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Original Mitsunobu triggered sequence involved in a one-pot domino process toward tetracyclic systems bearing bis-*N*,*O*-acetal junction

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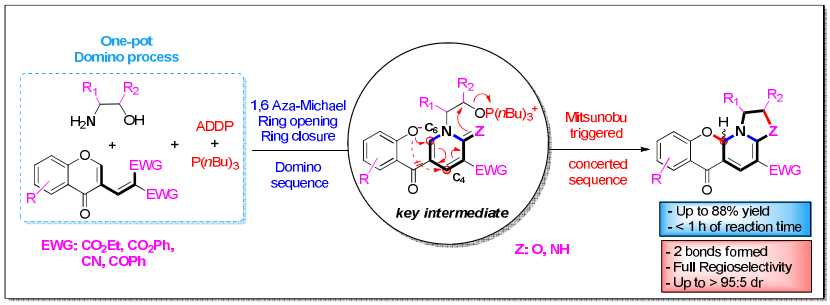
Keywords: 2-Pyridones, Chromone-based Michael acceptor, Mitsunobu reaction, one-pot domino reaction, bis-N,O-acetal junction.

ABSTRACT: Herein is reported an efficient one-pot domino process through a 1,6-aza-Michael addition-triggered sequence and an original Mitsunobu-type concerted sequence, for the synthesis of tetracyclic systems containing a bis-*N,O*-acetal junction. This methodology led to the construction of four new bonds, the cleavage of three C-O bonds and the generation of an asymmetric center. Mitsunobu activation afforded final ring closure involving the creation of two bonds which remains unprecedented among reported Mitsunobu-type sequences. The latter occurred in a regioselective fashion at the challenging C_6-position of 2-pyridone intermediates. In case of adequately substituted enantiopure amino alcohols, up to 95: 5 of diastereoisomeric excess was achieved. Computational studies allowed the discrimination of a favored pathway for Mitsunobu sequence and supported the regioselectivity as well as the diastereoselectivity observed for this step.



INTRODUCTION

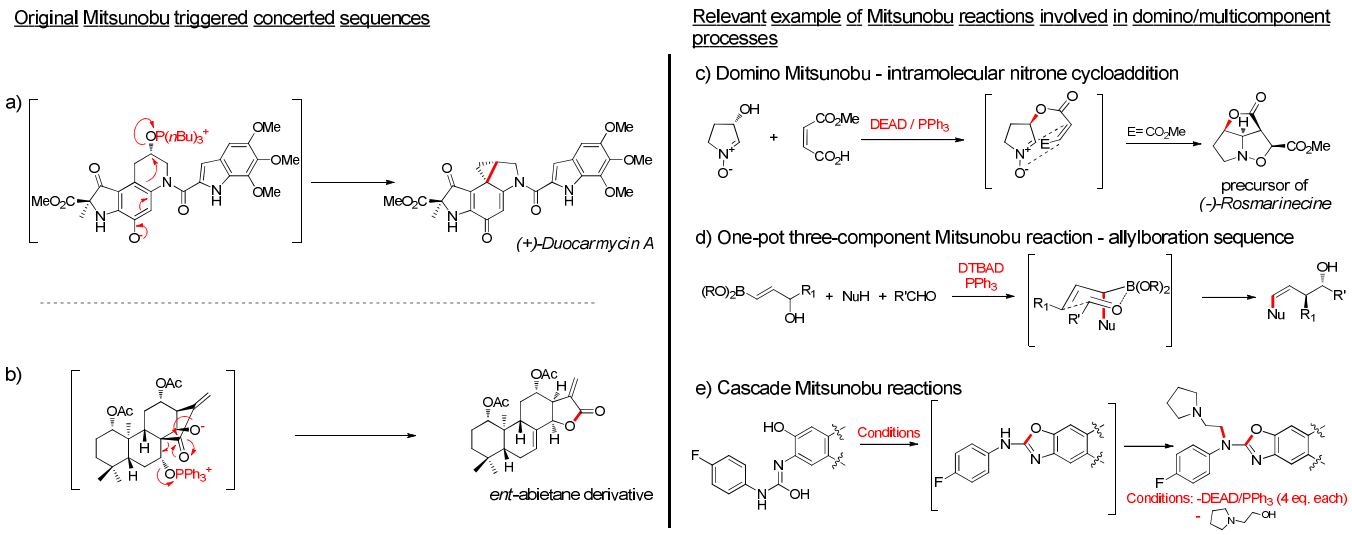
Late 20th-early 21st centuries have witnessed an unprecedented boom of powerful tools such as domino sequences,[1,2] or multicomponent[3,4] reactions to access architecturally complex molecular frameworks. Quickly, this modern conception of organic chemistry is replacing traditional stepwise approach to meet environmental and economic demands, in particular for the high-throughput screening of novel scaffolds of biological interest.

Fundamental named reactions have reached a privileged place in this new branch of research as they frequently are involved or even combined[5] in such processes. Among these, Michael addition,[6] Knoevenagel condensation,[7] Mannich reaction,[8] Claisen rearrangement[9] or Diels-Alder reaction[10] are widely used. Remarkable metal-catalyzed reactions such as Heck[11] or metathesis[12] coupling-reactions also have emerged in a wide range of domino sequences to achieve molecular complexity. Nevertheless, a few popular reactions among this restricted elite group still remain disregarded despite their high synthetic relevance.

Mitsunobu coupling is a commonly known essential reaction in organic synthesis.[13] Its broad synthetic versatility makes it a powerful strategy for the construction of novel C-O,[14] C-N,[15] C-S[16] or C-C[17] bonds. Interesting Mitsunobu-triggered concerted sequences which could be incorporated in domino strategies have been reported in the literature (Scheme 1, examples a and b). Among the very scarce examples known, one has been reported by Boger *et al.* in last step of *(+)-Duocarmycin-A* total synthesis,[18] to allow the pivotal cyclopropanation reaction (Scheme 1, example a). More recently Takeya and co-workers also proposed an interesting rearrangement under Mitsunobu activation for efficient transformation of 7,14-dihydroxy-*ent*-kaurene diterpenoids, commonly found in *Rabdosia* plant species, into *ent*-abietanes (Scheme 1, example b).[19]

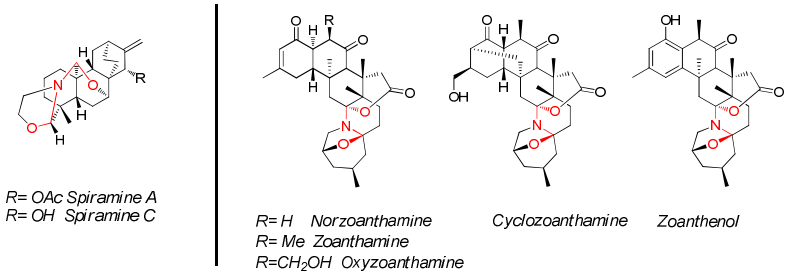
However, Mitsunobu activation remains too rarely involved in domino processes or multicomponent reactions. The first relevant example has been reported by Goti *et al*. in (-)-*Rosmarinecine* total synthesis (Scheme 1, example c).[20] Ring-fused tricyclic precursor of this bioactive alkaloid was achieved by an elegant domino Mitsunobu intramolecular nitrone cycloaddition process. Comparatively, Greshock *et al.* later reported a Mitsunobu triggered biomimetic pathway involving Diels-Alder cycloaddition for the total synthesis of *D,L-Stephacidin-A*.[21] More recently, Berrée and co-workers described the first and unique Mitsunobu transformation involved in a one-pot multicomponent reaction (Scheme 1, example d)[22] to provide enamides and enol benzoates. Finally, cascade/tandem sequences involving consecutive Mitsunobu activations also were studied by Yan *et al.* (Scheme 1, example e)[23] and Ganesan *et al.*[24] amongst two other groups.[25]

Scheme 1. Modern applications of Mitsunobu activation in domino/multicomponent/concerted sequences



Driven by the high efficiency of such strategies and in keeping with our previous work (Scheme 3),[26] we envisioned to develop a one-pot domino aza-Michael/Mitsunobu process to access tetracyclic frameworks bearing bis-*N,O*-acetal junction. This atypical junction is found in structurally complex bioactive natural products such as spiramine[27] and zoanthamine[28] alkaloids (Scheme 2).

