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Structural modification and biological activity studies of tagitinin C and its derivatives

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ABSTRACT

The Michael addition reaction of amines, phosphonates and thiols to Tagitinin C containing in its structure an α-methylene-γ-lactone motif and two α,β-unsaturated ketone systems has been described. 27 Tagitinin C derivatives were synthesized and isolated in good to excellent yield (up to 99% yield) under mild reaction conditions. The biological activity of Tagitinin C and its derivatives were evaluated against three human cancer cell lines (breast human cancer cells MCF-7, breast human cancer cells multi-resistant to drugs MCF7-MDR, pancreas cancer cells MiaPaCa-2) and on normal cell line (HEK-293) as control. We showed that the biological activity of Tagitinin C derivatives is remained. These compounds presented an enhanced water solubility that could improve their bioavailability and their pharmacological profiles.

1. Introduction

Tagitinin C (TC) is a germacranolide sesquiterpene lactone that is extracted from Tithonia diversifolia whose structure is well established as reported in the literature (Fig. 1) [1]. TC is described as the active component of a wide variety of biological and pharmacological properties such as antimicrobial [2a], anti-inflammatory [2b,c], cytotoxic [2d], antiviral, antibacterial, antifungal [2e], allelopathic activities [2f], effects on the central nervous and cardiovascular systems as well as anti-proliferative on various cancer cells [2g-i]. Their wide structural diversity and biological activity potential have made further interest to organic and medicinal chemists.

Several studies have been reported concerning the structural modifications of the α-methylene-γ-butyrolactone motif of sesquiterpene lactones. Among these synthetic approaches, the Michael addition reaction of amines to β position of α,β-unsaturated lactones has been much investigated. This prodrug method has transformed several sesquiterpene lactones such as ambrosin, arglabin, costunolide, parthenolide, zaluzanin C and zaluzanin D into successful clinical candidates [3]. As suggested in almost cases, introduction of a nitrogen atom containing functionality at β position of sesquiterpene lactone makes it possible to create an additional hydrogen bonding potential and to control the selectivity of the formed stereocenter. This can lead to new derivatives which are able of enhancing aqueous solubility, improving the pharmacokinetic profile, and maintaining or even increasing the biological activity of the parent molecules [4]. To our knowledge, only one patent relating to the preparation of Tagitinin C and F derivatives has been reported. However, in almost all cases, a mixture of aza-Michael adducts, resulting from addition to α,β-unsaturated ketone and α-methylene-γ-butyrolactone, was obtained [5].

We report herein the chemo-, regio- and stereoselective Michael addition reaction of amines, phosphonates and thiols to α,β-unsaturated ketone and α-methylene-γ-butyrolactone motifs of Tagitinin C. The diverse biological activities of these new Michael adducts will be evaluated and compared to parent Tagitinin C.

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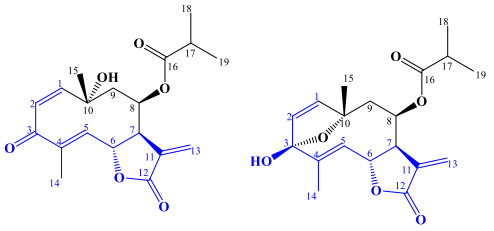


Fig. 1. Structure of tagitinin C (left) and tagitinin F (right).

2. Results and discussion

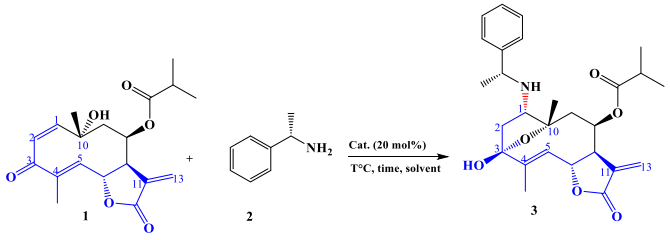
2.1. aza-Michael addition reaction of a primary amine to β position of α,β-unsaturated ketone motif of tagitinin C **1**

Conjugate addition reaction of nucleophiles to electron-deficient olefins, usually called Michael addition, is one of the fundamental bond-forming processes in the area of heterocyclic chemistry [6]. The aza-Michael addition reaction of a primary or secondary amine to an α,β-unsaturated ketone is very well documented and represents an extremely powerful tool for the synthesis of a variety of useful functionalized organic molecules for medicinal chemistry [4a,7].

We began our investigation by establishing the optimal reaction conditions for the catalytic aza-Michael addition of (*S*)-1-phenylethanamine **2** to TC **1** (Scheme 1). The catalytic trials were carried out using TC **1** (0.67 mmol), amine **2** (0.8 mmol, 1.2 equiv.), catalyst (20 mol%) in an organic solvent. The reaction conversion was monitored by ^{1}H NMR. Some significant results were presented in Table 1.

Initial investigations showed a significant impact of the nature of catalyst and solvent on the yield of expected product. As indicated in Table 1, when the reaction was performed using CAN (Ceric Ammonium Nitrate) as catalyst [8], whatever temperature, a mixture of unidentified products, probably due to the degradation of the substrate or other transformations, was observed by ^{1}H NMR analysis. Et_3N led to the formation of expected product in moderate yields (45–51%) using MeOH as solvent (Entries 3, 4). The best result was obtained when the reaction was carried out in DCM (CH_2Cl_2) along with 1 equiv. of amine **2** at 0 °C. In these reaction conditions, TC derivative **3** was isolated in 91% yield as a single isomer (Entry 5). A small amount of TC **1** was detected (less than 4%) by ^{1}H NMR of crude product due to a retro-Michael reaction during the work-up. This reaction was accelerated during purification of adduct **3** by chromatography on silica gel which could contaminate the purity of **3** as observed in some cases [9].

The results obtained showed that the addition of amine **2** to TC **1** was found to be highly chemo-, and regioselective as in almost all cases only adduct **3**, resulting from the addition of amine **2** to β position of α,β-unsaturated ketone 1,3-motif, was observed. No trace of other aza-Michael adducts was detected. This could be explained by the fact that ketone is more reactive than lactone and the α,β-unsaturated ketone-1,3 motif is less bulky than α,β-unsaturated ketone-5,3 due to the presence of a methyl group in position 4. It should be noted that, at higher temperature (30 °C), a mixture of aza-Michael adducts was detected. The structure of **3** was clearly determined by NMR analysis studies and mass spectrometry measurements. The stereochemistry of C-1 position in compound **3** was assigned by its NOESY experiment. The NOESY spectrum of compound **3c** showed a nuclear Overhauser effect (NOE) correlations between Me-15 and H-1 (see Supporting information for full details). On the other hand, the α attack of amine can be explained by the steric hindrance created by the methyl group on C-10 position, and the possibility of the formation of hydrogen bonding between the hydroxyl group OH-10 and an amine function which makes the α orientation more favorable. Moreover, the formation of C-3, C-10 ether bridge in the saturated cyclic ketone motif is easily obtained, and this structure is also well-known by biotransformation of the sesquiterpene lactone TC by the fungus Aspergillus terreus as reported in the literature [10].



Scheme 1. aza-Michael addition reaction of (*S*)-1-phenylethanamine **2** to TC **1**.

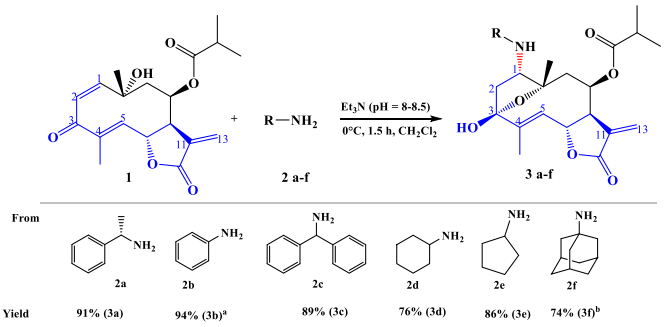
Table 1
Optimization of reaction conditions for the aza-Michael addition of (*S*)-1-phenylethanamine **2** to **1**.

Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	3 yield (%)[a]
1	CAN[b]	THF	60	32	nd
2	CAN	EtOH/H_2O	20	6	nd
3[c]	Et_3N	MeOH	20	2	45
4[c]	Et_3N	MeOH	0	1.5	51
5[c,d]	Et_3N	CH_2Cl_2	0	1.5	91

[a] Isolated yield.
[b] CAN: Ceric Ammonium Nitrate.
[c] Amount of Et_3N was adjusted at 8–8.5 pH.
[d] (*S*)-1-phenylethanamine **2**: 1 equiv.

Using primary amines **2b-f** as reagents under optimized reaction conditions previously described, a series of TC derivatives **3b-f** was isolated in good to excellent yields ranging from 74 to 94% with very high selectivity as only one product was detected in all cases (Scheme 2).

As illustrated in Scheme 2, addition of primary amines **2a-f** to TC **1** worked smoothly leading to the formation of expected products in good yields in all cases. In the case of amine **2f** (1-adamantanamine), no trace of expected product was detected even after 24 h using Et_3N as catalyst under standard reaction conditions. It can be explained by the less reactivity of 1-adamantanamine due to its steric hindrance. The reaction worked better when using DBU as a stronger basic catalyst, in this case, the



Scheme 2. aza-Michael addition reaction of primary amines **2a-f** to TC **1**. [a] DBU (20 mol%) was used as catalyst at 20 °C for 1.5 h; 90% yield with Et_3N at 0 °C for 3 h [b] DBU (20 mol%) was used as catalyst at 20 °C for 4 h; 0% conversion with Et_3N at 0 °C for 24 h.

adduct **3f** was isolated in 74% yield at 20 °C for 4 h. In the same way, better result was observed in the case of aromatic amine **2b** when using DBU as catalyst (94% yield at 20 °C for 1.5 h compared to 90% yield for 3 h with Et_3N as catalyst).

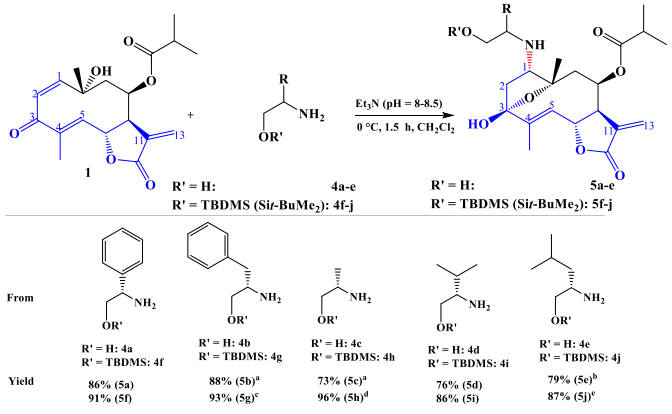
In the aim of our structure-activity relationship studies, a series of primary β-aminoalcohols **4a-e**, easily obtained from natural amino acids, and their O-silylated derivatives **4f-j** were then explored for the addition reaction to TC **1**. The incorporation of silicon moiety into known drug scaffolds can reduce toxicity, enhance biological activity in increasing the therapeutic potential of a drug, as reported in the literature [11]. Moreover, O-silyl function can be used as useful protecting groups for organic synthesis and prodrug strategies as the Si-OC bond is thermodynamically stable but dynamically labile in water and under acidic conditions. So, under standard reaction conditions described above (Et_3N, 0 °C, 1.5 h in DCM), 10 aza-Michael adducts **5a-j** were isolated in very good yields with excellent selectivity as expected (Scheme 3).

As showed in Scheme 3, the reaction worked well in all cases. In a few cases, reaction time was adjusted to achieve full conversions. No trace of oxa-Michael adduct was detected in these reaction conditions due to the higher nucleophilic character of the amino function compared to a hydroxyl one. In all cases, the O-silylated derivatives **4f-j** gave slightly better yields than the free hydroxyl functions **4a-e**, probably due to their greater stability with respect to a retro-Michael addition during the work-up.

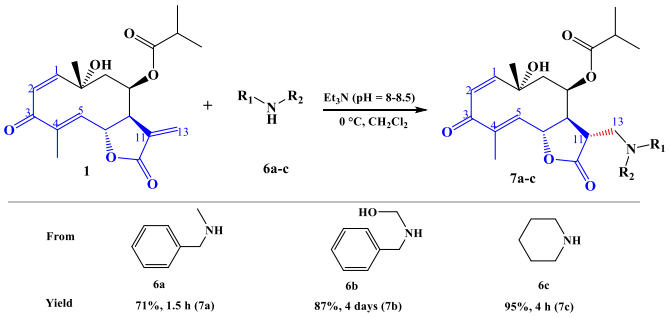
2.2. aza-Michael addition reaction of a secondary amine to β position of α,β-unsaturated-γ-lactone motif of tagitinin C **1**

Having these reaction conditions in hands, we were interested in studying the Michael addition of a secondary amine to TC **1**. A few secondary amines **6a-c** were explored for this reaction. Interestingly, in the courses of these processes, compound **7** was selectively isolated as a sole adduct, resulting from the addition of a secondary amine **6** to β position of α-methylene-γ-lactone substructure of Tagitinin C **1**. Good yields ranging from 71 to 95% were obtained. (Scheme 4).

As mentioned in the introduction part, the Michael addition reaction of amines to β position of α,β-unsaturated lactones motif of sesquiterpene lactones has been well documented. However, in our studies, for the first time, a highly chemo- and regioselective Michael addition reaction of an amine to TC **1** containing in its structure an α-methylene-γ-lactone motif and two α,β-unsaturated



Scheme 3. aza-Michael addition reaction of primary amines **4a-j** to TC **1**. [a] Reaction time: 4 h; [b] Reaction time: 6 h; [c] Reaction time: 5 h; [d] Reaction time: 46 h; [e] Reaction time: 7 h.



Scheme 4. aza-Michael addition reaction of secondary amines **6a-c** to TC **1**.

ketone systems has been described. Using a primary amine, only amine adduct, resulting from addition to α,β-unsaturated ketone motif was observed, while a secondary amine reacted on α-methylene-γ-lactone substructure. This could be explained by the fact that a secondary amine is more hindered than a primary amine and so that addition to monosubstituted-α,β-unsaturated ketone is more difficult, due to its hindrance, to α-methylene-γ-lactone which is less bulky.

