.5 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 5 mol%), CuI (4.7 mg, 5 mol%), 4-methylpent-1-yn-3-ol (69 µL, 0.65 mmol) and DIPEA (109 µL, 0.625 mmol) were stirred at room temperature during 5 h and gave **30** (66 mg, 3.65 mmol, 73 %) as a brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.02 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.97 (m, *J* = 6.8 Hz, 1H), 2.31 (d, *J* = 5.6 Hz, 1H), 4.40 (t, *J* = 5.6 Hz, 1H), 4.80 (d, *J* = 2.0 Hz, 2H), 6.18 (t, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 18.0, 18.2, 34.6, 68.5, 73.2, 75.8, 105.9, 123.0, 147.0, 173.4.

*4.1.21. Cleviolide (**31**)*

Phosphorous pentoxide (2.5 equiv) was portionwise added to a solution of **30** (0.2 mmol) in benzene (3 mL). The mixture was stirred at reflux during 2 h and was then allowed to cool to room temperature. The mixture was filtered over celite and the solvent evaporated to dryness. Crude was recrystallized from AcOEt:hexane to afford cleviolide **31** (81 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.91 (d, J = 1.2 Hz 3H), 1.96 (s, 3H), 4.82 (d, J = 2.0 Hz, 2H), 5.49 (q, J = 1.2 Hz, 1H), 6.11 (t, J = 2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 21.9, 25.6, 73.2, 81.9, 104.2, 104.4, 120.7, 148.0, 155.4, 173.9; consistent with literature data.[26c-d]

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Appendix A. Supplementary data

Supplementary data related to this article can be found at …

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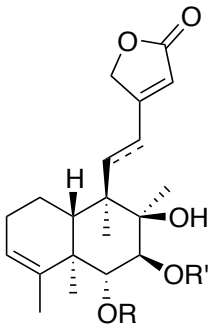
Furanone Natural Products



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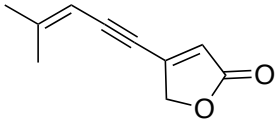

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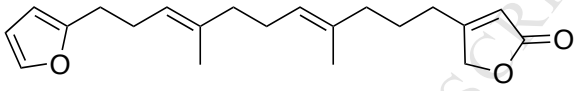

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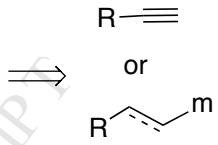

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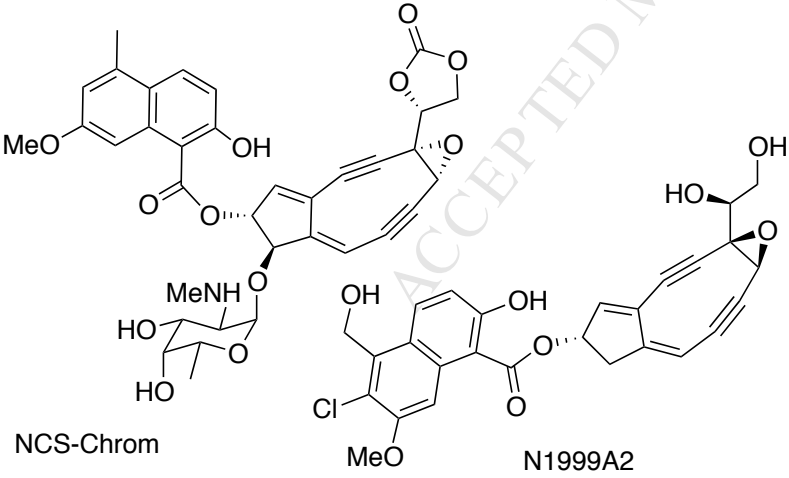

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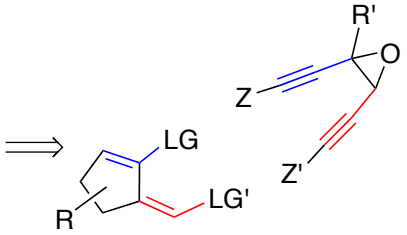

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