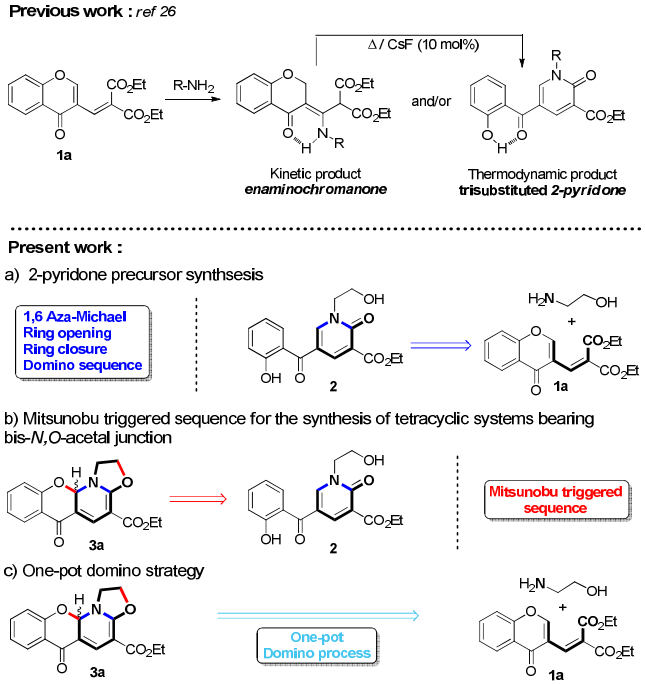
Scheme 2. Representative structures of Spiramine and Zoanthamine alkaloids



In this perspective, starting from adequately *N*-substituted 2-pyridone, we anticipated that Mitsunobu activation could be an attractive solution to achieve bis-*N,O*-acetal junction (Scheme 3, example b), allowing *in situ* generation of a leaving group on the alcohol moiety

and phenolic group deprotonation. This activation would not be incompatible with experimental conditions for 2-pyridone intermediate synthesis (Scheme 3, example a)[26] and would thus be suitable for the envisioned one-pot domino strategy (Scheme 3, example c). Moreover, the easy access to a large panel of amino alcohols and Michael acceptors bearing the chromone core offers an interesting flexibility in term of reaction scope. Mitsunobu-triggered final ring closure would lead to the intramolecular formation of two new bonds which has not been reported so far in Mitsunobu type sequences.

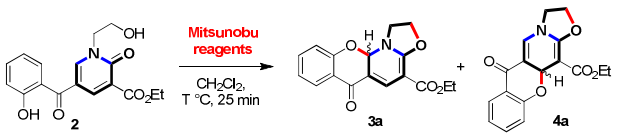
Scheme 3. Domino strategy for the synthesis of nitrogen fused oxazolopyridines analogues.



RESULTS AND DISCUSSION

We started to investigate Mitsunobu sequence on the 2-pyridone derivative **2** (Table 1) as model substrate, synthesized from **1a** according to our previous work.[26] Different conditions were screened and the results are summarized in Table 1.

Table 1. Screening of experimental conditions for Mitsunobu activation.



Entry	Diazo reagent (1.6 eq.)	PR_3 (1.6 eq.)	T (°C)	Conversion[a] / Yield (%)[b]	Ratios (3a : 4a)
1[c]	DEAD	PPh_3	t.a	79 (0)[d]	1 : 0
2	DEAD	PPh_3	t.a	100 (0)[d]	1 : 0
3[e]	ADDM	$P(nBu)_3$	t.a	100 (86)	1 : 0
4	ADDM	$P(nBu)_3$	40	100 (88)	1 : 0
5[f]	DDQ	$P(nBu)_3$	40	0	-
6	ADDP	$P(nBu)_3$	40	100 (92)	1 : 0
7	DCAD	$P(nBu)_3$	40	100 (91)	1 : 0
8[f]	ADDP	$P(OEt)_3$	40	0	-

9[f]	ADDP	$P(cy)_3$	40	0	-
10[f]	ADDP	$P(p\text{-mp})_3$[g]	40	0	-
11[h]	-	-	40	0	-

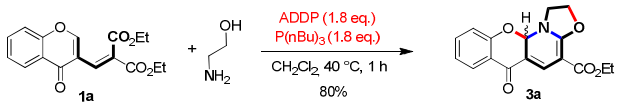
[a] Determined by ^1H NMR spectroscopy. [b] Isolated yield. [c] Reaction carried out for 1h in presence of 1.3 eq. of each Mitsunobu reagents. [d] Product **3a** was inseparable from Mitsunobu by-products. [e] The reaction appeared to be non reproducible. [f] The reaction was carried out for 1h. [g] $P(p\text{-mp})_3$: Tris(4-methoxyphenyl)phosphine. [h] Reaction carried out in presence of 1.1 eq. of NEt_3 as a base.

Usual Mitsunobu system (DEAD (diethyl azodicarboxylate) /PPh_3) was tested in a first attempt. We were pleased to observe that full conversion into the desired compound **3a** was achieved in only 25 minutes at ambient temperature (entry 2) when 1.6 equivalents of each Mitsunobu reagents were used. Moreover the reaction proceeded regioselectively at C_6-position of 2-pyridone ring since no traces of **4a** were detected. Unfortunately oxazolopyridine product appeared to be non-isolable from residuals dihydro-diethyl azodicarboxylate (DEAD-H_2) and triphenylphosphine oxide formed during Mitsunobu reaction.

In the past few years recurrent post purification problems of Mitsunobu reactions has led to the emergence of a new generation of Mitsunobu reagents (both phosphines and azidocarboxylates),[29] devised to facilitate the reaction workup. We thus turned our attention to ADDM (azodicarbonyl dimorpholide),[30] DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone),[31] ADDP (1,1′-(azodicarbonyl)dipiperidine)[32] and DCAD (Di-*p*-chlorobenzyl azidocarboxylate).[33] The latter have been proved to be at least as efficient as DEAD and their dihydro analogues more easily removable by column chromatography due to their higher polarity.[29] Satisfactorily, replacing DEAD/PPh_3 by ADDM/P(*n*Bu)$_3$ afforded the expected product in 86% of isolated yield (entry 3). We then decided to carry out the reaction at 40 °C as the latter was irreproducible depending on ambient temperature variation. Mitsunobu sequence was positively affected by increasing temperature since compound **3a** was isolated in 88% yield (entry 4). Unfortunately, when ADDM was replaced by DDQ the reaction was negatively impacted as no conversion was observed (entry 5). To conclude the screening on diazo reagents, ADDP and DCAD were tested without significant changes observed in the reaction profile in comparison to ADDM (entries 6 and 7). ADDP was finally chosen as most convenient azido reagent mainly due to its easier and cheaper access in comparison to DCAD. Different phosphines were finally compared to P(*n*Bu)$_3$ but none of them afforded the desired compound (entries 8-10). Only starting material was fully recovered. It can be mentioned that addition of P(*n*Bu)$_3$ in corresponding resulting mixtures afforded full conversion into **3a** indicating that all tested phosphines did not react with ADDP.

Having established optimal reaction conditions for Mitsunobu-triggered sequence we then tested their efficiency in the one-pot domino process starting from substrate **1a** (Scheme 4).