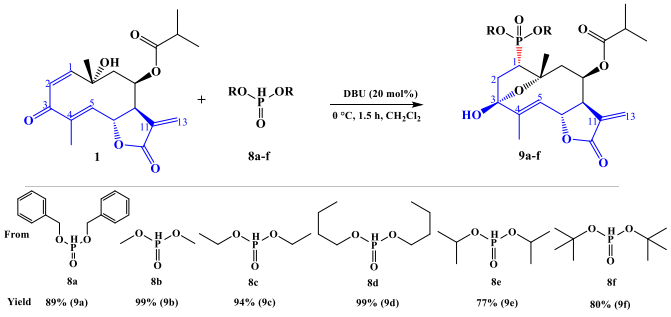
2.3. Highly selective addition of phosphonates and thiols to β position of α,β-unsaturated ketone motif of tagitinin C **1**

In a continuation of our research on the SAR studies, we next decided to develop the Michael addition reaction of some other nucleophiles such as phosphonates and thiols to TC **1**. For this purpose, 6 phosphonates more or less hindered and 2 thiols were chosen as reagents. The results obtained were presented in Schemes 5 and 6.

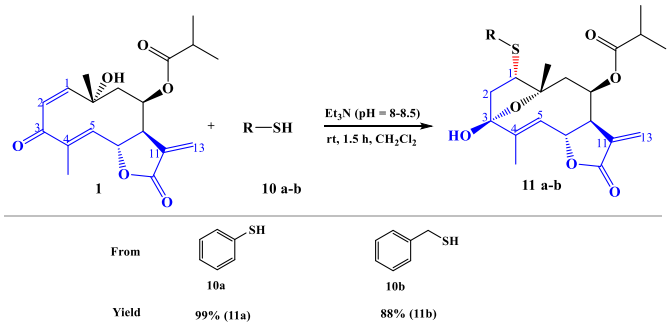
In the case of phosphonate nucleophiles, the reaction did not work at all under standard conditions (Et_3N, 0 °C, 1.5 h in DCM). On the other hand, when DBU was used as the basic catalyst instead of Et_3N, full conversions were observed in all cases. In these conditions, phospha-Michael adducts were isolated in good yields ranging from 77 to 99% (Scheme 5). Again, the addition of phosphonates to TC **1** proved to be very highly chemo-, regio- and stereoselective as only adduct, resulting from addition of phosphonate to β position of α,β-unsaturated ketone 1,3-motif of TC **1**, was detected as previously observed in the case of a primary amine.

In the same way, aromatic and aliphatic thiols **10a-b** were added selectively to TC **1** without complication under standard reaction conditions leading to the formation of expected products in excellent yields (Scheme 6).

The structures of all these molecules as well as their relative and absolute configurations of stereocenters were clearly determined



Scheme 5. Phospha-Michael addition reaction of phosphonates **8a-f** to TC **1**.



Scheme 6. Thia-Michael addition reaction of thiols **10a-b** to TC **1**.

by organic physical chemical analysis methods (see Supporting Information for full details).

To sum up, we have developed an efficient procedure for the synthesis of Tagitinin C derivatives via a highly chemo-, regio- and stereoselective Michael addition reaction of amines, phosphonates and thiols. These compounds were obtained in very good yields under mild reaction conditions. These Tagitinin C derivatives were next evaluated for their biological activities.

2.4. Biological activity studies of tagitinin C and its derivatives

We first tested the cytotoxic activity at 1 μM of TC **1** and seven of its derivatives against three human cancer cell lines (human breast cancer cells MCF-7, multi-resistant human breast cancer cells MCF7-MDR, pancreas cancer cells MiaPaCa-2) and on a normal cell line (human embryonic kidney cells HEK-293) as control. The cell viability was measured after 72 h of incubation at a concentration of 1 μM for each compound. As shown in Fig. 2, the new derivatives showed quite the same activity as TC **1** on each cell line except for the phosphonate derivative **9a** that showed very slight or no cytotoxicity whatever the cell line. In regard to the cell line, the new synthesized molecules and TC **1** were not active on MCF-7-MDR. This was not surprising as this cell line is one of the most resistant to drugs. Nonetheless, breast cancer cells were not very sensible to this family of compounds as the survival of cell is ranging between 52 and 80% at a concentration 1 μM.

The most sensitive cell line was the pancreatic one (MiaPaCa-2) as more than 80% of cancerous cells did not survive after 72 h of incubation. Moreover, at the tested concentration, the new derivatives were more cytotoxic than the parent drug TC **1** (22% cell viability for TC **1** versus 6.6%–21% for the new compounds).

These first results allowed us to choose MiaPaCa-2 as model cell line to evaluate the cytotoxicity profile of all the other compounds. The HEK cell line was also tested as non-cancerous cell line. For this second study, we chose two fixed concentration of 500 and 250 nM of drugs to evaluate their cytotoxicity. At 250 nM, all the tested compounds exhibited a lower or similar cytotoxicity on MiaPaCa-2 compared to TC **1** and the survival of cells ranged from 60.6% to 99.5% (See Supporting Information). Nevertheless, this concentration is not relevant as the observed inhibition are low. At 500 nM (Table 2), the results are more significant as the survival of MiaPaCa-2 cells is between 21.3% (**5b**) and 90.2% (**9a**).

Aza-Michael adducts **3a-f** obtained with primary amine, exhibited moderate cytotoxic activities compared to TC **1** except for **3e**, bearing a cyclopentyl group (only 27.6% of cell survival). Surprisingly, the structurally similar cyclohexyl adduct **3d** was the less active compound of the series. Moreover, the very bulky

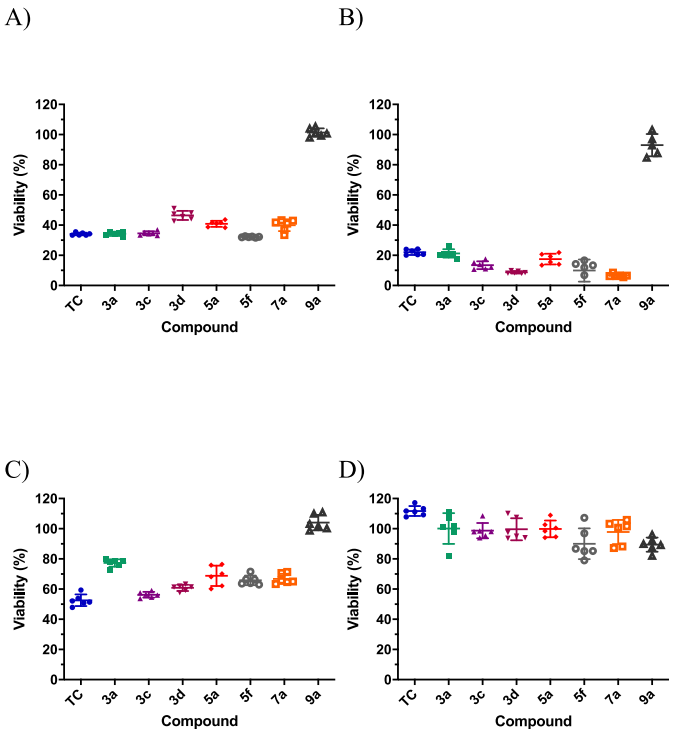


Fig. 2. Cell survival of selected compounds at a concentration of 1 μM after 72 h incubation on A) HEK, B) MiaPaCa-2, C) MCF-7, D) MCF7- MDR.

Table 2
Cytotoxicity of selected compounds on MiaPaCa-2, measured by the cell survival.

Compounds	logP[a]	Cell Survival (%) at 500 nM		SI[b]
		Miapaca-2	HEK	
TC 1	1.16	36.7 ± 2.9	32.0 ± 3.3	0.87
3a	3.09	46.3 ± 11.2	78.0 ± 11.7	**1.68**
3b	3.28	57.7 ± 4.8	67.4 ± 2.6	1.17
3c	4.05	44.8 ± 4.5	43.5 ± 3.2	0.97
3d	2.58	66.4 ± 12.9	65.6 ± 10.4	0.99
3e	2.18	27.6 ± 4.5	30.9 ± 3.2	1.12
3f	3.46	43.3 ± 1.6	39.0 ± 1.5	0.90
5a	2.09	34.6 ± 10.3	32.9 ± 2.7	0.95
5b	2.20	21.3 ± 3.0	33.4 ± 1.9	1.57
5c	1.05	23.1 ± 1.2	31.5 ± 2.0	1.36
5d	1.52	43.1 ± 3.6	44.3 ± 8.1	1.03
5e	2.14	NT	NT	
5f	5.07	53.0 ± 9.3	42.2 ± 3.1	0.80
5g	5.25	38.7 ± 4.6	41.0 ± 2.2	1.06
5h	4.29	47.1 ± 5.3	52.5 ± 5.1	1.11
5i	4.70	39.2 ± 4.9	43.4 ± 6.3	1.11
5j	5.02	47.1 ± 7.1	54.9 ± 2.7	0.95
7a	2.63	70.9 ± 14.1	83.3 ± 5.3	1.18
7b	1.72	50.3 ± 6.3	53.4 ± 6.9	1.06
7c	2.02	33.0 ± 2.5	38.5 ± 3.2	1.17
9a	3.85	90.2 ± 4.5	92.7 ± 6.9	1.03
9b	1.40	ND	ND	
9c	2.06	83.4 ± 14.2	92.9 ± 6.5	1.11
9d	3.07	ND	ND	
9e	2.52	ND	ND	
9f	3.31	82.3 ± 15.8	96.8 ± 9.8	1.18
11a	3.99	76.0 ± 17.4	86.1 ± 2.0	1.13
11b	3.77	58.2 ± 5.8	67.9 ± 3.8	1.17

ND: not determined.
[a] logP: Calculated logP with Virtual Computational Chemistry Laboratory, http://www.vcclab.org, 2005 [12].
[b] SI: Selectivity Index calculated from Cell Survival on HEK versus Miapaca cells at 500 nM.

adamantanyl derivative **3f** seems to have a negative effect on cytotoxicity. In this type of adducts, introduction of one (**3a**, **3b**) or more (**3c**) aromatic moieties in TC **1** structure provoked a decrease in the biological activity.

The second family of adducts studied was issued from the aza-Michael addition of primary β-aminoalcohols **5a-j**. These compounds exhibited more potent activities on MiaPaCa-2 cell survival. In this series, the most cytotoxic compounds were **5b** and **5c** bearing respectively a benzyl or a methyl moiety at the β-position in regard to the reactive amine (21.3% and 23.1% cell survival respectively.). Comparing the cytotoxicity of **5c** (methyl) with **5d** (isopropyl) and **5a** (phenyl), it seems that the enhancement of steric hindrance near the amine function has a negative effect on biological activity. The introduction of silica atom in our case did not enhance biological activity as most of the silylated derivatives are less active than their non silylated counterpart (**5a**/**5f**; **5b**/**5g**; **5c**/**5h**), suggesting a potential interaction between the hydroxyl group of the molecule and the cellular target of the drug.

In regard to adduct **7a,** obtained by addition of *N*-methylbenzylamine to the α-methylene-γ-lactone motif of TC **1**, the biological activity was much lower than that observed with TC **1** (70.9% vs 36.7% cell survival respectively). Adding a hydroxyl moiety on this structure (*N*-hydroxymethylbenzylamine **7b**), restored partially the biological activity (50.3% cell survival). This observation agreed with the enhancement observed with adducts obtained from primary β-aminoalcohols. Nevertheless, this alcohol moiety does not restore a good biological activity. Regarding the cyclic secondary amine **7c**, the cytotoxicity observed with this compound was similar to the TC **1**'s (33.0% vs 36.7% cell survival respectively).

Finally, phospha-Michael and thio-Michael adducts gave rise to inactive molecules whatever the substitutions of phosphonates or thiols (**9a**, **9c**, **9f**, **11a**, **11b**). This confirmed the previously observed results on different cell lines (Fig. 2).

The selectivity index (SI) is the ratio of MiaPaCa-2 survival on HEK survival and represents the selectivity of the cytotoxicity of a compound against cancerous cells compared to normal cells. The best selectivity index is obtained for compound **3a**. Despite its moderate cytotoxicity on MiaPaCa-2, **3a** is one of the most interesting compounds as its toxicity on normal cell is low. The IC_{50} of this compound was then evaluated on MiaPaCa-2 cell line (Fig. 3). As expected, the IC_{50} of **3a** is slightly worse than that of TC **1** (0.74 μM vs 0.36 μM respectively) but remained in the same order of magnitude.

Regarding the biological part of the study, we did not manage to improve significantly the cytotoxicity of TC **1** by introducing new moieties by Michael addition. Nevertheless, the biological activities of the new compounds remain in the same order than the parent molecule Tagitinin C. All synthesized Tagitinin C derivatives exhibit logPs between 1.05 and 5.25. These values are in line with the Lipinski's rules and should allowed the molecules to pass across tissue membranes. Thus, the bioavailability of these new compounds should be ensured [13].

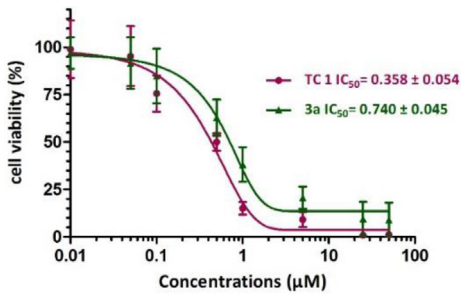


Fig. 3. IC_{50} of TC **1** and **3a** on MiaPaCa-2 cell line.