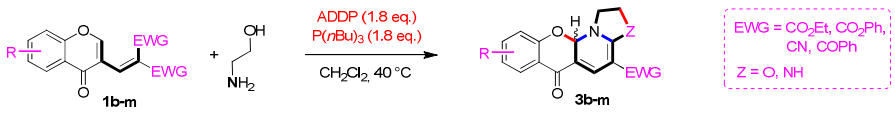
Scheme 4. One-pot domino sequence under optimized Mitsunobu conditions

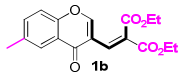
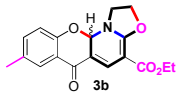
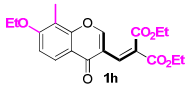
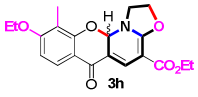
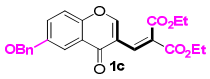
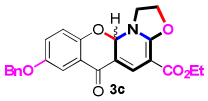
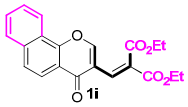
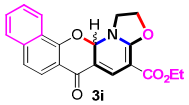
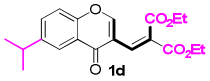
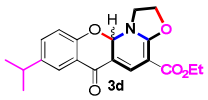
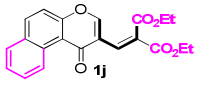
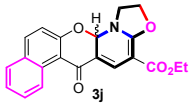
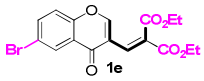
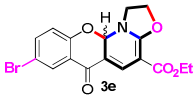
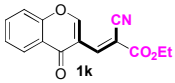
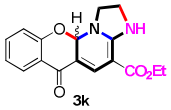
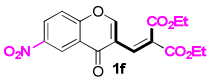
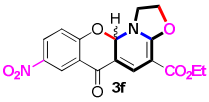
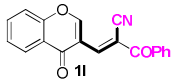
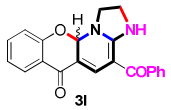
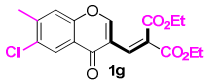
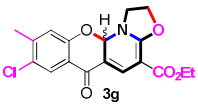
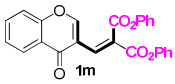
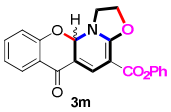


Pleasingly, starting from ethanolamine, Michael acceptor **1a** and 1.8 equivalents of each Mitsunobu reagents, the reaction led to desired nitrogen fused oxazolopyridine **3a** in full conversion and satisfactory 80% of isolated yield.

Scope and limitations of the reaction were then investigated on different chromone acceptors reacting with diversified amino alcohols. As it could be anticipated, depending on the chromone moiety substitution, phenolate reactivity of zwitterionic 2-pyridone intermediate directly impacted Mitsunobu sequence (Table 2).

Table 2. Impact of Michael acceptors substitution on domino process



Entry	Michael acceptor	Product	Time (min)	Yield (%)	Entry	Michael acceptor	Product	Time (min)	Yield (%)[a]
1	 1b	 3b	40	83	7	 1h	 3h	60	41
2	 1c	 3c	40	88	8	 1i	 3i	70	45
3	 1d	 3d	40	69	9	 1j	 3j	50	71
4	 1e	 3e	60	38 (54)[b]	10	 1k	 3k	50	63[d]
5	 1f	 3f	120	0[c]	11	 1l	 3l	40	69
6	 1g	 3g	60	60	12	 1m	 3m	40	81

[a] Isolated Yield. [b] Achieved by addition of an extra equivalent of Mitsunobu reagents in the reaction mixture after 1 h of reaction time. [c] The reaction stopped at the zwitterionic-2-pyridone stage. [d] Only 7% of conversion into the corresponding cyano oxazolopyridine was observed by ^{1}H NMR.

Electron donating groups (EDG) enhancing phenol nucleophilicity such as 5-substituted methylchromone or benzyloxychromone afforded corresponding oxazolo-pyridines **3b** and **3c**, respectively in 83% and 88% of isolated yields (entries 1 and 2). High reactivity was also observed for 5-substituted isopropylchromone although **3d** was isolated in 69% of yield (entry 3). On the other hand, when phenol group nucleophicility was weakened, the reaction was negatively impacted. A strong electron withdrawing group (EWG) such as nitro group in *para* position prevented Mitsunobu-domino sequence. Only the zwitterionic 2-pyridone intermediate was indeed observed after 2 hours of reaction time. Comparatively, 5-bromo substituted *α,β*-unsaturated chromone afforded desired product **3e** in modest 38% of isolated yield. In this case the decrease of phenolate reactivity also led to an incomplete conversion from corresponding 2-pyridone zwitterionic intermediate since the latter was detected in the reaction mixture at the end of the reaction. In a second attempt, an extra equivalent of

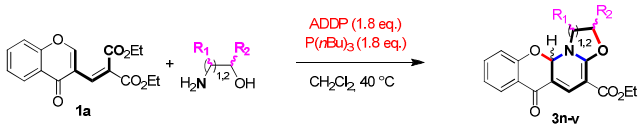
ADDP/P(nBu)$_3$ was added to the reaction media after 1 h of reaction time, in order to shift equilibrium in favor of oxazolopyridine derivative. However, no significant improvement was observed since **3e** was isolated in 54% yield. Domino process was then investigated with diverse electronic withdrawing groups on the Michael acceptor moiety. Interestingly, in case of non-symmetrical Michael acceptors bearing cyano/ester or cyano/ketone groups, excellent chemoselectivity was achieved in favor of imidazopyridines derivatives since **3k** and **3l** were obtained in respectively 93:7 and >99:1 ratios. This chemoselectivity could be explained by the higher reactivity of cyano group in the first ring closure step of the domino process, and the presence of an intramolecular hydrogen bond involved in formed imidazopyridines stabilization. It is worth mentioning that in the latter cases Mitsunobu sequence led to the formation of one C-O bond and one C-N bond. The structure of **3l** was confirmed by X-ray diffraction analysis (CCDC 1477526) (Figure 1). One molecule of dichloromethane appeared to be trapped in each asymmetric unit of the crystal matrix.

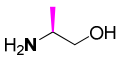
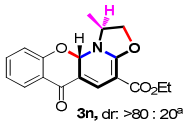
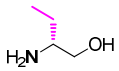
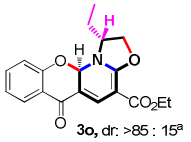
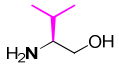
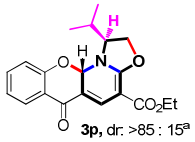
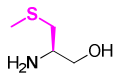
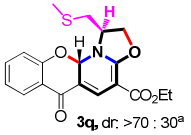
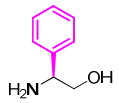
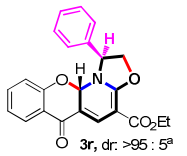
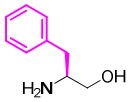
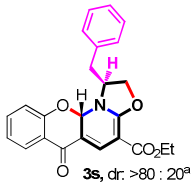
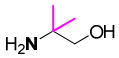
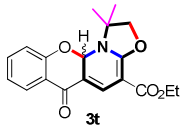
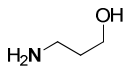
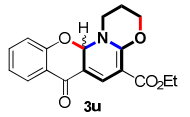
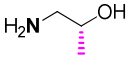
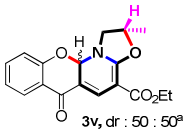
Figure 1. X-ray structure of 3l (asymmetric unit in thermal ellipsoid representation with 50% of probability)

On the other hand, in case of keto-ester or nitro-ester Michael acceptors, no chemoselectivity was observed since desired oxazolopyridines were obtained in moderate to low ratios among complex mixtures of unidentified by-products. Finally, di-benzoate substituents afforded desired compound **3m** in 81% of isolated yield. Interestingly, no competitive intermolecular Mitsunobu reaction was observed. The latter could have occurred with phenol group released in the ring closure step.

The investigation was then focused on the amino-alcohol moiety (Table 3). It was anticipated that substitution in α-position of the nitrogen atom with sterically hindered groups might have an influence on the formed asymmetric center stereocontrol. Gratifyingly, good diastereoselectivity was achieved with a variety of enantiopure 2-substituted ethanolamines. Hindered substituents such as methyl or ethyl groups afforded desired compounds **3n** and **3o** in good yields and satisfactory >80:20 and >85:15 diastereoisomeric excess (Table 3, entries 1 and 2). Surprisingly, isopropyl group did not enhance diastereoisomeric excess. The best result was obtained for phenyl group which afforded desired compound **3r** in 75% of yield and >95:5 diastereoselectivity (Table 3, entry 5).

Table 3. Impact of amino alcohols substitution on domino process

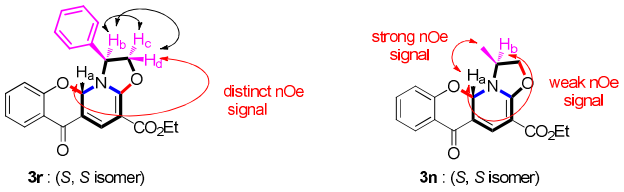


Entry	Amino alcohol	Product	Time (min)	Yield (%)[b]
1		 **3n**, dr: >80 : 20[a]	60	84
2		 **3o**, dr: >85 : 15[a]	60	77
3		 **3p**, dr: >85 : 15[a]	60	67
4		 **3q**, dr: >70 : 30[a]	60	69
5		 **3r**, dr: >95 : 5[a]	60	75
6		 **3s**, dr: >80 : 20[a]	60	77
7		 **3t**	40	52[c]
8		 **3u**	120	0[d]
9		 **3v**, dr : 50 : 50[a]	60	35

[a] Ratio determined by ^{1}H NMR spectroscopy. [b] Isolated yield. [c] Enaminochromanone kinetic product was observed in the crude mixture. [d] The reaction stopped at zwitterionic 2-pyridone stage.