3. Conclusions

We have described, for the first time, the highly chemo-, and regioselective Michael addition reaction of amines, phosphonates and thiols to Tagitinin C. 27 new Tagitinin C derivatives were successfully synthesized in very good yields under mild reaction conditions. Using a primary amine, a phosphonate or a thiol, only Michael adduct, resulting from addition to α,β-unsaturated ketone motif was observed, while a secondary amine reacted on α-methylene-γ-lactone substructure of Tagitinin C. Although, we did not manage to improve significantly the cytotoxicity of these new Michael adducts, nevertheless, the biological activities of the compounds remain in the same order than the parent molecule Tagitinin C. Moreover, aminoalcohols derived from Tagitinin C presented an enhanced solubility in water that could improve their bioavailability and/or their pharmacological profiles. Development of new Tagitinin C derivatives *via* coupling reactions is currently under investigation in our laboratory.

4. Experimental section

4.1. General information

Proton NMR spectra were recorded on Bruker 250, 360 or 400 MHz spectrometers. Proton chemical shifts are reported in ppm (δ) relative to tetramethylsilane as internal reference (TMS, δ *ppm* = 0.0). *J* values are given in hertz (Hz). Carbon NMR spectra were recorded on Bruker 250 MHz (62.9 MHz), 300 MHz (75.45 MHz) or 360 MHz (90.6 MHz) spectrometers with complete proton decoupling. Flash column chromatography was performed using silica gel Merck (0.04–0.063 μm). High-resolution mass spectra were obtained with a MAT95 Thermo-Finnigan spectrometer using electrospray analysis. IR spectra were recorded on a FTIR spectrometer (PerkinElmer spectrum one, NaCl pellets or Bruker Vertex 70 ATR Pike Germanium) and are reported in cm^{-1}. Optical rotations were measured on an Anton Paar's MCP 150 polarimeter and reported as follows: $[\alpha]^{T}_{D}$ (concentration (g/100 mL), solvent).

All reactions were carried out in Schlenk tubes. All solvents were distilled from appropriate drying agents prior to use. All reagents are commercially available and were used without further purification except as indicated below.

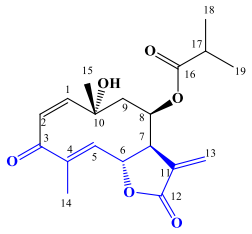
4.2. Characterization of compounds

4.2.1. Extraction and isolation of Tagitinin C

The dried leaves of *T. diversifolia* (500 g) were powdered and extracted 3 times with 5 L of dichloromethane at room temperature for 5 min. After evaporation of solvent under reduced pressure, the dry extract (TDD) was re-suspended in MeOH/H_2O (7/3), followed by partitioning with the same volume of *n*-hexane and dichloromethane, yielding two subfractions named TDD/CH_2Cl_2 (dichloromethane-soluble fraction) and TDD/*n*-hexane (*n*-hexane-soluble fraction). A silica gel column (6 × 100 cm) was packed using *n*-hexane as solvent. TDD/CH_2Cl_2 (~12 g) was coated with 10 g of silica gel and then subjected to chromatography column on silica gel with successive elution by a *n*-hexane/AcOEt and AcOEt/MeOH gradient. Subfractions with the same TLC pattern were combined and thus six fractions were obtained: *(a): 0–10% ethyl acetate/n-hexane (E/H), (b) 10–30% ethyl acetate/n-hexane, (c) 30–50% ethyl acetate/n-hexane, (d) 50–70% ethyl acetate/n-hexane, (e) 70–100% ethyl acetate/n-hexane, (f): 0–20% methanol/ethyl acetate.* The collected fractions were then concentrated under reduced pressure at 40 °C

using rotary evaporator. Tagitinin C (100 mg, with high purity of 97%) was observed in fraction (c) and isolated as a pale oil. ^{1}H and ^{13}C NMR spectra data are in agreement with that of literature [2i].

Tagitinin C (1):



$[\alpha]_D^{28} = -187.5$ (c = 1.2, MeOH), pale oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ *ppm* 6.96 (d, J = 17.1 Hz, 1H, H1), 6.35 (d, J = 2.0 Hz, 1H, Hα13), 6.25 (d, J = 17.0 Hz, 1H, H2), 5.87 (dd, J = 9.0, 2.0 Hz, 1H, H5), 5.81 (d, J = 1.5 Hz, 1H, Hβ13), 5.43 (d, J = 9.0 Hz, 1H, H6), 5.36 (ddd, J = 10.0, 6.0, 3.0 Hz, 1H, H8), 3.57 (s, 1H, H7), 2.48 (dd, J = 13.0, 5.5 Hz, 1H, Hα9), 2.48–2.38 (m, 2H, H17), 1.99 (d, J = 4.0 Hz, 1H, Hβ9), 1.95 (d, J = 1.0 Hz, 3H, H14), 1.53 (s, 3H, H15), 1.11–1.02 (m, 6H, H18, H19).

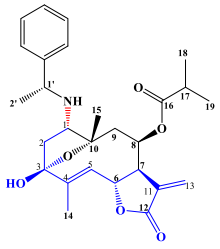
^{13}C NMR (75 MHz, CDCl$_3$) δ *ppm* 196.7 (C3), 176.2 (C16), 169.6 (C12), 159.9 (C1), 138.9 (C4), 137.1 (C5), 136.0 (C11), 129.6 (C2), 124.5 (C13), 75.9 (C6), 73.9 (C8), 72.1 (C10), 48.4 (C9), 47.0 (C7), 34.0 (C17), 29.1 (C14), 19.7 (C15), 18.8 (C18), 18.6 (C19). **IR** cm^{-1}: 3438, 2974, 2931, 1766, 1735, 1655, 1467, 1386, 1280, 1192, 1152, 1122, 1069, 992, 918, 818, 731, 705, 604. **HRMS**: *m/z* calculated for $C_{19}H_{24}O_6$ $[M+Na]^+$ 371.1573 found 371.1456.

4.2.2. General procedure for the synthesis of Tagitinin C amine derivatives

To a solution of amine (1 equiv.), basic catalyst (trimethylamine or DBU) in dichloromethane (1.5 mL) at 0 °C in maintaining the pH of 8–8.5 was added a solution of Tagitinin C (1 equiv.) in dichloromethane (1.5 mL). The mixture was stirred at 0 °C or room temperature (22 °C) in dark for the required time (see Table). The reaction was monitored by TLC and NMR. After completion, water was added and the reaction mixture was extracted with dichloromethane (3 × 5 ml). Solvent was evaporated under vacuum and the crude product was purified by filtration on silica gel.

(1S,3R,6R,7R,8R,E)-3-hydroxy-4,10-dimethyl-11-methylene-12-oxo-1-(((R)-1′-phenylethyl) amino)-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (3a):

Reaction of L-α-phenylethylamine (0.36 mmol, 44 mg), Tagitinin C (0.36 mmol, 126 mg), in dichloromethane.



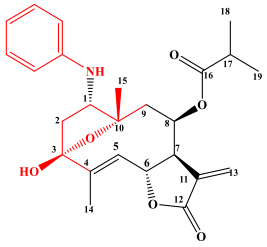
Yield: 91% (0.33 mmol, 154 mg), yellow pale oil.

$[\alpha]_D^{28} = -36.1$ (c = 0.1, MeOH).

^{1}H NMR (400 MHz, CDCl$_3$): δ ppm 7.36–7.32 (m, 5H, H$_{Ar}$), 6.24 (d, J = 2.7 Hz, 1H, Hα13), 5.62 (d, J = 5.0 Hz, 1H, H5), 5.69–5.58 (m, 1H, H8), 5.56 (d, J = 3.0 Hz, 1H, Hβ13), 5.40–5.38 (m, 1H, H6), 4.14 (s, 1H, H7), 3.81 (dt, J = 13.0, 6.0 Hz, 1H, H1′), 3.21 (dd, J = 11.5, 6.0 Hz, 1H, H1), 2.58 (dd, J = 12.5, 6.0 Hz, 2H, Hα2), 2.43 (dt, J = 14.0, 7.0 Hz, 1H, H17), 1.99 (d, J = 12 Hz, 1H, Hα9) 1.82 (d, J = 5.0 Hz, 1H, Hβ9), 1.80 (s, 1H, H14), 1.77 (d, J = 3.0 Hz, 2H, Hβ2), 1.34 (d, J = 7.0 Hz, 3H, H2′), 1.29 (s, 3H, H15),1.10–1.03 (m, 6H, H18,19). **^{13}C NMR (75 MHz, CDCl$_3$)** δ ppm 176.1 (C16), 169.8 (C12), 145.1 (C1′), 140.8 (C4), 136.3 (C11), 128.5 (C5), 127.9 (CAr), 127.2 (CAr), 126.6 (CAr), 122.7 (C13), 103.8 (C3), 82.5 (C10), 75.6 (C6), 70.7 (C8), 63.1 (C20), 57.2 (C1), 49.4 (C7),43.3 (C2), 35.4 (C9), 34.0 (C17), 26.1 (C2′), 25.3 (C15), 22.8 (C14), 19.2 (C18), 18.7 (C19). **IR** cm^{-1}: 3446, 2972, 2933, 1760, 1734, 1451, 1376, 1331, 1280, 1262, 1187, 1149, 1124, 1066, 987, 914, 816, 763, 702. **HRMS**: *m/z* calculated for $C_{27}H_{35}NO_6$ $[M+H]^+$ 470.2464, found 470.2388.

(1S,6R,7R,8R,10S,E)-3-hydroxy-4,10-dimethyl-11-methylene-12-oxo-1-(phenylamino)-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (3b):

Reaction of Aniline (0.13 mmol, 12 mg), Tagitinin C (0.13 mmol, 46 mg), in dichloromethane.



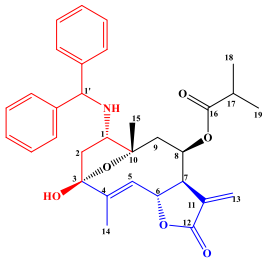
Yield: 94% (0.12 mmol, 54 mg), yellow pale oil.

$[\alpha]_D^{22} = -128.8$ (c = 1.0, MeOH).

^{1}H NMR (300 MHz, CDCl$_3$) δ ppm ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.19–7.06 (m, 2H, H$_{Ar}$), 6.63 (dd, J = 7.0, 4.0 Hz, 1H, H$_{Ar}$), 6.62–6.59 (m, 2H, H$_{Ar}$), 6.19 (d, J = 3.0 Hz, 1H, Hα13), 5.60–5.56 (m, 1H, H8), 5.53 (d, J = 9.0 Hz, 1H, H5), 5.60 (d, J = 2.0 Hz, 1H, Hβ13), 5.33 (s, 1H, H6), 4.35 (ddd, J = 12.0, 10.0, 7.0 Hz, 1H, H1), 4.08 (d, J = 2.0 Hz, 1H, H7), 3.56 (d, J = 9.0 Hz, 1H, NH), 2.60 (dd, J = 13.0, 6.0 Hz, 1H, Hα2), 2.39 (dt, J = 14.0, 7.0 Hz, 1H, H17), 1.98 (dd, J = 14.0, 11.0 Hz, 1H, Hα9), 1.87 (d, J = 12.0 Hz, 1H, Hβ2), 1.75 (s, 3H, H14), 1.73 (dd, J = 14.0, 5.0 Hz, 1H, Hβ9), 1.50 (s, 3H, H15), 1.01–0.96 (m, 6H, H18,19). **^{13}C NMR (75 MHz, CDCl$_3$)** δ ppm 176.0 (C16), 169.9 (C12), 146.8 (CAr), 140.7 (C4), 136.1 (C11), 129.5 (CAr), 128.2 (C5), 123.1 (C13), 113.4 (CAr), 103.3 (C3), 82.2 (C10), 75.6 (C6), 70.5 (C8), 60.7 (C1), 49.5 (C7), 43.2 (C2), 35.7 (C9), 34.1 (C17), 27.3 (C15), 22.7 (C14), 19.2 (C18), 18.6 (C19). **IR** cm^{-1}**:** 3389, 2974, 2932, 1753, 1736, 1603, 1499, 1448, 1385, 1326, 1279, 1184, 1151, 1127, 1073, 988, 912, 816, 751, 694. **HRMS:** *m/z* calculated for $C_{25}H_{31}NO_6$ $[M+H]^+$ 441.2151, found 442.2207.

(1S,6R,7R,8R,10S,E)-1-(benzhydrylamino)-3-hydroxy-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (3c):

Reaction of Amino-diphenylmethane (0.45 mmol, 83 mg), Tagitinin C (0.45 mmol, 158 mg), in dichloromethane.



Yield: 89% (0.40 mmol, 213 mg), yellow pale oil.

$[\alpha]_D^{28} = -95.9$ (c = 0.1, MeOH).

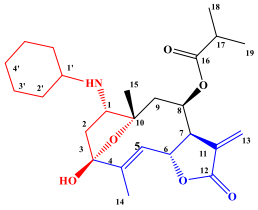
^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.38–7.22 (m, 10H, H$_{Ar}$), 6.25

(d, J = 3.0 Hz, 1H, H_α13), 5.67 (d, J = 5.0 Hz, 1H, H5), 5.65–5.60 (m, 1H, H8), 5.58 (d, J = 2.0 Hz, 1H, H_β13), 5.35 (d, J = 1.0 Hz, 1H, H6), 4.86 (s, 1H, H1′), 4.11 (s, 1H, H7), 3.41–3.33 (m, 1H, H1), 2.50 (dd, J = 13.0, 6.2 Hz, 1H, H_α2), 2.39 (dd, J = 14.0, 7.0 Hz, 1H, H_β2), 2.03 (dd, J = 11.0 Hz, 1H, H_α9), 2.01 (m, 1H, H17), 1.84 (dd, 1H, J = 5.0 Hz, 1H, H_β9), 1.74 (s, 3H, H14), 1.41 (s, 3H, H15), 1.02 (m, 6H, H18, 19).

^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 176.2 (C16), 169.8 (C12), 145.5 (CAr), 143.9 (CAr), 143.2 (CAr), 140.8 (C4), 136.3 (C11), 128.1 (C5), 122.8 (C13), 103.7 (C3), 82.5 (C10), 75.6 (C6), 70.7 (C8), 66.3 (C1′), 59.7 (C1), 49.4 (C7), 43.3 (C2), 35.6 (C9), 34.1 (C17), 26.7 (C15), 22.8 (C14), 19.2 (C18), 18.6 (C19). **IR** cm^{-1}: 3386, 2972, 2932, 1761, 1732, 1599, 1493, 1452, 1385, 1333, 1280, 1186, 1150, 1128, 1068, 987, 914, 816, 746, 701. **HRMS:** m/z calculated for $C_{32}H_{37}NO_6$ $[M+H]^+$ 532.2621, found 532.2677.

(1S,6R,7R,8R,10S,E)-1-(cyclohexylamino)-3-hydroxy-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (3d):

Reaction of Cyclohexylamine (0.33 mmol, 33 mg), Tagitinin C (0.33 mmol, 114 mg), in dichloromethane.



Yield: 76% (0.25 mmol, 112 mg), yellow pale oil.

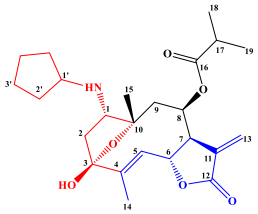
$[\alpha]_D^{28}$ = −84.4 (c = 0.1, MeOH).

^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 6.24 (d, J = 3.0 Hz, 1H, H_α13), 5.67 (d, J = 5.0 Hz, 1H, H5), 5.60 (d, J = 6.0 Hz, 1H, H8), 5.58 (s, 1H, H_β13), 5.38 (s, 1H, H6), 4.17 (s, 1H, H7), 3.55 (dd, J = 12.0, 6.0 Hz, 1H, H1), 2.53–2.44 (m, 1H, H1′), 2.42 (m, 1H, H17), 2.40 (d, J = 9.0 Hz, 1H, H_α9), 1.97 (d, J = 9.0 Hz, 1H, H_β9), 1.82 (d, J = 10.0 Hz, 1H, H_α2) 1.73 (s, 3H, H14), 1.71 (d, J = 11.0 Hz, 1H, H_β2), 1.48 (s, 3H, H15), 1.05–1.02 (m,16H, H 18,19, 2′,3′,4′).

^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 176.1 (C16), 169.9 (C12), 141.4 (C4), 136.4 (C11), 127.6 (C5), 122.6 (C13), 103.5 (C3), 82.5 (C10), 75.7 (C6), 70.8 (C8), 62.6 (C1), 55.8 (C2), 50.4 (C1′), 49.5 (C7), 44.5 (C17), 36.3 (C9), 34.0 (C2′), 25.9 (C3′), 25.1 (C4′), 22.9 (C14), 19.2 (C15), 18.6 (C18,19). **IR** cm^{-1}: 3375, 2972, 2929, 2854, 1764, 1734, 1657, 1467, 1450, 1371, 1348, 1280, 1184, 1152, 1128, 1068, 987, 915, 816, 739, 704 cm^{-1}. **HRMS:** m/z calculated for $C_{25}H_{37}NO_6$ $[M+H]^+$ 448.2621, found 448.2669.

(1S,6R,7R,8R,10S,E)-1-(cyclopentylamino)-3-hydroxy-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (3e):

Reaction of Cyclopentylamine (0.34 mmol, 29 mg), Tagitinin C (0.34 mmol, 118 mg), in dichloromethane.



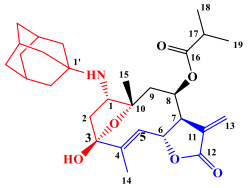
Yield: 86% (0.29 mmol, 127 mg), yellow pale oil.

$[\alpha]_D^{28}$ = −126.1 (c = 0.1, MeOH).

^{1}H NMR (360 MHz, CDCl$_3$) δ ppm 6.25 (d, J = 3.0 Hz, 1H, H_α13), 5.65–5.62 (m, 1H, H8), 5.61 (d, J = 5.0 Hz, 1H, H5), 5.58 (d, J = 2.0 Hz, 1H, H_β13), 5.37 (dd, J = 6.0, 4.0 Hz, 1H, H6), 4.16 (ddd, J = 7.0, 5.0, 3.0 Hz, 1H, H7), 3.46 (dd, J = 12.0, 6.0 Hz, 1H, H1), 3.11–3.07 (m, 1H, H1′), 2.55 (dd, J = 13.0, 6.0 Hz, 1H, H_α9), 2.42 (dt, J = 13.9, 6.9 Hz, 1H, H_α2), 2.42 (m, 1H, H17), 1.98 (d, J = 11.0 Hz, 1H, H_β9), 1.82 (s, 3H, H14), 1.74 (d, J = 5.0 Hz, 1H, H2′), 1.71 (d, J = 11.0 Hz, 1H, H_β2), 1.50 (s, 3H, H15), 1.25 (d, J = 4.0 Hz, 1H, H3′), 1.08–1.01 (m, 6H, H18,19). **^{13}C NMR (75 MHz, CDCl$_3$)** δ ppm 176.1 (C16), 169.8 (C12), 140.8 (C4), 136.3 (C11), 128.0 (C5), 122.6 (C13), 103.7 (C3), 82.7 (C10), 75.6 (C6), 70.7 (C8), 64.3 (C1), 59.0 (C2), 49.5 (C7), 45.9 (C1′), 35.4 (C9), 34.1 (C17), 26.8 (C2′), 23.9 (C3′), 22.8 (C14), 18.6 (C18,19). **IR** cm^{-1}: 3459, 2968, 2871, 1761, 1734, 1658, 1468, 1385, 1333, 1281, 1186, 1151, 1127, 1068, 988, 965, 915, 816, 750, 678. **HRMS**: m/z calculated for $C_{25}H_{37}NO_6$ $[M+H]^+$ 434.2464, found 434.2534.

(1S,3R,6R,7R,8R,E)-1-((1's,3R)-adamantan-1′-ylamino)-3-hydroxy-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10 epoxycyclodeca[b]furan-8-yl isobutyrate (3f):

Reaction of 1-Adamantylamine (0.14 mmol, 20 mg), Tagitinin C (0.14 mmol, 47 mg), in dichloromethane.



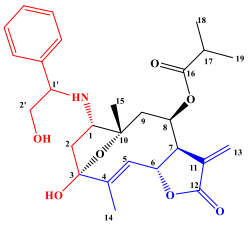
Yield: 74% (0.10 mmol, 52 mg), yellow pale oil.

$[\alpha]_D^{22}$ = −82.0 (c = 0.5, MeOH).

^{1}H NMR (360 MHz, CDCl$_3$) δ ppm 6.24 (d, J = 3.0 Hz, 1H, H_α13), 5.60 (dd, J = 4.0, 3.0 Hz, 1H, H8), 5.58 (d, J = 2.4 Hz, 1H, H5), 5.40 (d, J = 2.7 Hz, 1H, H13), 5.36 (d, J = 6.5 Hz, 1H, H6), 4.17 (s, 1H, H7), 3.55 (m, 1H, H1), 2.43 (dd, J = 13.0, 7.0 Hz, 1H, Hα9) 2.42 (dt, J = 13.0, 7.0 Hz, 1H, H17), 2.05 (m, 3H, H_{Adam}), 1.96 (dd, J = 11.0 Hz, 7.0 Hz, 1H, Hβ9), 1.96 (t, J = 2.0 Hz, 1H, H_α2), 1.82 (d, J = 2.0 Hz, 1H, H_β2), 1.75–1.25 (m, 18H, H_{Adam}, H14, H15), 1.10–1.06 (m, 6H, H18,19). **^{13}C NMR (75 MHz, CDCl$_3$)** δ ppm 176.1 (C16), 169.8 (C12), 141.0 (C4), 136.4 (C11), 127.7 (C5), 122.5 (C13), 103.4 (C3), 82.8 (C10), 75.7 (C6), 70.8 (C8), 57.8 (C1), 50.5 (CAdam), 49.3 (C7), 46.2 (CAdam), 42.6 (C2), 36.5 (C9), 36.3 (CAdam), 34.1 (C17), 29.8 (CAdam), 25.9 (C14), 22.9 (C15), 19.2 (C18), 18.6 (C19). **IR cm^{-1}:** 3371, 2906, 2849, 1766, 1734, 1654, 1468, 1452, 1369, 1279, 1186, 1151, 1066, 990, 914, 816, 749. **HRMS**: m/z calculated for $C_{29}H_{41}NO_6$ $[M+H]^+$ 500.2934, found 434.2997.

(1S,3R,6R,7R,8R,E)-3-hydroxy-1-(2′-hydroxy-1′-phenyléthyl) amino)-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (5a):

Reaction of S-phenyl glycinol (0.43 mmol, 58 mg), Tagitinin C (0.43 mmol, 167 mg), in dichloromethane.



Yield: 86% (0.37 mmol, 180 mg), yellow pale oil.

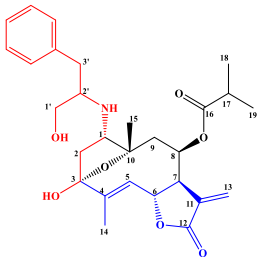
$[\alpha]_D^{28}$ = −49.1 (c = 0.1, MeOH).

^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.44–7.30 (m, 5H, H_{Ar}), 6.27 (d, J = 3.0 Hz, 1H, H_α13), 5.68 (dt, J = 11.0, 5.0, 5 Hz, 1H, H8), 5.61 (d, J = 3.0 Hz, 1H, H_β13), 5.59 (dd, J = 4.0, 2.0 Hz, 1H, H5), 5.36 (m, 1H, H6), 4.14 (m, 1H, H7), 3.82 (dd, J = 11.0, 4.0 Hz, 1H, H1′), 3.70 (dd, J = 11.0, 4.0 Hz, 1H, H_α2′), 3.53 (dd, J = 11.0, 9.0 Hz, 1H, H_β2′), 3.46 (m, 1H, H1), 2.47 (dt, J = 14.0, 7.0 Hz, 1H, H17), 2.14 (dd, J = 13.0,

6.4 Hz, 1H, $H_{\alpha}2$), 2.05 (dd, J = 9.0, 5.0 Hz, 1H, $H_{\alpha}9$), 1.86 (dd, J = 14.0, 4.4 Hz, 1H, Hβ9), 1.75 (s, 3H, H14), 1.70 (dd, J = 13.0, 12.0 Hz, 1H, Hβ2) 1.54 (s, 3H, H15), 1.09 (d, J = 7.0 Hz, 6H, H18,19). **^{13}C NMR (75 MHz, $CDCl_3$)** δ ppm 176.2 (C16), 169.8 (C12), 140.5 (C4), 136.1 (C11), 128.9 (CAr), 128.3 (CAr), 128.1 (C5), 127.0 (CAr), 122.9 (C13), 103.5 (C3), 82.7 (C10), 75.4 (C6), 70.6 (C8), 66.9 (C2′), 64.6 (C1′), 64.2 (C1), 49.5 (C7), 44.2 (C2), 34.1 (C9), 27.4 (C17), 22.6 (C15), 19.2 (C14), 19.0 (C18), 18.7 (C19).IR cm^{-1}: 3458, 2974, 2936, 2876,1756, 1735, 1659, 1454, 1385, 1335, 1282, 1186, 1153, 1064, 988, 966, 914, 817, 761, 704, 677. **HRMS**: *m/z* calculated for $C_{27}H_{35}NO_7$ $[M+H]^+$ 486.2414, found 486.2469.

(1S,3R,6R,7R,8R,E)-3-hydroxy-1-(1′-hydroxy-3′-phenylpropan-2′-yl)amino)-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (5b):

Reaction of (*S*)-(−)-2-Amino-3-phenyl-1-propanol (0.38 mmol, 57 mg), Tagitinin C (0.38 mmol, 132 mg), in dichloromethane.



Yield: 88% (0.33 mmol, 167 mg), yellow pale oil.

$[\alpha]_D^{28}$ = −154.8 (c = 0.1, MeOH).

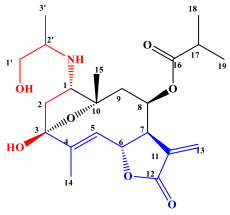
^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 7.39−7.12 (m, 5H, H_{Ar}), 6.25 (d, J = 4.0 Hz, 1H, $H_{\alpha}13$), 5.63−5.59 (m, 1H, H8), 5.60 (d, J = 4.0 Hz, 1H, Hβ13),5.59 (dd, J = 4.0, 2.0 Hz, 1H, H5),5.25−5.23 (m, 1H, H6), 4.10 (s, 1H, H7), 3.62 (dd, J = 11.0, 4.0 Hz, 1H, $H_{\alpha}1'$), 3.46 (dd, J = 12.0, 6.0 Hz, 1H, H1), 3.36 (dd, J = 11.0, 5.0 Hz, 1H, Hβ1′), 2.95−2.89 (m, 1H, H2′), 2.89−2.81 (m, 1H, $H_{\alpha}3'$), 2.78 (dd, J = 7.0, 3.0 Hz, 1H, Hβ3′), 2.41 (dt, J = 20.0, 7.0 Hz, 1H, H17), 2.34 (d, J = 6.0 Hz, 1H, $H_{\alpha}9$), 1.95 (d, J = 9.0 Hz, 1H, $H_{\alpha}2$), 1.79 (s, 3H, H14), 1.71 (d, J = 5.0 Hz, 1H, Hβ9), 1.49 (s, 3H, H15), 1.44 (d, J = 12.0 Hz, 1H, Hβ2), 1.09−1.06 (m, 6H, H18,19). **^{13}C NMR (75 MHz, $CDCl_3$)** δ ppm 176.0 (C16), 169.7 (C12), 140.4 (C4), 137.98 (CAr), 136.1 (C11), 129.1 (C5), 128.8 (CAr), 126.8 (CAr), 122.9 (C13), 103.4 (C3), 82.4 (C10), 75.3 (C6), 70.4 (C8), 63.7 (C1′), 62.9 (C2′), 59.7 (C1), 49.4 (C7), 43.2 (C2), 38.6 (C9), 34.1 (C17), 26.7 (C14), 22.7 (C15), 19.1 (C18), 18.7 (C19).

IR cm^{-1}: 3462, 2972, 2935, 2879, 1761, 1734, 1658, 1454, 1386, 1335, 1281, 1186, 1151, 1066, 988, 967, 914, 816, 746, 702, 681.