Absolute configurations of **3n** and **3r** asymmetric centers were determined by NOESY experiments (Scheme 5). The results show that H_a and H_b are *trans*-oriented in both cases. Consequently, absolute configurations of the new asymmetric centers were assigned as (*S*)-isomers.

Scheme 5. NOESY interactions for 3n and 3r

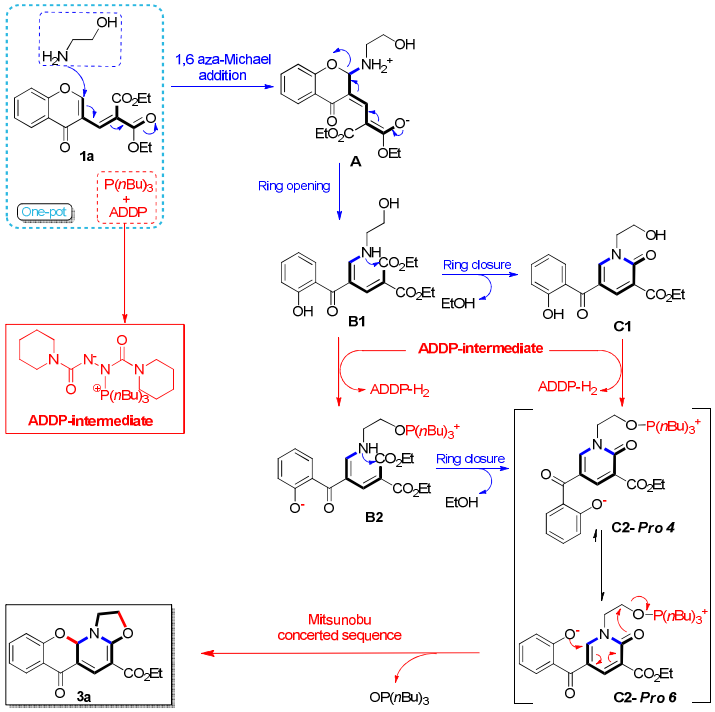


Finally, when 2-(benzyl)ethanolamine was used, the corresponding dihydro-oxazolopyridine **3s** was obtained in 77% yield and >80:20 of diastereoisomeric excess (Table 3, entry 6).

Mitsunobu sequence was less tolerant to secondary alcohols since compound **3v** was isolated in 35% yield (entry 9). As it could be envisioned, this substitution did not have any influence on asymmetric center stereocontrol. In case of tertiary alcohol no conversion into targeted product was observed. The presence of dimethyl group in α-position of nitrogen atom enhanced the reactivity of Mitsunobu sequence by Thorpe Ingold effect.[34] Nevertheless, beside desired oxazolopyridine, the steric hindrance of **3t** led to a substantial proportion of kinetic enaminochromanone side product as reported in our previous work involving primary amines and Michael acceptors.[26] The latter explains the moderate 52% of isolated yield observed for **3t**. In case of cyclohexyl group, only enaminochromanone was observed in the crude mixture after 2 hours of reaction time. Finally, 6-membered oxazino ring was attempted but surprisingly domino process stopped at the zwitterionic 2-pyridone stage.

A plausible mechanism in accordance with previous work and DFT calculations is depicted in Scheme 6. Domino process would be

Scheme 6. Plausible mechanism of domino process



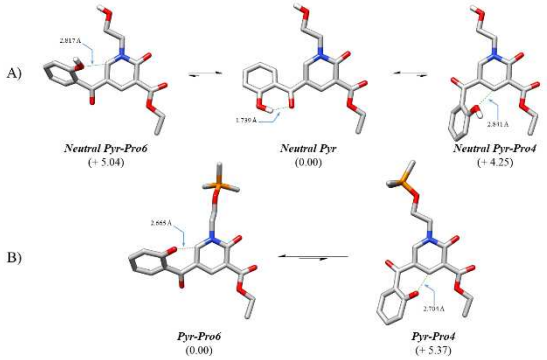
initiated by a 1,6-aza-Michael addition of primary amino alcohols onto chromone acceptors leading first to a non-isolable intermediate **A**. The latter would then undergo a ring opening step to provide **B1**. At this stage, **C2** (in **Pro4** *vs.* **Pro6** conformation) intermediate would be accessed *via* two competitive pathways, both of them involving a ring closure step (**B1** to **C1** or **B2** to **C2**) and the generation of zwitterion species by active Mitsunobu reagent (**B1** to **B2** or **C1** to **C2**). Finally, 2-pyridone zwitterion **C2** in favorable **Pro6** conformation would undergo regioselective Mitsunobu-triggered sequence, allowing final ring closure to afford desired tetracyclic nitrogen bridged dihydro-oxazolopyridines.

Mechanistic study by DFT calculations

To support the proposed mechanism of Mitsunobu concerted sequence, a complete DFT investigation was conducted using state of the art M06-2X functional at the 6-31G(d,p) level of the theory. The solvent effect was taken into account using the PCM (Polarizable Continuum Model) formalism during optimization and frequency calculations.[35] As further specified the domino process involves a first step leading to the formation of the 2-pyridone zwitterion intermediate followed by the intramolecular Mitsunobu triggered sequence yielding tetracyclic nitrogen bridged dihydro-oxazolopyridines.

a) Selectivity at C_6- vs. C_4-position. From the first step of the one-pot process, the formation of *N*-hydroxyethyl-2-pyridone (**2** ≡ **Pyr**) could be anticipated. In order to reduce the computational cost of the study and to simplify the system, we assumed the use of trimethylphosphine instead of *n*-tributylphosphine. At this point, two positions (C_4 and C_6) of zwitterionic **Pyr** could be involved in the intramolecular addition of phenolate moiety. Therefore, the regioselectivity should be influenced by the conformational preference of zwitterionic **Pyr** and then by the energetic barrier level of the cyclization process. The nature of **Pyr** (neutral or zwitterionic) appeared to have an important impact on conformational preference. Concerning the neutral state **Neutral Pyr**, the existence of an intramolecular H-bonding greatly stabilizes the structure and thus strongly influences the orientation of different conformers (Scheme 7, A). This affirmation is supported by the high relative free Gibbs energy computed for the two other C_6 (**Neutral Pyr-Pro6**) and C_4 (**Neutral Pyr-Pro4**) conformers, respectively of 5.04 kcal/mol and 4.25 kcal/mol.

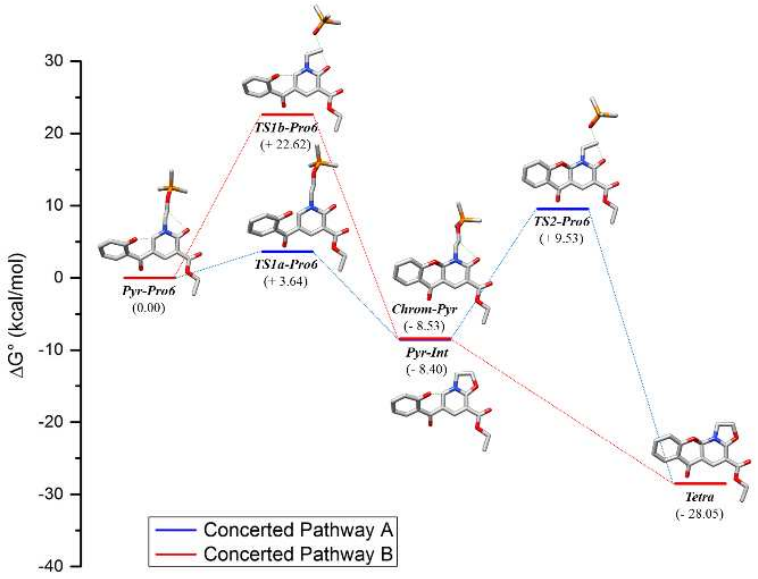
Scheme 7. Conformational analysis of 2-pyridone intermediates at the neutral (A) and zwitterionic state (B) calculated at the PCM/M06-2X/6-31G(d,p) level of theory.[36]