HRMS: *m/z* calculated for $C_{28}H_{37}NO_7$ $[M+H]^+$ 500.2570, found 500.2626.

(1S,3R,6R,7R,8R,E)-3-hydroxy-1-(1′-hydroxypropan-2′-yl) amino)-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (5c):

Reaction of (*S*)-(+)-2-Amino-1-propanol (0.34 mmol, 26 mg), Tagitinin C (0.34 mmol, 120 mg), in dichloromethane.



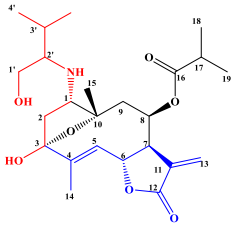
Yield: 73% (0.25 mmol, 105 mg), yellow pale oil.

$[\alpha]_D^{28}$ = −119.1 (c = 0.09, MeOH).

^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 6.25 (d, J = 3.0 Hz, 1H, $H_{\alpha}13$), 5.69 (d, J = 5.0 Hz, 1H, 5), 5.60 (d, J = 5.0 Hz, 1H, Hβ13), 5.64−5.60 (m, 1H, H8), 5.36 (dd, J = 3.0, 2.0 Hz, 1H, H6), 4.14 (s, 1H, H7), 3.57 (dd, J = 11.0, 7.0 Hz, 1H, $H1_{\beta}$'), 3.48 (dd, J = 12.0, 4.0 Hz, 1H, H1), 3.22 (dd, J = 11.0, 7.0 Hz, 1H, $H1_{\alpha}$'), 2.96 (m, 1H, H2′), 2.82 (dd, J = 7.0, 3.0 Hz, 1H, $H2_{\alpha}$), 2.56 (d, J = 6.0 Hz, 1H, $H2_{\beta}$), 2.49 (d, J = 7.0 Hz, 1H, Hα9), 2.47−2.39 (m, 1H, H17), 2.39 (d, J = 7.0 Hz, 1H, Hβ9), 2.04 (s, 3H, H14), 1.54 (s, 3H, H3′), 1.50 (s, 3H, H15), 1.11−1.03 (m, 6H, H18,19). **^{13}C NMR (75 MHz, $CDCl_3$)** δ ppm 176.1 (C16), 169.8 (C12), 140.6 (C4), 136.1 (C11), 128.2 (C5), 122.9 (C13), 103.5 (C3), 82.6 (C10), 75.5 (C6), 73.9 (C2′), 70.5 (C8), 69.3, 65.7 (C1′), 63.9 (C1), 55.3 (C2), 49.5 (C7), 44.5, 42.4 (C9), 34.1 (C17), 29.7 (C3′), 26.8 (C14), 22.8 (C15), 19.8 (C18), 18.6 (C19). **IR** cm^{-1}: 3463, 2971, 2935, 2877, 1762, 1733, 1655, 1452, 1377, 1342, 1281, 1186, 1153, 1068, 989, 916, 818, 746, 699, 678. **HRMS**: *m/z* calculated for $C_{22}H_{33}NO_7$ $[M+H]^+$ 424.2257, found 424.2314.

(1S,3R,6R,7R,8R,E)-3-hydroxy-1-(1′-hydroxy-3′-méthylbutan-2′-yl)amino)-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (5d):

Reaction of L-Valinol (0.66 mmol, 68 mg), Tagitinin C (0.66 mmol, 230 mg), in dichloromethane.



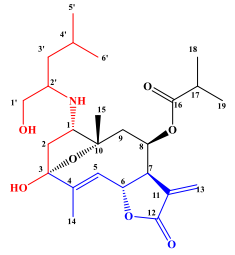
Yield: 76% (0.50 mmol, 227 mg), pale oil.

$[\alpha]_D^{22}$ = −110.0 (c = 0.1, MeOH).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.25 (d, J = 3.0 Hz, 1H, $H_{\alpha}13$), 5.62−5.61 (m 2H, H5,8), 5.59 (d, J = 2.0 Hz, 1H, Hβ13), 5.39−5.34 (m, 1H, H6), 4.45 (t, J = 9.0 Hz, 1H, H7), 4.15 (ddd, J = 6.0, 4.0, 2.0 Hz, 1H, H1), 3.59 (dd, J = 11.0, 4.0 Hz, 1H, Hα1′), 3.47 (dd, J = 12.0, 6.0 Hz, 1H), 3.41 (d, J = 6.0 Hz, 1H), 3.39−3.35 (m, 1H, Hβ1′), 2.78 (dd, J = 14.0, 7.0 Hz, 1H, Hα2), 2.55 (dd, J = 13.0, 6.0 Hz, 2H, Hβ2, Hα9), 2.49−2.39 (m, 3H, Hβ9, H17), 1.77 (s, 3H, H14), 1.52 (s, 3H, H15), 1.19 (t, J = 7.0 Hz, 7H), 1.06−0.91 (m, 6H, H18,19). **^{13}C NMR (75 MHz, $CDCl_3$)** δ ppm 176.9 (C16), 169.8 (C12), 140.7 (C4), 136.5 (C11), 128.2 (C5), 122.9 (C13), 103.4 (C3), 82.5 (C10), 75.50 (C6), 71.9 (C8), 69.4, 65.3 (C1), 60.6 (C2), 49.4 (C7), 47.56 (s), 44.0 (C17), 42.0, 34.0 (C9), 28.9 (C14), 22.8 (C15), 19.4 (C18), 18.7 (C19), 18.1 (C4′). **IR** cm^{-1}: 3463, 2969, 2934, 2875, 1764, 1734, 1655, 1468, 1371, 1344, 1280, 1186, 1153, 1068, 990, 917, 817, 733, 692, 681. **HRMS:** *m/z* calculated for $C_{24}H_{37}NO_7$ $[M+H]^+$ 452.2570, found 452.2629.

(1S,3R,6R,7R,8R,E)-3-hydroxy-1-(1′-hydroxy-4′-methylpentan-2′-yl)amino)-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (5e):

Reaction of L-(+) Leucinol (0.37 mmol, 43 mg), Tagitinin C (0.37 mmol, 128 mg), in dichloromethane.



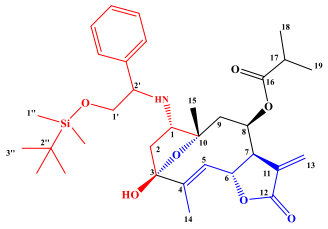
Yield: 79% (0.29 mmol, 136 mg), yellow pale oil.

$[\alpha]_D^{28} = -140.3$ (c = 0.1, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.23 (d, J = 3.0 Hz, 1H, H_α13), 5.62 (dd, J = 8.0, 3.0 Hz, 1H, H8), 5.60–5.55 (m, 2H, H5,H_β13), 5.35 (m, 1H, H6), 4.16–4.11 (m, 1H, H7), 3.61 (dd, J = 11.0, 4.0 Hz, 1H, Hα1′), 3.46 (dd, J = 12.0, 6.0 Hz, 1H, H1), 3.24 (dd, J = 11.0, 5.3 Hz, 1H, H_β1′), 2.71 (d, J = 7.0 Hz, 1H, H2′), 2.53 (d, J = 6.0 Hz, 1H, H17), 2.43–2.37 (m, 2H, H_α9, H_β2), 1.95 (m, 1H, H_β9), 1.81 (s, 3H, H14), 1.75 (d, J = 7.0 Hz, 1H, H_β2), 1.48 (s, 3H, H15), 1.15 (d, J = 7.0 Hz, 1H), 1.06–0.99 (m, 6H, H18,19), 0.92–0.85 (m, 6H, H5′,6′). **^{13}C NMR (75 MHz, $CDCl_3$)** δ ppm 176.1 (C16), 169.8 (C12), 140.8 (C4), 136.1 (C11), 128.1 (C5), 122.9 (C13), 103.4 (C3), 82.4 (C10), 75.5 (C6), 71.8 (C8), 70.49, 63.7 (C1), 56.5 (C2), 49.4 (C7), 45.87, 44.0 (C17), 41.9, 35.5, 34.0 (C9), 28.9 (C15), 26.6 (C14), 24.8 (C), 23.0, 22.6 (C24), 19.2 (C18), 18.6 (C19). **IR** cm^{-1}: 3455, 2956, 2934, 2872, 2362, 2338, 1760, 1737, 1659, 1468, 1368, 1333, 1281, 1186, 1152, 1066, 989, 915, 817, 745, 680. **HRMS:** m/z calculated for $C_{25}H_{39}NO_7$ $[M+H]^+$ 466.2727, found 466.2795.

(1S,3R,6R,7R,8R,E)-1-(1'-((tert-butyldimethylsilyl)oxy)-2′-phenyléthyl)amino)-3-hydroxy-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (5f):

Reaction of 2-((tert-butyldimethylsilyl)oxy)-1-phenylethanamine (0.46 mmol, 160 mg), tagitinin C (0.46 mmol, 116 mg), in dichloromethane.



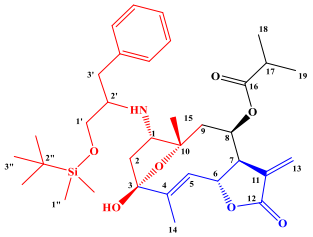
Yield: 91% (0.42 mmol, 251 mg), yellow pale oil.

$[\alpha]_D^{28} = -65.4$ (c = 0.15, MeOH).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.41–7.30 (m, 1H, Har), 6.25 (d, J = 3.0 Hz, 1H, H_α13), 5.68 (dt, J = 11.0, 5.0 Hz, 1H, H8), 5.59 (d, J = 2.0 Hz, 1H, H_β13), 5.56 (dd, J = 3.0, 2.0 Hz, 1H, H5), 5.37 (dt, J = 6.0, 3.0 Hz, 1H, H6), 4.13 (td, J = 4.0, 2.0 Hz, 1H, H7), 3.89–3.80 (m, 1H, H2′), 3.60 (dd, J = 10.0, 4.0 Hz, 1H, H_α1′), 3.49–3.41 (m, 1H, H1), 3.41 (dd, J = 10.0, 4.0 Hz, 1H, H_β1′), 2.44 (dt, J = 14.0, 7.0 Hz, 1H, H17), 2.16–2.07 (m, 1H, H_α2), 2.16–2.07 (m, 1H, H_α9), 1.78 (d, J = 6.0 Hz, 1H, H_β2), 1.73 (s, 1H, H14), 1.71 (d, J = 12.0 Hz, 1H, H_β9), 1.49 (s, 1H, H15), 1.08 (dd, J = 8.0, 7.0 Hz, 6H,H18,19), 0.91–0.88 (m, 9H, H3″), 0.01 (d, J = 3.0 Hz, 6H, H1″). **^{13}C NMR (91 MHz, $CDCl_3$)** δ ppm 176.1 (C16), 169.9 (C12), 142.1 (C4), 140.5 (CAr), 136.4 (C11), 128.3 (CAr), 126.9 (C5), 122.7 (C13), 103.3 (C3), 82.3 (C10), 75.7 (C6), 70.7 (C8), 64.0 (C20), 63.7 (C1), 57.5 (C21), 49.6 (C7), 45.8 (C2), 44.7, 35.4 (C9), 34.0 (C2″), 27.7 (C15), 22.8 (C14), 19.3 (C17), 18.5 (C18,19), 10.8 (C3″), −5.5 (C1″). **IR** cm^{-1}: 3456, 2954, 2930, 2857, 2362, 2339, 1764, 1736, 1661, 1470, 1361, 1331, 1281, 1187, 1151, 1093, 989, 912, 814, 764, 667. **HRMS:** m/z calculated for $C_{33}H_{49}NO_7Si$ $[M+H]^+$ 600.3278, found 600.3330.

(1S,3R,6R,7R,8R,E)-1-(1'-((tert-butyldimethylsilyl)oxy)-3′-phenylpropan-2′-yl)amino)-3-hydroxy-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (5 g):

Reaction of (S)-1-((tert-butyldimethylsilyl)oxy)-3-phenylpropan-2-amine (0.34 mmol, 91 mg), tagitinin C (0.34 mmol, 120 mg), in dichloromethane.



Yield: 93% (0.32 mmol, 194 mg), pale oil.

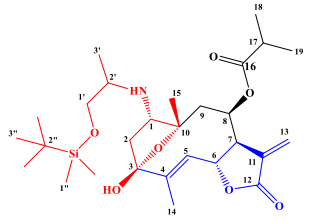
$[\alpha]_D^{28} = -124.0$ (c = 0.2, MeOH).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.34–7.12 (m, 1H, Har), 6.23 (d, J = 3.0 Hz, 1H, H_α13), 5.61 (dd, J = 8.0, 3.0 Hz, 1H, H8), 5.58 (d, J = 6.0 Hz, 1H, H5), 5.57 (d, J = 2.0 Hz, 1H, H_β13), 5.27 (d, J = 2.0 Hz, 1H, H6), 4.12 (dd, J = 5.0, 3.0 Hz, 1H, H7), 3.58 (dd, J = 10.0, 4.0 Hz, 1H, H1), 3.48 (dd, J = 9.0, 4.0 Hz, 1H, H_α1′), 3.42 (dd, J = 11.0, 5.0 Hz, 1H, H_β1′), 3.09 (dt, J = 12.0, 6.0 Hz, 1H, H2′), 2.79 (dd, J = 12.0, 5.0 Hz, 1H, H_α3′), 2.51 (dd, J = 13.0, 8.0 Hz, 1H, H_β3′), 2.44–2.39 (m, 1H, H17), 2.32 (dd, J = 13.0, 6.0 Hz, 1H, H_α2), 1.92 (dd, J = 11.0, 6.0 Hz, 1H, H_α9), 1.78 (s, 3H, H14), 1.67 (dd, J = 14.0, 5.0 Hz, 1H, H_β9), 1.55 (dd, J = 13.0, 7.7 Hz, 1H, H_β2), 1.48 (s, 3H, H15), 1.05 (t, J = 7.0 Hz, 6H, H18,19), 0.90 (s, 9H, H3″), 0.03 (d, J = 2.0 Hz, 6H, H1″). **^{13}C NMR (75 MHz, $CDCl_3$)** δ ppm 176.2 (C16), 169.9 (C12), 140.7 (C4), 139.2 (CAr), 136.4 (C11), 129.4 (CAr), 128.6 (C5), 126.5 (CAr), 122.8 (C13), 103.8 (C3), 83.1 (C10), 75.6 (C6), 70.8 (C8), 67.6 (C1′), 64.4 (C2′), 63.4 (C1), 59.9 (C3′), 49.6 (C7), 43.9 (C2), 40.6, 38.6 (), 35.6 (C9), 34.2 (C17), 27.1 (C15), 26.06 (C2″), 22.9 (C14), 19.3 (C18), 18.8 (C19), 18.4 (C3″), −5.2 (C1″).

IR cm^{-1}: 3454, 2954, 2930, 2857, 2362, 2336, 1765, 1735, 1662, 1471, 1361, 1331, 1281, 1186, 1150, 1107, 988, 914, 815, 778, 669. **HRMS:** m/z calculated for $C_{34}H_{51}NO_7Si$ $[M+H]^+$ 614.3435, found 614.3490.

(1S,3R,6R,7R,8R,E)-1-(1'-(tert-butyldimethylsilyl)oxypropan-2′-yl)amino)-3-hydroxy-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (5 h):

Reaction of (S)-1-((tert-butyldimethylsilyl)oxy)propan-2-amine (0.36 mmol, 68 mg), Tagitinin C (0.36 mmol, 126 mg), in dichloromethane.



Yield: 96% (0.35 mmol, 186 mg), yellow pale oil.

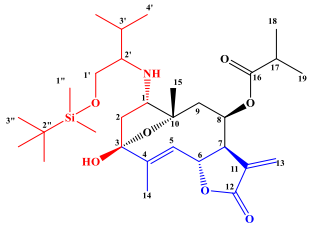
$[\alpha]_D^{28} = -100.0$ (c = 0.09, MeOH).

^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 6.25 (d, J = 3.0 Hz, 1H, H_α13), 5.67–5.62 (m, 1H, H8), 5.61 (dd, J = 3.0, 2.0 Hz, 1H, H5), 5.58 (d, J = 2.0 Hz, 1H, H_β13), 5.38 (d, J = 2.0 Hz, 1H, H6), 4.15 (tt, J = 5.0, 3.0 Hz, 1H, H7), 3.55 (dd, J = 10.0, 5.0 Hz, 1H, H1), 3.52 (dd, J = 5.0, 2.7 Hz, 1H H_α1′), 3.35 (dd, J = 10.0, 7.0 Hz, 1H, H_β1′), 2.84–2.76 (m, 1H, H2′), 2.48 (dd, J = 13.0, 6.0 Hz, 1H, H_α2), 2.40 (dt, J = 14.0, 7.0 Hz, 1H, H17), 2.04 (dd, J = 15.0, 11.0 Hz, 1H, H_α9), 1.88 (d, J = 12.0 Hz, 1H, H_β2), 1.82 (s, 3H, H14), 1.72 (dd, J = 14.0, 5.0 Hz, 1H, H_β9), 1.51 (s, 3H, H15), 1.07–0.99 (m, 6H, H18,19), 0.89 (d, J = 7.0 Hz, 9H, H3″), 0.05 (dd, J = 21.0, 16.0 Hz, 6H, H1″). **^{13}C NMR (75 MHz, $CDCl_3$)** δ ppm 176.2 (C16), 170.0 (C12), 140.9 (C4), 136.4 (C11), 128.2 (C5), 122.9 (C13), 103.8 (C3), 83.0 (C10), 75.7 (C6), 70.8 (C8), 67.3 (C1′), 63.1 (C1), 53.8 (C2′), 49.7 (C7), 45.0 (C2), 35.4 (C9), 34.2 (C17), 27.4 (C15),

26.0 (C3′), 23.0 (C14), 19.4 (C18), 18.7 (C19), 18.4 (C3″), 17.6 (C2″), −5.2 (C1″). **IR** cm^{-1}: 3453, 2957, 2930, 2857, 2362, 2337, 1755, 1728, 1661, 1471, 1361, 1330, 1278, 1185, 1153, 1100, 987, 914, 816, 779, 670. **HRMS**: *m/z* calculated for $C_{28}H_{47}NO_7Si$ $[M+H]^+$ 538.3122, found 538.3173.

(1S,3R,6R,7R,8R,E)-1-(1′-((tert-butyldimethylsilyl)oxy)-3′-methylbutan-2′-yl)amino)-3-hydroxy-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (5i):

Reaction of (S)-1-((tert-butyldimethylsilyl)oxy)-3-methylbutan-2-amine (0.36 mmol, 68 mg), Tagitinin C (0.36 mmol, 126 mg), in dichloromethane.



Yield: 86% (0.31 mmol, 175 mg), yellow pale oil.

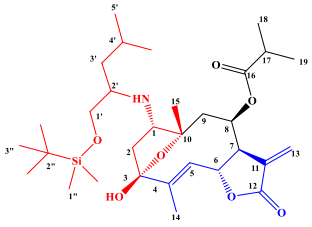
$[\alpha]_D^{28} = -93.5$ (c = 0.08, MeOH).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.25 (d, *J* = 3.0 Hz, 1H, H_α13), 5.65 (dd, *J* = 8.0, 3.0 Hz, 1H, H5), 5.63−5.60 (m, 1H, H8), 5.59 (d, *J* = 2.0 Hz, 1H, H_β13), 5.43−5.35 (m, 1H, H6), 4.16 (ddd, *J* = 7.0, 5.0, 3.0 Hz, 1H, H7), 3.68−3.60 (m, 2H), 3.58−3.52 (m, 1H, H1), 3.48 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.40 (dd, *J* = 10.0, 8.0 Hz, 1H), 3.01 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.62−2.55 (m, 1H), 2.49−2.39 (m, 3H, Hα2, H17), 2.31 (dd, *J* = 10.0, 5.0 Hz, 1H, Hα9), 1.96 (s, 3H, H14), 1.84−1.80 (m, 4H, Hβ2, Hβ9), 1.49 (s, 3H, H15), 1.09−1.02 (m, 6H, H18,19), 0.94−0.87 (m, 9H, H3″), 0.06−0.04 (m, 6H, H1″)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 176.1 (C16), 169.8 (C12), 140.8 (C4), 136.3 (C11), 127.9 (C5), 122.7 (C13), 103.8 (C3), 83.1 (C10), 75.6 (C6), 70.8 (C8), 66.2 (C2′), 63.2 (C1), 58.3 (C2), 49.5 (C7), 45.7 (C9), 34.0 (C17), 29.0 (C15), 26.9, 22.9 (C14), 19.1 (C18), 18.4 (C19), 10.61 (C3″), −5.4 (C1″). **IR cm^{-1}:** 3447, 2956, 2931, 2858, 1766, 1736, 1660, 1470, 1387, 1362, 1332, 1281, 1254, 1186, 1151, 1099, 989, 936, 909, 837, 777. **HRMS**: *m/z* calculated for $C_{30}H_{51}NO_7Si$ $[M+H]^+$ 566.3435, found 566.3494.

(1S,3R,6R,7R,8R,E)-1-(1′-((tert-butyldimethylsilyl)oxy)-4′-methylpentan-2′-yl)amino)-3-hydroxy-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (5j):

Reaction of (S)-1-((tert-butyldimethylsilyl)oxy)-4-methylpentan-2-amine (0.45 mmol, 125 mg), Tagitinin C (0.45 mmol, 156 mg), in dichloromethane.



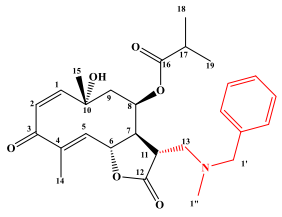
Yield: 87% (0.39 mmol, 227 mg), yellow pale oil.

$[\alpha]_D^{28} = -126.6$ (c = 0.2, MeOH).

^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 6.24 (d, *J* = 3.0 Hz, 1H, H_α13), 5.64 (dd, *J* = 8.0, 3.0 Hz, 1H, H5), 5.62−5.59 (m, 1H, H8), 5.58 (d, *J* = 2.0 Hz, 1H, H_β13), 5.38 (s, 1H, H6), 4.15 (ddd, *J* = 7.0, 5.0, 3.0 Hz, 1H, H7), 3.63−3.56 (m, 2H), 3.56−3.51 (m, 1H, H1), 3.37 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.29 (dd, *J* = 10.0, 8.0 Hz, 1H), 2.90 (ddd, *J* = 14.0, 7.0, 4.0 Hz, 1H), 2.62 (dd, *J* = 11.0, 6.0 Hz, 1H, Hα), 2.47 (dd, *J* = 13.0, 6.0 Hz, 1H, Hα2), 2.40 (dd, *J* = 14.0, 7.0 Hz, 1H, H17), 2.08−1.96 (m, 2H, Hβ2, Hβ9), 1.82 (s, 3H, H14), 1.73 (d, *J* = 5.0 Hz, 1H), 1.70−1.66 (m, 1H), 1.64 (d, *J* = 7.0 Hz, 1H), 1.48 (s, 3H, H15), 1.23 (d, *J* = 7.0 Hz, 2H), 1.15 (dd, *J* = 150.0 8.0 Hz, 3H), 1.05 (t, *J* = 7.0 Hz, 6H, H18, 19), 0.92−0.87 (m, 9H), 0.05 (d, *J* = 6.0 Hz, 6H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ ppm 176.3 (C16), 170.0 (C12), 140.9 (C4), 136.5 (C11), 128.2 (C5), 122.8 (C13), 103.9 (C3), 83.2 (C10), 75.7 (C6), 70.9 (C8), 68.8 (C24), 64.8 (C20), 62.8 (C1), 56.0 (C2), 50.8 (C7), 49.7, 43.0 (C4′), 41.6 (C9), 35.6 (C2″), 34.2 (C17), 27.1 (C14), 26.1 (C3″), 24.9 (C5′), 23.1 (C15), 18.7 (C18), 18.4 (C19), −5.2 (C1″). IR cm^{-1}: 3260, 2956, 2931, 2858, 1754, 1720, 1662, 1470, 1365, 1329, 1278, 1186, 1149, 1103, 987, 918.824, 786, 673. **HRMS**: *m/z* calculated for $C_{31}H_{53}NO_7Si$ $[M+H]^+$ 580.3591, found 580.3651.

(6R,7R,8R,10R,11R,1Z,4E)-11-((benzyl(methyl)amino)methyl)-10-hydroxy-4,10-dimethyl-3,12-dioxo-3,6,7,8,9,10,11,12-octahydrocyclodeca[b]furan-8-yl isobutyrate (7a):

Reaction of N-benzyl methyl amine (0.35 mmol, 42 mg), Tagitinin C (0.35 mmol, 122 mg), in dichloromethane.



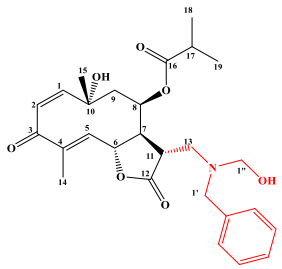
Yield: 71% (0.25 mmol, 117 mg), yellow pale oil.

$[\alpha]_D^{22} = -114.6$ (c = 1.0, MeOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 7.38−7.15 (m, 1H, H_{Ar}), 6.76 (d, *J* = 17.0 Hz, 1H, H1), 6.13 (d, *J* = 17.0 Hz, 1H, H2), 5.83 (dd, *J* = 9.0, 2.0 Hz, 1H, H5), 5.64−5.43 (m, 1H, H8), 5.29 (d, *J* = 9.0 Hz, 1H, H6), 3.73 (s, 1H, H7), 3.62−3.60 (m, 1H, H11), 3.22 (dd, *J* = 9.0, 4.0 Hz, 1H, H_α13), 2.92 (dd, *J* = 9.0, 4.0 Hz, 1H, H_β13), 2.76 (dd, *J* = 13.0, 5.0 Hz, 1H, Hα9), 2.58−2.45 (m, 1H), 2.43−2.32 (m, 1H, H17), 2.16 (s, 3H, H14), 1.88 (d, *J* = 1.0 Hz, 1H, Hβ9), 1.46 (s, 3H, H15), 1.05−1.03 (m, 6H, H18,19). **^{13}C NMR (75 MHz, $CDCl_3$)** δ ppm 196.7 (C3), 176.8 (C16), 176.2 (C12), 160.1 (C1), 141.0 (C4), 139.0 (C5), 138.9 (C11), 128.9 (C2), 128.4 (C13), 128.3, 83.82 (C6), 71.8 (C8), 69.7 (C10), 62.2, 55.4, 53.5 (C9), 43.1 (C7), 39.50, 35.2 (C17), 29.3, 22.5, 19.7 (C15), 18.7 (C18), 18.5 (C19). **IR cm^{-1}:** 3456, 2974, 2935, 1765, 1732, 1654, 1465, 1454, 1373, 1346, 1277, 1254, 1196, 1154, 1125, 1067, 1024, 993, 914, 818, 735, 700. **HRMS**: *m/z* calculated for $C_{27}H_{35}NO_6$ $[M+H]^+$ 470.25, found 470.2517.

(6R,7R,8R,10R,11R,1Z,4E)-11-((benzyl(hydroxymethyl)amino)methyl)-10-hydroxy-4,10-dimethyl-3,12-dioxo-3,6,7,8,9,10,11,12-octahydrocyclodeca[b]furan-8-yl isobutyrate (7b):

Reaction of N-benzylethanolamine (0.46 mmol, 70 mg), Tagitinin C (0.46 mmol, 161 mg), in dichloromethane.



Yield: 86% (0.40 mmol, 192 mg), yellow pale oil.