On the other hand when zwitterionic **Pyr** was considered (negative charge on the phenolic moiety and positive charge on the phosphonium), the conformational analysis of **Pyr** pointed out two conformers characterized by a tight distance between the phenoxide moiety and C_6 (**Pyr-Pro6**) or C_4 (**Pyr-Pro4**) positions of the 2-pyridone ring. The computed Boltzmann distribution definitively shows that **Pyr-Pro6** is quasi-exclusively favored (relative ΔG° of +5.37 kcal/mol calculated for **Pyr-Pro4** conformer at room temperature, Scheme 7, B). Moreover, calculations clearly revealed that the distance between reactive centers for **Pyr-Pro6** (2.665 Å) is slightly closer than **Pyr-Pro4** (2.704 Å) (see SI section). These results are in perfect agreement with the regioselectivity observed experimentally.

b) Concerted path A vs. path B for Mitsunobu sequence. DFT calculations were pursued with the study of the Mitsunobu sequence pathway and the localization of possible transition states and intermediates involved in this process leading to final tetracyclic product (**Tetra**) and the release of trimethylphophine oxide by-product (**TMP**). Herein, from **Pyr-Pro6** transition state, two different concerted pathways can be hypothesized. On the one hand, a concerted pathway A in which phenoxide ion of **Pyr-Pro6** induces a nucleophilic attack at C_6-position of 2-pyridone ring could be envisioned. The latter leads to a chromenopyridone intermediate (**Chrom-Pyr**) which then undergoes a nucleophilic substitution of phosphonium group by the oxygen of the 2-pyridone carbonyl group to form final **Tetra** (Scheme 8, see SI section)**.** On the other hand, another plausible concerted pathway B also was taken into account. The latter is initiated by the formation of dihydro-oxazole ring from **Pyr-Pro6**, probably due to the impulse of nitrogen atom electron's lone pair which generates a furtive pyridinium intermediate (**Pyr-Int**). Finally, **Pyr-Int** reacts in a barrierless fashion to yield final **Tetra** product since several attempts failed to localize any transition state (Scheme 8, see SI section). The overall processes from **Pyr-Pro6** to **Tetra** was calculated to be exothermic with a free Gibbs energy variation of -28.05 kcal/mol (see SI section).

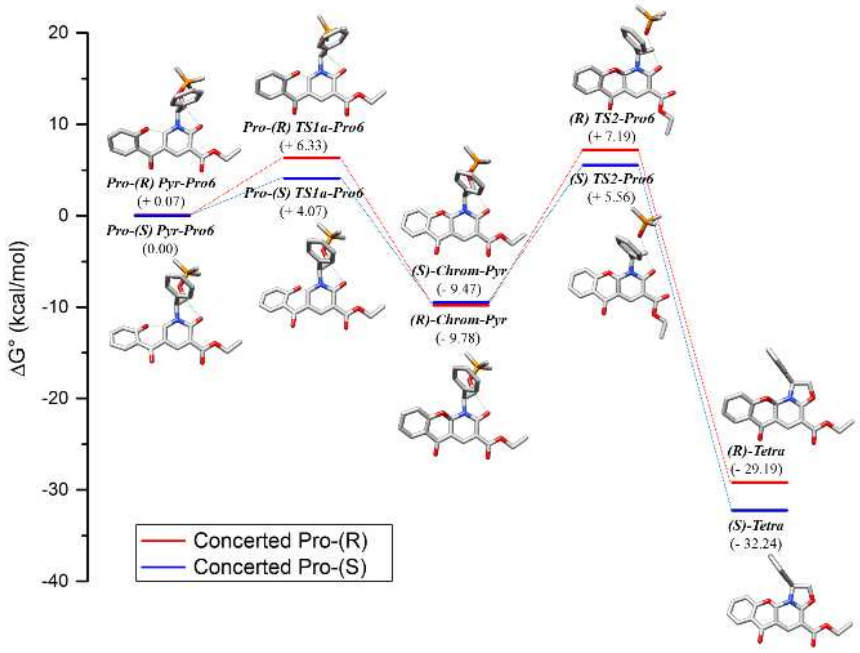
Scheme 8. Energetic profiles of Mitsunobu sequence computed at the PCM/M062X/6-31G(d,p) level of theory.[36]



According to these calculations, it was assumed that Mitsunobu-triggered sequence follows the concerted pathway A since **TS1a-Pro6** transition state (+3.64 kcal/mol) is highly favored over **TS1b-Pro6** (+22.62 kcal/mol) regarding its lower activation barrier (Scheme 8). Moreover, computed interatomic distance of transition states **TS1a-Pro6** (2.089 Å) and **Pyr-Int** (2.495 Å) also supported the proposed mechanism (Scheme SI 1, see SI). As calculations proved that concerted pathway A is greatly favored, the latter was applied on *β*-substituted amino alcohols in order to justify the diastereoselectivity observed in these cases.

c) Diastereoselectivity. Since the best diastereoselectivity was observed (> 95:5) for the 2-pyridone derivative bearing a (*S*)-1-amino-2-phenylethanol moiety, the latter was chosen as model structure.[37]

Scheme 9. Comparison of Pro-(*R*) and Pro(*S*) concerted mechanism A of Mitsunobu sequence calculated at the PCM/M06-2X/6-31G(d,p) level of theory.[36]



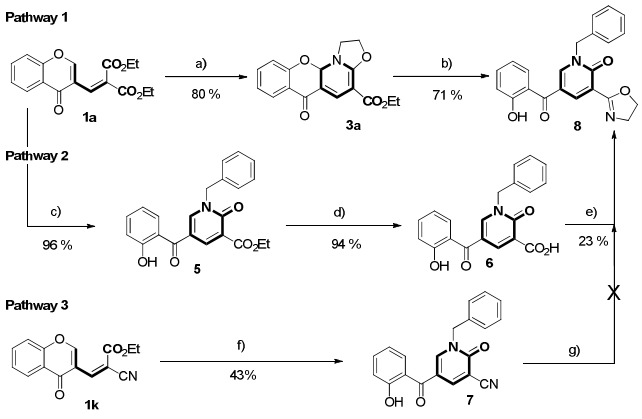
First transition states (**TS1a-Pro6**) implying the phenolate nucleophilic attack at C_6-position were calculated to be significantly different in term of energy with +6.33 and +4.07 kcal/mol for Pro-(*R*) and Pro-(*S*) processes, respectively (Scheme 9, see SI section). The calculated difference in term of energy barriers ($\Delta\Delta G^{\ddagger}$ of 2.19 kcal/mol) favors the Pro-(*S*) process and can already explain the diastereoselectivity observed when applying the Curtin-Hammett Principle.[38] Moreover, taking into account the last step of Mitsunobu sequence characterized by a second transition state (**TS2-Pro6**), the computed free Gibbs energy barrier for Pro-(*S*) (+15.03 kcal/mol) is also favored over Pro-(*R*) (+16.97 kcal/mol) process. Finally, when considering pathway A, Pro-(S) process was modeled to be more favorable in term of energy and these theoretical results are correlated to the experimentally observed diastereoselectivity for **3r**. Despite this good correlation between both aspects, Pro-(*R*) and Pro-(*S*) processes were also computed through the concerted pathway B. Indeed, on a chemical point of view the latter was first considered as more plausible to control the newly formed stereogenic center through the furtive chiral oxazolopyridinium

intermediate (**Pyr Int**). Nevertheless, the calculations did not support this hypothesis, since this pathway remains improbable regarding the high activation barriers required (+19.71 kcal/mol for Pro-(*R*) and +19,12 kcal/mol for Pro-(*S*)). Moreover, in this case, no significant differences were highlighted in term of free Gibbs energy barriers that could explain the diastereoselectivity observed ($\Delta\Delta G^{\ddagger}$ of 0.66 kcal/mol, see SI section).

As final conclusion of calculations part, the Mitsunobu triggered sequence pathway was elucidated by DFT calculations. This domino sequence follows the concerted pathway A in a remarkable C_6-regioselective and diastereoselective fashion.