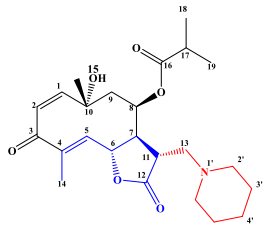
$[\alpha]_D^{22} = -81.3$ (c = 0.1, MeOH).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.39−7.24 (m, 5H, H_{Ar}), 6.70 (d, *J* = 17.0 Hz, 1H, H1), 6.12 (d, *J* = 17.0 Hz, 1H, H2), 5.62 (dd, *J* = 9.0, 1.0 Hz, 1H, H5), 5.53−5.43 (m, 1H, H8), 5.22 (d, *J* = 9.0 Hz, 1H, H6),

3.80 (m, 2H, H1′), 3.69–3.62 (m, 1H, H11), 3.52 (d, J = 14.0 Hz, 1H, H7), 3.02–2.88 (m, 1H, H$_\alpha$13), 2.83–2.76 (m, 1H, H9), 2.76–2.65 (m, 1H, H13), 2.55 (dd, J = 15.0, 8.0 Hz, 1H, H17), 2.40 (dd, J = 14.0, 7.0 Hz, 1H, H2), 1.88 (s, 1H, H14), 1.87–1.77 (m, 1H, H9), 1.48 (d, J = 8.0 Hz, 1H, H2), 1.47 (s, 1H, H15), 1.17–1.10 (m, 1H), 1.10–1.05 (m, 6H, H18,19). **^{13}C NMR (75 MHz, CDCl$_3$)** δ ppm 196.7 (C3), 176.5 (C16), 159.9 (C1), 139.2 (C4), 136.6 (C5), 129.2 (C2), 128.6, 128.3, 127.5, 72.1 (C10), 69.6 (C8), 60.8 (C11), 60.1, 59.3, 53.4, 52.8 (C13), 50.5, 47.5 (C9), 44.2, 39.8, 34.2 (C17), 29.55 (C15), 19.79 (C14), 18.77 (C18), 18.57 (C19). **IR cm^{-1}:** 3476, 2974, 2936, 2877, 2829, 1770, 1731, 1653, 1454, 1387, 1373, 1347, 1273, 1252, 1180, 1155, 1092, 994, 930, 918, 869, 850, 738. **HRMS**: m/z calculated for $C_{27}H_{35}NO_6$ $[M+H]^+$ 470.25, found 470.2517.

(6R,7R,8R,10R,11R,1Z,4E)-10-hydroxy-4,10-dimethyl-3,12-dioxo-11-((piperidin-1′-ylmethyl)-3,6,7,8,9,10,11,12-octahydrocyclodeca[b]furan-8-yl isobutyrate (7c):

Reaction of Piperidine (0.17 mmol, 15 mg), Tagitinin C (0.17 mmol, 59 mg), in dichloromethane.



Yield: 95% (0.16 mmol, 70 mg), yellow pale oil.

$[\alpha]_D^{22}$ = −92.3 (c = 0.1, MeOH).

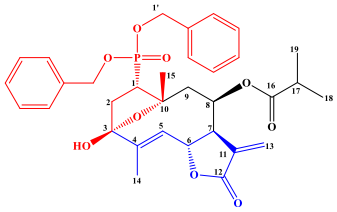
^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 6.86 (d, J = 17.0 Hz, 1H, H1), 6.19 (d, J = 17.0 Hz, 1H, H2), 6.06 (dd, J = 9.0, 101 Hz, 1H, H5), 5.46 (t, J = 8.0 Hz, 1H, H8), 5.37 (d, J = 9.0 Hz, 1H, H6), 3.16 (d, J = 9.0 Hz, 1H, H7), 3.03 (dd, J = 10.0, 4.0 Hz, 1H, Hα13), 3.05–2.97 (m, 1H, H11), 2.69 (d, J = 4.0 Hz, 1H, Hα9), 2.65 (d, J = 4.0 Hz, 1H, Hβ13), 2.54 (dd, J = 14.0, 7.0 Hz, 1H, H17), 2.42 (dd, J = 14.0, 7.0 Hz, 6H), 2.31 (s, 3H), 2.22 (d, J = 3.0 Hz, 1H), 1.95 (s, 3H, H14), 1.80 (d, J = 9.0 Hz, 1H, Hβ9), 1.48 (s, 3H, H15), 1.06 (dd, J = 7.0, 3.0 Hz, 6H, H18,19). **^{13}C NMR (75 MHz, CDCl$_3$)** δ ppm 196.7 (C3), 177.2 (C16), 176.3 (C12), 159.8 (C1), 139.4 (C4), 137.0 (C5), 129.5 (C2), 76.8 (C10), 72.1 (C6), 69.7 (C8), 54.6 (C11), 53.7 (C7), 47.9 (C13), 44.9 (C9), 39.2, 34.3 (C17), 29.5, 26.2, 24.4 (C14), 20.0 (C15), 18.9 (C18), 18.8 (C19). **IR** cm^{-1}**:** 3486, 2971, 2936, 2879, 2854, 2362, 2337, 1774, 1733, 1655, 1469, 1452, 1377, 1350, 1255, 1184, 1154, 1128, 1070, 1025, 991, 932, 870, 739, 716. **HRMS:** m/z calculated for $C_{24}H_{35}NO_6$ $[M+H]^+$ 434.2464, found 434.2520.

4.2.3. General procedure for the synthesis of Tagitinin C phosphonate (or thiol) derivatives

To a solution of nucleophile (phosphonate or thiol, 1 equiv.) and catalyst (trimethylamine or DBU, 0.2 equiv.) was added a solution of Tagitinin C (1 equiv.) in dichloromethane (1 ml) at 22 °C. The mixture was stirred in dark for the required time. The reaction was monitored by TLC and NMR. After completion, water was added and the reaction mixture was extracted with dichloromethane (3 × 5 ml). Solvent was evaporated under vacuum and the crude product was purified by filtration on silica gel.

(1S,3R,6R,7R,8R,E)-1-(bis(benzyloxy)phosphoryl)-3-hydroxy-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (9a):

Reaction of Dibenzyl phosphite (0.13 mmol, 35 mg), Tagitinin C (0.13 mmol, 46 mg), in dichloromethane.



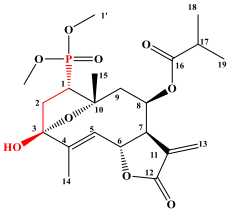
Yield: 89% (0.12 mmol, 71 mg), yellow pale oil.

$[\alpha]_D^{22}$ = −183.3 (c = 0.1, MeOH).

^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.41–7.27 (m, 10H, Har), 6.22 (d, J = 3.0 Hz, 1H, H$_\alpha$13), 5.60 (d, J = 2.0 Hz, 1H, H5), 5.55 (d, J = 2.0 Hz, 1H, Hβ13), 5.28 (s, 1H, H6), 5.07–4.93 (m, 1H, H1′), 4.93–4.86 (m, 1H, H8), 4.04 (s, 1H, H7), 2.79 (ddd, J = 19.0, 13.0, 6.1 Hz, 1H, H1), 2.37 (dd, J = 13.0, 6.0 Hz, 1H, H$_\alpha$2), 2.44–2.17 (m, 1H, H17), 2.24 (d, J = 13.0 Hz, 1H, H$_\alpha$9), 2.26 (d, J = 12.0 Hz, 1H, Hβ2), 1.90 (dd, J = 14.0, 5.0 Hz, 1H, Hβ9), 1.80 (s, 3H, H14), 1.53 (s, 3H, H15), 1.06–1.01 (m, 6H, H17,18). **^{13}C NMR (75 MHz, CDCl$_3$)** δ ppm 176.0 (C16), 169.8 (C12), 139.6 (C4), 136.2 (C11), 129.0, 128.9, 128.3, 128.3 (C5), 122.9 (C13), 104.6 (C3), 84.4 (C10), 75.5 (C6), 70.3 (C8), 67.9 (C1′), 50.0 (C7), 46.5 (C1), 44.5, 39.6 (C2), 37.5 (C9), 34.2 (C17), 28.0 (C15), 22.7 (C14), 19.3 (C18), 18.8 (C19). **IR** cm^{-1}**:** 3275, 2973, 2881, 2840, 2362, 2337, 1763, 1732, 1653, 1472, 1454, 1379, 1357, 1248, 1202, 1126, 1076, 1023, 988, 963, 927, 838, 744, 720, 701, 616. **HRMS**: m/z calculated for $C_{33}H_{39}O_9P$ $[M+H]^+$ 611.2332, found 611.2397.

(1S,3R,6R,7R,8R,E)-1-(dimethyloxyphosphoryl)-3-hydroxy-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (9b):

Reaction of Dimethyl phosphite (0.32 mmol, 35 mg), Tagitinin C (0.32 mmol, 110 mg), in dichloromethane.



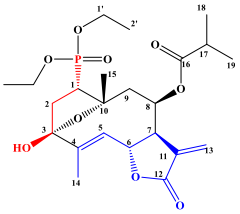
Yield: 99% (0.32 mmol, 145 mg), yellow pale oil.

$[\alpha]_D^{22}$ = −86.7 (c = 0.7, MeOH).

^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 6.23 (d, J = 3.0 Hz, 1H, H$_\alpha$13), 5.67–5.60 (m, 1H, H8), 5.60 (d, J = 5.0 Hz, 1H, H5), 5.57 (d, J = 2.0 Hz, 1H, Hβ13), 5.38 (d, J = 2.0 Hz, 1H, H6), 4.08 (ddd, J = 7.0, 5.0, 2.0 Hz, 1H, H7), 3.76 (dd, J = 11.0, 1.0 Hz, 6H, H1′), 2.81 (ddd, J = 19.0, 13.0, 6.0 Hz, 1H, H1), 2.42 (ddd, J = 14.0, 10.0, 5.0 Hz, 1H, H17), 2.37 (d, J = 2.0 Hz, 1H, H$_\alpha$2), 2.29 (dd, J = 13.0, 11.0 Hz, 1H, H$_\alpha$9), 2.29 (d, J = 2.0 Hz, 1H, Hβ2), 1.89 (dd, J = 15.0, 5.0 Hz, 1H, Hβ9), 1.83 (s, 3H, H14), 1.60 (s, 3H, H15), 1.04 (t, J = 7.0 Hz, 6H, H18,19). **^{13}C NMR (75 MHz, CDCl$_3$)** δ ppm 176.2 (C16), 169.9 (C12), 139.9 (C4), 136.3 (C11), 128.9 (C5), 122.9 (C13), 104.7 (C3), 84.2 (C10), 75.5 (C6), 70.4 (C8), 52.7 (C1′), 50.0(C7), 45.6 (s), 43.6 (C1), 39.7 (C2), 37.4 (C9), 34.2 (C17), 27.9 (C15), 22.8 (C14), 19.2 (C18), 18.8 (C19). **IR** cm^{-1}: 3282, 2972, 2876, 2853, 1764, 1730, 1647, 1469, 1375,1248, 1219, 1126, 1074, 1034, 988, 965, 920, 836, 748, 717, 616. **HRMS**: m/z calculated for $C_{21}H_{31}O_9P$ $[M+H]^+$ 459.1706, found 459.1777.

(1S,3R,6R,7R,8R,E)-1-(diethyloxyphosphoryl)-3-hydroxy-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (9c):

Reaction of Diethyl phosphite (0.17 mmol, 23 mg), Tagitinin C (0.17 mmol, 59 mg), in dichloromethane.



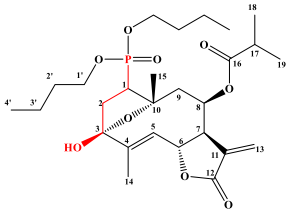
Yield: 94% (0.16 mmol, 78 mg), yellow pale oil.

$[\alpha]_D^{22} = -146.8$ (c = 0.3, MeOH).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.24 (d, J = 3.0 Hz, 1H, H_α13), 5.64 (d, J = 2.0 Hz, 1H, H5), 5.63–5.58 (m, 1H, H8), 5.57 (d, J = 2.0 Hz, 1H, H_β13), 5.38 (d, J = 1.0 Hz, 1H, H6), 4.11 (ddd, J = 12.0, 8.0, 4.0 Hz, 5H, H7), 2.83–2.71 (m, 1H, H1), 2.49–2.26 (m, 6H, H17), 2.35 (dd, J = 13.0, 6.0 Hz, 4H, H2, H17, H_α9), 2.28 (d, J = 13.0 Hz, 1H, Hβ2), 1.92 (dd, J = 14.0, 5.0 Hz, 2H, H_β9), 1.84 (s, 3H, H14), 1.60 (s, 3H, H15), 1.32 (dd, J = 10.0, 4.0 Hz, 6H, H2′), 1.04 (t, J = 7.0 Hz, 6H, H18,19). **^{13}C NMR (75 MHz, $CDCl_3$)** δ ppm 176.0 (C16), 169.7 (C12), 139.7 (C4), 136.1 (C11), 128.9 (C5), 122.8 (C13), 104.8 (C3), 84.2 (C10), 75.4 (C6), 70.3 (C8), 62.1 (C1′), 49.8 (C7), 46.0 (C1), 44.0 (C2), 39.6, 37.2 (C9), 34.0 (C17),27.9 (C15), 22.6 (C14), 19. (C-18), 18.7 (C19), 16.6 (C2′). **IR** cm^{-1}**:** 3282, 2976, 1763, 1731, 1469, 1389, 1247, 1218, 1126, 1074, 1020, 988, 965, 918, 818, 748, 729, 615. **HRMS**: *m/z* calculated for $C_{23}H_{35}O_9P$ $[M+H]^+$ 487.2019, found 487.2073.

(1S,3R,6R,7R,8R,E)-1-(dibutyloxyphosphoryl)-3-hydroxy-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (9d):

Reaction of Dibutyl phosphite (0.2 mmol, 39 mg), Tagitinin C (0.2 mmol, 69 mg), in dichloromethane.



Yield: 99% (0.2 mmol, 108 mg), yellow pale oil.

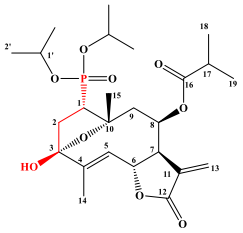
$[\alpha]_D^{22} = -117.5$ (c = 1.0, MeOH).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.24 (d, J = 3.0 Hz, 1H, H_α13), 5.67–5.58 (m, 2H, H5,8), 5.57 (d, J = 2.0 Hz, 1H, H_β13), 5.37 (d, J = 2.0 Hz, 1H, H6), 4.11–4.00 (m, H, H7), 2.85–2.73 (m, 1H, H1), 2.45–2.28 (m, 4H, H_α2,H_α9,17, H_β2), 1.92 (dd, J = 15.0, 5.0 Hz, 1H, H_β9), 1.84 (s, 3H, H14), 1.70–1.62 (m, 4H, H2′), 1.61 (s, 3H, H15), 1.39 (dd, J = 15.0, 7.3 Hz, 4H, H3′), 1.12 (dd, J = 7.0, 2.0 Hz, 1H), 1.04 (dd, J = 7.0, 6.0 Hz, 6H, H18,19), 0.94 (t, J = 7.0 Hz, 6H, H4′). **^{13}C NMR (75 MHz, $CDCl_3$)** δ ppm 175.9 (C16), 169.7 (C12), 139.8 (C4), 136.1 (C11), 128.8 (C5), 122.8 (C13), 104.6 (C3), 84.1 (C10), 75.4 (C6), 70.3 (C8), 65.8 (C1′), 49.9 (C7), 46.0 (C1), 44.0 (C2), 39.6 (C17), 37.3 (C9), 32.5 (C2′), 27.9 (C15), 22.6 (C14), 19.1 (C18), 18.8 (C19), 18.6 (C3′), 13.6 (C4′).

IR cm^{-1}: 3298, 2962, 1763, 1733, 1648, 1466, 1385, 1281, 1248, 1218, 1125, 1060, 1019, 989, 912, 819, 750, 723, 617. **HRMS**: *m/z* calculated for $C_{27}H_{43}O_9P$ $[M+H]^+$ 543.2645, found 543.2699.

(1S,3R,6R,7R,8R,E)-1-(diisopropyloxyphosphoryl)-3-hydroxy-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (9e):

Reaction of Diisopropyl phosphite (0.17 mmol, 28 mg), Tagitinin C (0.17 mmol, 59 mg), in dichloromethane.



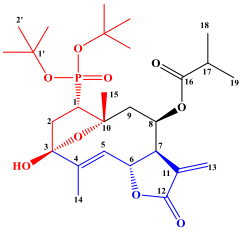
Yield: 77% (0.13 mmol, 67 mg), yellow pale oil.

$[\alpha]_D^{22} = -105.6$ (c = 1.0, MeOH).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.23 (d, J = 3.0 Hz, 1H, H_α13), 5.62 (d, J = 2.0 Hz, 1H, H5), 5.63–5.58 (m, 1H, H8), 5.56 (d, J = 2.0 Hz, 1H, H_β13), 5.37 (d, J = 2.0 Hz, 1H, H6), 4.77–4.64 (m, 2H, H1′), 4.11–4.05 (m, 1H, H7), 2.71 (ddd, J = 19.0, 13.0, 6.0 Hz, 1H, H1), 2.65 (d, J = 6.0 Hz, 1H, H_α9), 2.45–2.31 (m, 1H, H17), 2.28 (d, J = 11.0 Hz, 1H, H_β9), 2.24 (d, J = 13.0 Hz, 1H, H_α2), 1.93 (dd, J = 15.0, 5.0 Hz, 1H, H_β2), 1.83 (s, 3H, H14), 1.60 (s, 3H, H15), 1.31 (t, J = 6.0 Hz, 12H, H2′), 1.05–1.02 (t, J = 7.0, 4.0 Hz, 6H, H18,19). **^{13}C NMR (75 MHz, $CDCl_3$)** δ ppm 176.0 (C16), 169.8 (C12), 140.1 (C4), 136.2 (C11), 128.6 (C5), 122.7 (C13), 104.6 (C3), 84.1 (C10), 75.5 (C6), 70.8 (C8), 70.5 (C1′), 49.8 (C7), 46.8 (C1), 44.8 (C2), 39.7 (C17), 37.2 (C9), 34.1,27.9 (C15), 24.1 (C2′), 22.7 (C14), 19.0 (C18), 18.7 (C19). **IR** cm^{-1}: 3287, 2978, 1763, 1729, 1648, 1469, 1387, 1282, 1247, 1216, 1126, 1053, 1014, 988, 910, 818, 748, 718, 616. **HRMS:** *m/z* calculated for $C_{25}H_{39}O_9P$ $[M+H]^+$ 515.2332, found 515.2378.

(1S,3R,6R,7R,8R,E)-1-(di-tert-butyloxyphosphoryl)-3-hydroxy-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (9f):

Reaction of Ditertbutyl phosphite (0.17 mmol, 28 mg), Tagitinin C (0.17 mmol, 59 mg), in dichloromethane.



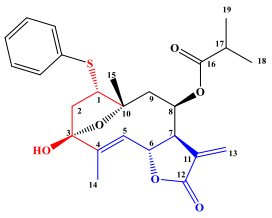
Yield: 80% (0.14 mmol, 74 mg), yellow pale oil.

$[\alpha]_D^{22} = -62.1$ (c = 0.5, MeOH).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.21 (d, J = 3.0 Hz, 1H, H_α13), 5.62–5.52 (m, 3H, H5,H8,H_β13), 5.34 (d, J = 2.0 Hz, 1H, H6), 4.09 (s, 1H, H7), 2.69–2.61 (m, 1H, H1), 2.57 (s, 1H), 2.44–2.31 (m, 3H, H_α9, H17, H_α2), 2.29–2.14 (m, 1H), 2.00–1.94 (m, 2H, H_β2, H_β9), 1.83 (s, 3H, H14), 1.60 (s, 3H, H15), 1.49 (d, J = 3.0 Hz, 18H, H2′), 1.02–0.98 (m, 6H,H18,19). **^{13}C NMR (75 MHz, $CDCl_3$)** δ ppm 175.9 (C16), 169.9 (C12, 140.7 (C4), 136.4 (C11), 128.3 (C5), 122.8 (C13), 104.2 (C3), 84.2 (C10), 75.7 (C6), 70.7 (C8), 53.6 (C1′), 50.0 (C7), 47.4 (C1), 40.7 (C2), 37.4 (C9), 34.2 (C17), 30.5 (2′), 28.1 (C14), 22.9 (C15), 19.1 (C18), 18.9 (C19). **IR** cm^{-1}: 3303, 2978, 1763, 1732, 1648, 1469, 1395, 1284, 1259, 1207, 1124, 1040, 1011, 984, 920, 820, 753, 715, 616. **HRMS:** *m/z* calculated for $C_{25}H_{39}O_9P$ $[M+H]^+$ 543.2645, found 543.2514.

(1S,3R,6R,7R,8R,E)-3-hydroxy-4,10-dimethyl-11-methylene-12-oxo-1-(phenylthio)-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (11a):

Reaction of Phenyl thiol (0.14 mmol, 15 mg), Tagitinin C (0.14 mmol, 50 mg), in dichloromethane.



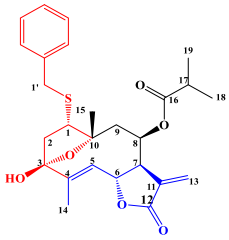
Yield: 99% (0.14 mmol, 64 mg), yellow pale oil.

$[\alpha]_D^{22} = -145.1$ (c = 0.5, MeOH).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H, H_{Ar}), 6.17 (d, J = 3.0 Hz, 1H, H_α13), 5.56 (dd, J = 6.0, 4.0 Hz, 2H, H5, H8), 5.51 (d, J = 3.0 Hz, 1H, H_β13), 5.31 (s, 1H, H6), 4.05 (ddd, J = 7.0, 4.0, 2.0 Hz, 1H, H7), 3.76 (ddd, J = 12.0, 6.0, 3.0 Hz, 1H, H1), 2.56 (d, J = 7.0 Hz, 1H, H_α9), 2.46–2.39 (d, J = 4.0 Hz, 1H, H_α2), 2.40–2.35 (m, 1H, H17), 2.07 (d, J = 7.0 Hz, 1H,H_β9), 1.86 (d, J = 4.0 Hz, 1H, H_β2), 1.74 (s, 1H, H14), 1.38 (s, 1H, H15), 1.00 (dd, J = 9.0, 7.0 Hz, 6H, H18,19). **^{13}C NMR (75 MHz, $CDCl_3$)** δ ppm 176.1 (C16), 169.8 (C12), 140.1 (C4), 136.1 (C5), 132.1 (C11), 129.3 (CAr), 128.6 (CAr), 127.7 (CAr), 126.9 (CAr) 122.9 (C13), 104.1 (C3), 84.4 (C10), 75.4 (C6), 70.6 (C8), 55.2 (C7), 49.6 (C1), 44.9 (C2), 36.9 (C9), 34.1 (C17), 26.7 (C14), 22.66 (C15), 19.1 (C18), 18.7 (C19). **IR** cm^{-1}**:** 3454, 2971, 2931,1765, 1734, 1583, 1469, 1439, 1381, 1335, 1281, 1254, 1184, 1149, 1122, 1067, 1018, 987, 910, 815, 742, 692. **HRMS**: *m/z* calculated for $C_{25}H_{30}O_9S$ $[M+H]^+$ 459.1763, found 459.1822.

(1S,3R,6R,7R,8R,E)-1-(benzylthio)-3-hydroxy-4,10-dimethyl-11-methylene-12-oxo-1,2,3,6,7,8,9,10,11,12-decahydro-3,10-epoxycyclodeca[b]furan-8-yl isobutyrate (11b):

Reaction of Benzylthiol (0.19 mmol, 24 mg), Tagitinin C (0.19 mmol, 66 mg), in dichloromethane.



Yield: 88% (0.17 mmol, 79 mg), yellow pale oil.

$[\alpha]_D^{22} = -130.7$ (c = 0.4, MeOH).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.22 (dd, J = 12.0, 4.0 Hz, 5H, H_{Ar}), 6.15 (d, J = 3.0 Hz, 1H, H_α13), 5.53–5.50 (m, 1H, H8), 5.49 (d, J = 2.0 Hz, 1H, H5), 5.48 (dd, J = 6.0, 4.0 Hz, 1H, H_β13), 5.26 (dd, J = 6.0, 4.0 Hz, 1H, H6), 4.05–3.98 (m, 1H, H7), 3.70 (d, J = 3.0 Hz, 1H, H1′), 3.26 (dd, J = 13.0, 6.0 Hz, 1H, H1), 2.41 (d, J = 6.0 Hz, 1H, H_α9), 2.34 (dd, J = 10.0, 4.0 Hz, 1H, H17), 2.00 (d, J = 5.0 Hz, 1H, H_α2), 1.93 (d, J = 6.0 Hz, 1H, H_β9), 1.76 (d, J = 5.0 Hz, 1H, H_β2), 1.72 (s, 3H, H14), 1.33 (s, 3H, H15), 0.96 (d, J = 7.0 Hz, 6H, H18, H19). **^{13}C NMR (75 MHz, $CDCl_3$)** δ ppm 176.0 (C16), 169.8 (C12), 140.2 (C4), 137.7 (C5), 136.2 (C11), 128.9 (CAr), 128.7 (CAr) 127.4 (CAr), 122.8 (C13), 104.2 (C3), 84.2 (C10), 75.5 (C6), 70.5 (C8), 51.6 (C7), 49.5 (C1), 45.2 (C9), 37.0 (C1′), 36.0 (C2), 34.0 (C17), 26.5 (C14), 22.7 (C15), 19.1 (C18), 18.6 (C19). **IR** cm^{-1}: 3460, 2974, 2939, 1763, 1733, 1585, 1467, 1454, 1380, 1333, 1281, 1254, 1185, 1151, 1122, 1070, 1016, 988, 912, 816, 736, 704. **HRMS:** *m/z* calculated for $C_{26}H_{32}O_9S$ $[M+H]^+$ 473.1920, found 473.1980.

4.3. Biological tests

4.3.1. In vitro cell-proliferation assay

Four cell lines have been used for the in vitro evaluation of the designed Tagitinin-C analogs in comparison to the parent drug: tagitinin C (Tag-C): one normal cell line: HEK-293 (Human embryonic kidney cells) and three cancerous cell line: MiaPaCa-2 (Pancreatic Cancer), MCF-7 (Breast cancer) and MCF-7 MDR (multi-drug resistant Breast cancer). All cells were grown in DMEM (Dulbecco's Modified Eagle Medium) supplemented with 10% of fetal calf serum (FCS) and 100 U/mL penicillin and 100 μg/mL streptomycin (Invitrogen) in a 5% CO_2 and 95% hygrometry environment at 37 °C.

The Cytotoxic activity of all the designed analogs (X) have been investigated using the MTS ((3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium)) method (Promega). The cells (100 μL) were seeded in 96-well plates at optimal cell density determined previously and incubated overnight at 37 °C in presence 5% CO_2 and 95% hygrometry. Firstly, a broad study of the analogs activity was fulfilled by testing at 1 μM to establish the most sensitive cell line. Assay using 250 nM and 500 nM concentration of each designed analog was then fulfilled. Finally, a more precise IC_{50} determination study was conducted on the most potent analogs. To do so, after adhesion of the cells overnight, they were treated with 100 μL of each compound at different concentrations (i.e. 0.0025, 0.005, 0.025, 0.05, 0.25, 0.5, 2.5, 5, 25, 50 μM). After 72 h, the media was aspirated and 100 μL of a MTS solution (10% in media) were added in each well. Depending on the cell line, 2–5 h incubation at 37 °C in presence 5% CO_2 and 95% hygrometry were needed to obtain the optimum optical density which was measured at 490 nm wavelength using a microplate reader (Infinite M200 Pro, Tecan trading AG, Switzerland). Untreated cells were used as control. Each concentration was tested in six replicates and the experiment was fulfill in triplicates. The concentration inhibiting 50% of the cell proliferation (IC_{50}) was determined using with GraphPad Prism software (GraphPad Software Inc, San Diego, CA, USA).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132248.

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