An interesting application that underlines the potential of this methodology is pointed out in Scheme 10. It was shown that resulting tetracyclic systems could be useful synthetic intermediates to access a new class of *N*,3,5-trisubstituted 2-pyridones bearing oxazoline group at C_3-position. As illustrated in Scheme 10 (pathway 1), the treatment of compound **3a** with benzylamine afforded 2-pyridone **8** in 71% of yield. It is proposed that the latter was achieved through the addition of benzylamine at C_{11a}-position of **3a** followed by a ring opening/aza-Claisen rearrangement/ring closure sequence. Oxazoline group could thus been introduced at C_3-position in two steps in 57% of overall yield starting from Michael acceptor **1a.**

Scheme 10. Application of the developed methodology



a) ethanolamine (1.05 eq.), ADDP/*Pn*(Bu)$_3$ (1.8 eq. each), CH_2Cl_2, 40 °C, 40 min. b) benzylamine (1.2 eq.), CH_2Cl_2, 40 °C 40h. c) benzylamine (1.05 eq.), CsF (10 mol %), CH_2Cl_2, 40 °C, 1h. d) Ac_2O / HCl (37%) (3 : 1), 90 °C, h. e) ethanolamine (1.00 eq.), PPh_3 (3 eq.), Et_3N (3 eq.), CCl_4 (4 eq.), MeCN/Pyr, t.a 14h. f) benzylamine (1.05 eq.), CsF (10 mol %), EtOH, 60 °C, 2h. g) ethanolamine (2.00 eq.), $ZnCl_2$ (0.50 eq.), chlorobenzene, reflux, 16h.

On the other hand, classical reported methodologies appeared to be much less efficient to access **8** starting from carboxylic acid[39] or cyano precursors.[40] The latter was synthetized in three steps in 21% of overall yield *via* pathway 2 while cyano group failed to provide **8** through pathway 3 (Scheme 10).

CONCLUSION

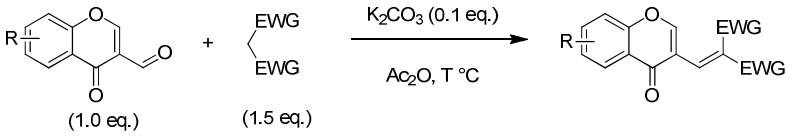
In conclusion an original Mitsunobu triggered sequence has been successfully developed and incorporated in a global domino process for the generation of an interesting class of tetracyclic systems bearing atypical bis-*N*,*O*-acetal junction. This powerful one-pot methodology operates in mild conditions and has demonstrated its tolerance to a large scope of Michael acceptors and readily available either racemic or

chiral amino alcohols. The concerted mechanism proposed for Mitsunobu triggered sequence was corroborated by experimental and theoretical mechanism studies. From a synthetic point of view Mitsunobu activation has shown its significant interest being incorporated in domino strategies. Furthermore, this is the first time that Mitsunobu reaction leads to the formation of two bonds. Ultimately, it was demonstrated that the formed tetracyclic nitrogen bridged dihydro-oxazolopyridines can be useful synthetic intermediates to access a new class of *N*,3,5-trisubstituted 2-pyridones of biological interest.

EXPERIMENTAL SECTION

General Details. Unless otherwise specified, reagents and starting materials were purchased from traditional suppliers and were used without further purification. Reactions were carried out in standard glassware. NMR spectra were recorded at 300 MHz for ^{1}H and 75 MHz for ^{13}C in deuterated chloroform ($CDCl_3$) at room temperature, using TMS as internal standard ($\delta = 0$). High resolution ESI mass spectra were measured on Q-TOF System spectrometer. Column chromatography purifications were performed using Si_2O (40-63 μm) as solid phase and a mixture of dichloromethane/ethyl acetate or cyclohexane/ethyl acetate as eluents. Melting points were recorded on a Scientific analyzer SMP 10 apparatus and are uncorrected. Infrared spectra were performed as neat on FT-IR spectrophotometer and only broad or strong signals are reported.

I. General procedure for *α,β*-unsaturated chromones synthesis (1)



Michael acceptors bearing the chromone core were prepared by an improved method according to Ghosh's procedure.[41] To a previously stirred solution of malonate derivative (1.5 eq.) and K_2CO_3 (0.1 eq.) in acetic anhydride, the appropriate 3-formylchromone was added and the mixture was heated at adequate temperature until no starting material was observed (TLC analysis). After cooling at room temperature or at 0°C, the precipitate formed was filtered and washed with cyclohexane to afford the corresponding Michael acceptors.

Diethyl 2-[(4-oxo-4H-chromen-3-yl)methylene]malonate (1a). White powder (precipitation in Ac_2O), $R_f = 0.31$, eluent (ethyl acetate / cyclohexane 1:4), mp = 112-114 °C, 5.00 g scale reaction (in 15 mL of Ac_2O) for 3h at 90 °C, 8.81 g was isolated, 97% yield. IR (ν_{max} / cm^{-1}): 1716, 1650, 1632, 1460, 1213. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.34 (s, 1H), 8.26 (dd, J = 8.0, 1.7 Hz, 1H), 7.79 (s, 1H), 7.71 (ddd, J = 8.6, 7.1, 1.7 Hz, 1H), 7.50 – 7.42 (m, 2H), 4.34 (2xq, J = 7.2 Hz, 4H), 1.50 (t, J = 7.2 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 175.1, 165.9, 163.9, 156.4, 155.9, 134.3, 133.1, 128.12, 126.4, 126.0, 123.8, 119.1, 118.2, 61.8, 61.8, 14.1, 14.0.

Physical and NMR spectral data are in accordance with those previously reported.[41]

Diethyl 2-((6-methyl-4-oxo-4H-chromen-3-yl)methylene)malonate (1b). Pale yellow powder (precipitation in cold Ac_2O), $R_f = 0.33$, eluent (ethyl acetate / cyclohexane 3:7), mp = 67-69 °C, 5.00 g scale reaction (in 15 mL of Ac_2O) for 3h at 90 °C, 5.90 g was isolated, 67% yield. IR (ν_{max} / cm^{-1}): 1715, 1654, 1620, 1481, 1201. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.26 (s, 1H), 7.97 (s, 1H), 7.73 (s, 1H), 7.47 (dd, J = 8.6, 2.2 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 4.29 (2xq, J = 7.1 Hz, 4H), 2.42 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C

NMR (75 MHz, $CDCl_3$): δ_C 175.1, 165.9, 163.9, 156.4, 154.1, 136.0, 135.4, 133.2, 127.9, 125.5, 123.3, 118.8, 117.9, 61.7, 61.4, 20.9, 14.1, 14.0. Physical and NMR spectral data are in accordance with those previously reported.[41]

Diethyl 2-((6-(benzyloxy)-4-oxo-4H-chromen-3-yl)methylene)malonate (1c). Yellow powder (precipitation in Ac_2O), R_f = 0.40, eluent (ethyl acetate / cyclohexane 1:9), mp = 130-132 °C, 0.20 g scale reaction (in 4 mL of Ac_2O) for 1h at 90 °C, 0.27 g was isolated, 90% yield. IR (ν_{max} / cm^{-1}): 1724, 1687, 1658, 1483, 1450, 1220. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.30 (s, 1H), 7.78 (s, 1H), 7.70 (d, *J* = 2.6 Hz, 1H), 7.31 - 7.49 (m, 7H), 5.15 (s, 2H), 4.32 (qx2, *J* = 7.3 Hz, 4H), 1.32 (tx2, *J* = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 174.9, 165.9, 163.9, 156.6, 156.2, 150.8, 136.0, 133.2, 128.7 (x2), 128.3, 128.0, 127.7 (x2), 124.7, 124.4, 119.7, 118.3, 106.7, 70.7, 61.7 (x2), 14.1, 14.0. HRMS (ESI^+): calcd for $C_{24}H_{23}O_7$ $[M+H]^+$ 423.1444, found 423.1427

Diethyl 2-((6-isopropyl-4-oxo-4H-chromen-3-yl)methylene)malonate (1d). Pale yellow powder (precipitation in Ac_2O at 0 °C), R_f = 0.65, eluent (ethyl acetate / cyclohexane 3:7), mp = 59-61 °C, 1.00 g scale reaction (in 4 mL of Ac_2O) for 3h at 90 °C, 1.45 g was isolated, 88% yield. IR (ν_{max} / cm^{-1}): 1723, 1658, 1604, 1487, 1463, 1243. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.30 (d, *J* = 1.0 Hz, 1H), 8.08 (d, *J* = 2.4 Hz, 1H), 7.78 (d, *J* = 1.0 Hz, 1H), 7.58 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 4.33 (dq, *J* = 10.1, 7.1 Hz, 4H), 3.04 (hept, *J* = 6.9 Hz, 1H), 1.40 – 1.28 (m, 6H), 1.31 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 175.3, 165.9, 163.9, 156.3, 154.3, 147.0, 133.3, 133.1, 127.9, 123.5, 123.1, 118.8, 118.1, 61.7 (x2), 33.8, 23.9 (x2), 14.1, 14.0. HRMS (ESI^+): calcd for $C_{20}H_{23}O_6$ $[M+H]^+$ 359.1495, found 359.1508.

Diethyl 2-((6-bromo-4-oxo-4H-chromen-3-yl)methylene)malonate (1e). White powder (precipitation in cold Ac_2O), R_f = 0.56, eluent (ethyl acetate / cyclohexane 4:6), mp = 89-91 °C, 1.00 g scale reaction (in 4 mL of Ac_2O) for 2h at 90 °C, 1.34 g was isolated, 89% yield. IR (ν_{max} / cm^{-1}): 1720, 1643, 1610, 1456, 1235. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.34 – 8.38 (m, 1H), 8.32 (s, 1H), 7.79 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.72 (s, 1H), 7.39 (d, *J* = 8.9 Hz, 1H), 4.33 (2xq, *J* = 7.1 Hz, 4H), 1.33 (2xt, *J* = 7.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 173.8, 165.7, 163.7, 156.5, 154.6, 137.3, 132.5, 128.9, 128.7, 125.0, 120.2, 119.5, 119.2, 61.9 (x2), 14.1, 14.0. HRMS (ESI^+): calcd for $C_{17}H_{16}BrO_6$ $[M+H]^+$ 395.0130, found 395.0138.

Diethyl 2-((6-nitro-4-oxo-4H-chromen-3-yl)methylene)malonate (1f). Pale yellow powder (precipitation in Ac_2O), R_f = 0.66, eluent (ethyl acetate / cyclohexane 1:1), mp = 158-160 °C, 3.50 g scale reaction (in 10 mL of Ac_2O) for 2h, 3.86 g was isolated, 67% yield. IR (ν_{max} / cm^{-1}): 1720, 1657, 1626, 1531, 1465, 1345, 1202. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 9.11 (d, *J* = 2.7 Hz, 1H), 8.55 (dd, *J* = 9.2, 2.8 Hz, 1H), 8.40 (d, *J* = 1.0 Hz, 1H), 7.70 (d, *J* = 1.0 Hz, 1H), 7.67 (d, *J* = 9.2 Hz, 1H), 4.34 (qx2, *J* = 7.1 Hz, 4H), 1.35 (tx2, *J* = 7.1, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 173.7, 165.5, 163.5, 158.6, 156.5, 145.2, 131.6, 129.8, 128.6, 123.8, 123.0, 120.1, 119.8, 62.0 (x2), 14.1, 14.0. HRMS (ESI^+): calcd for $C_{17}H_{16}NO_8$ $[M+H]^+$ 362.0876, found 362.0886.

Diethyl 2-((6-chloro-7-methyl-4-oxo-4H-chromen-3-yl)methylene)malonate (1g). Colorless crystals (crystallization in Ac_2O), R_f = 0.80, eluent (ethyl acetate / cyclohexane 1:1), mp = 140-142 °C, 1.00 g scale reaction (in 4 mL of Ac_2O) for 2h at 90 °C, 1.17 g was isolated, 71% yield. IR (ν_{max} / cm^{-1}): 1723, 1646, 1616, 1556, 1458, 1375, 1189. ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.29 (d, *J* = 1.0 Hz, 1H), 8.20 (s, 1H), 7.74 (d, *J* = 1.0 Hz, 1H), 7.37 (d, *J* = 0.9 Hz, 1H), 4.34 (2xq, *J* = 7.1 Hz, 4H), 2.52 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 174.0, 165.8, 163.8, 156.3, 154.1, 143.7, 132.7, 132.7, 128.4, 126.0, 122.8, 120.0, 119.0, 61.8 (x2), 20.9, 14.1, 14.0. **HRMS (ESI^+):** calcd for $C_{18}H_{18}ClO_6$ $[M+H]^+$ 365.0792, found 365.0805.

Diethyl 2-((7-ethoxy-8-methyl-4-oxo-4H-chromen-3-yl)methylene)malonate (1h). White solid (precipitation in Ac_2O), R_f = 0.80, eluent (ethyl acetate / cyclohexane 1:1), mp = 101-102 °C, 0.63 g scale reaction (in 2 mL of Ac_2O) for 3h at 90 °C, 0.83 g was isolated, 82% yield. IR (ν_{max} / cm^{-1}): 1723, 1656, 1616, 1460, 1240. ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.32 (d, *J* = 1.0 Hz, 1H), 8.08 (d, *J* = 8.9 Hz, 1H), 7.80 (d, *J* = 1.0 Hz, 1H), 6.99 (d, *J* = 8.9 Hz, 1H), 4.34 (2xq, *J* =7.1 Hz, 4H), 4.19 (q, *J* = 7.0 Hz, 2H), 2.30 (s, 3H), 1.49 (t, *J* = 7.0 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 175.1, 166.1, 164.0, 161.3, 156.3, 155.1, 133.5, 127.5, 124.8, 118.2, 117.4, 114.4, 110.0, 64.5, 61.7, 61.7, 14.8, 14.2, 14.0, 8.1. HRMS (ESI^+): calcd for $C_{20}H_{23}O_7$ $[M+H]^+$ 375.1444, found 375.1458.

Diethyl 2-((4-oxo-4H-benzo[h]chromen-3-yl)methylene)malonate (1i). Beige powder (precipitation in cold Ac_2O), R_f = 0.52, eluent (ethyl acetate / cyclohexane 1:2), mp = 140-142 °C, 4.00 g scale reaction (in 15 mL of Ac_2O) for 4h, 4.73 g was isolated, 73% yield. IR (ν_{max} / cm^{-1}): 1718, 1648, 1569, 1510, 1367, 1206. ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.51 (s, 1H), 8.45 (d, *J* = 7.9 Hz, 1H), 8.16 (d, *J* = 8.8 Hz, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 7.85 (s, 1H), 7.65 – 7.82 (m, 3H), 4.36 (2xq, *J* = 7.2 Hz, 4H), 1.34 (2xt, *J* = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 175.0, 165.9, 163.8, 155.5, 153.5, 136.0, 133.0, 129.7, 128.5, 128.2, 127.5, 126.1, 123.7, 122.2, 120.9, 120.3, 120.2, 61.8, 61.8, 14.2, 14.0. Physical and NMR spectral data are in accordance with those previously reported.[42]

Diethyl 2-((1-oxo-1H-benzo[f]chromen-2-yl)methylene)malonate (1j). Pale yellow powder (precipitation in cold Ac_2O), R_f = 0.77, eluent (ethyl acetate / cyclohexane 1:1), mp = 84-86 °C, 4.00 g scale reaction (in 10 mL of Ac_2O) for 5h, 5.10 g was isolated, 78% yield. IR (ν_{max} / cm^{-1}): 1715, 1654, 1591, 1514, 1440, 1218. ^1H NMR (300 MHz, $CDCl_3$): δ_H 9.94 (d, *J* = 8.4 Hz, 1H), 8.33 (s, 1H), 8.02 – 8.11 (m, 1H), 7.84 – 7.95 (m, 2H), 7.70 – 7.82 (m, 1H), 7.57 – 7.69 (m, 1H), 7.40 – 7.53 (m, 1H), 4.35 (2xq, *J* = 7.2 Hz, 4H), 1.34 (2xt, *J* = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 176.7, 165.9, 163.8, 157.2, 153.8, 136.1, 133.5, 130.8, 130.4, 129.6, 128.3, 128.3, 127.1, 127.0, 121.4, 117.3, 117.1, 61.8, 61.8, 14.2, 14.0. HRMS (ESI^+): calcd for $C_{21}H_{19}O_6$ $[M+H]^+$ 367.1182, found 367.1194.

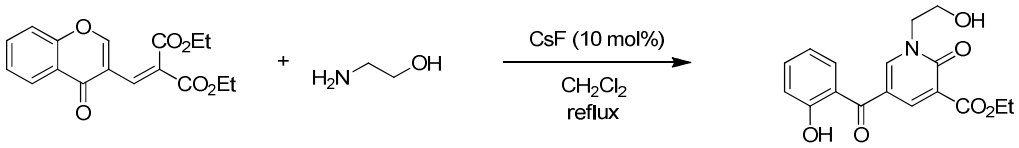
Ethyl 2-cyano-3-(4-oxo-4H-chromen-3-yl)acrylate (1k). Orange powder (precipitation in cold Ac_2O), R_f = 0.77, eluent (ethyl acetate / cyclohexane 1:1), mp = 128-130 °C, 3.00 g scale reaction (in 8 mL of Ac_2O) for 5h at room temperature, 3.23 g was isolated, 70% yield. IR (ν_{max} / cm^{-1}): 2221, 1726, 1654, 1605, 1557, 1450, 1274. ^1H NMR (300 MHz, $CDCl_3$): δ_H 9.17 (d, *J* = 0.9 Hz, 1H), 8.67 (d, *J* = 0.9 Hz,

1H), 8.30 (ddd, *J* = 8.0, 1.7, 0.5 Hz, 1H), 7.79 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H), 7.60 – 7.49 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 174.5, 161.5, 158.3, 155.8, 145.7, 134.9, 126.6, 126.5, 123.6, 118.6, 117.8, 115.4, 103.6, 62.9, 14.2. Physical and NMR spectral data are in accordance with those previously reported.[41]

2-Benzoyl-3-(4-oxo-4H-chromen-3-yl)acrylonitrile (1l). White powder (precipitation in Ac_2O followed by column chromatography), R_f = 0.31, eluent (ethyl acetate / cyclohexane 1:4), mp = 140-142 °C, 500 mg scale reaction (in 1 mL of Ac_2O) for 2h at room temperature, 507 mg was isolated, 58% yield. IR (ν_{max} / cm^{-1}): 2220, 1729, 1616, 1560, 1463. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 9.25 (s, 1H), 8.41 (s, 1H), 8.28 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.88 (d, *J* = 7.2 Hz, 2H), 7.84 – 7.77 (m, 1H), 7.71 – 7.64 (m, 1H), 7.61 – 7.50 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 188.5, 174.7, 158.1, 155.9, 146.0, 135.4, 135.0, 133.6, 129.4 (x2), 128.8 (x2), 126.7, 126.5, 123.5, 118.6, 118.1, 116.4, 110.9. HRMS (ESI$^+$): calcd for $C_{19}H_{12}NO_3$ $[M+H]^+$ 302.0817, found 302.0823.

Diphenyl 2-((4-oxo-4H-chromen-3-yl)methylene)malonate (1m). Yellow powder (precipitation in cold Ac_2O), R_f = 0.77, eluent (ethyl acetate / cyclohexane 1:1), mp = 123-124 °C, 3.00 g scale reaction (in 8 mL of Ac_2O) for 5h at room temperature, 3.23 g was isolated, 70% yield. IR (ν_{max} / cm^{-1}): 1756, 1725, 1661, 1614, 1485, 1461, 1239. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.48 (s, 1H), 8.34 (d, *J* = 7.9 Hz, 1H), 7.99 (s, 1H), 7.76 (t, *J* = 7.9 Hz, 1H), 7.57 – 7.41 (m, 6H), 7.39 – 7.24 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 174.7, 163.9, 162.7, 158.1, 155.8, 150.6, 150.6, 136.2, 134.5, 129.6 (x2), 129.6 (x2), 126.9, 126.6, 126.3, 126.2 (x2), 123.8, 121.7 (x2), 121.5 (x2), 118.9, 118.2. HRMS (ESI$^+$): calcd for $C_{25}H_{17}O_6$ $[M+H]^+$ 413.1025, found 413.1031.

II. General procedure for pyridones synthesis (2)

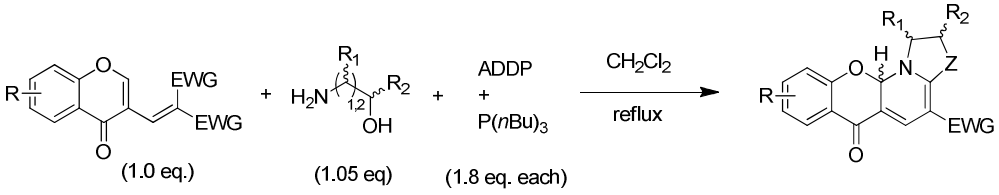


To a previously stirred solution containing *α,β*-unsaturated chromone and CsF (10.0 mol%) in dichloromethane, the corresponding amine (1.05 equiv.) was added. The reaction mixture was stirred under reflux until full consumption of substrates was observed (followed by TLC). After concentration under reduced pressure, the resulting mixture yielded pure *N*,3,5-trisubstituted-pyridin-2-one after purification on silica gel column chromatography.

Ethyl 5-(2-hydroxybenzoyl)-1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (2). Pale yellow powder (column chromatography), R_f = 0.24, eluent (ethyl acetate / dichloromethane 1:1), mp = 146-148 °C, 1.00 g scale reaction (in 5 mL of CH_2Cl_2) for 1h, 0.75 g was isolated, 71% yield. IR (ν_{max} / cm^{-1}): 3448, 1722, 1625, 1530, 1341, 1218. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 11.39 (s, 1H), 8.53 (d, *J* = 2.7 Hz, 1H), 8.34 (d, *J* = 2.7 Hz, 1H), 7.62 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.51 (ddd, *J* = 8.7, 7.2, 1.6 Hz, 1H), 7.05 (d, *J* = 8.2 Hz,

1H), 6.93 (t, *J* = 7.5 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.20 (t, *J* = 4.9 Hz, 2H), 4.02 – 3.92 (m, 2H), 3.43 (t, *J* = 5.2 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 194.4, 163.9, 162.4, 159.1, 148.6, 144.1, 136.4, 131.8, 119.3, 119.2, 118.7, 118.6, 115.3, 61.6, 59.9, 53.4, 14.2. HRMS (ESI$^+$): calcd for $C_{17}H_{18}NO_6$ $[M+H]^+$ 332.1134, found 332.1142.

III. General procedure for tetracyclic nitrogen fused tetrahydro-oxazolopyridines synthesis (3)



To a previously stirred solution containing *α,β*-unsaturated chromones under reflux in dichloromethane, the corresponding amine (1.05 equiv.), ADDP (1.8 eq.) and P(*n*Bu)$_3$ were added. The reaction mixture was stirred under reflux until full consumption of substrates was observed (followed by TLC). The resulting mixtures yielded pure tetrahydro-oxazolopyridines derivatives after purification on silica gel column chromatography.

Ethyl 6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (3a). Bright yellow amorphous solid (column chromatography), R_f = 0.53, eluent (ethyl acetate / dichloromethane 1:1), mp = 168-169 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 40 min, 79 mg were isolated, 80% yield. Product sensitive to $CDCl_3$ acidity. IR (ν_{max} / cm^{-1}): 1657, 1616, 1460, 1279. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.97 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.93 (s, 1H), 7.50 (ddd, *J* = 8.3, 7.2, 1.8 Hz, 1H), 7.10 (ddd, *J* = 8.1, 7.3, 1.1 Hz, 1H), 6.95 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.57 (s, 1H), 4.98 – 4.89 (m, 1H), 4.84 (q, *J* = 9.2 Hz, 1H), 4.35 – 4.26 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.79 (q, *J* = 9.5 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 179.9, 163.7, 163.5, 155.3, 136.0, 135.6, 127.6, 123.9, 122.6, 117.8, 110.6, 86.6, 81.5, 69.5, 59.8, 45.1, 14.5. HRMS (ESI$^+$): calcd for $C_{17}H_{16}NO_5$ $[M+H]^+$ 314.1028, found 314.1033.

Ethyl 8-methyl-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (3b). Bright yellow amorphous solid (column chromatography), R_f = 0.46, eluent (ethyl acetate / dichloromethane 1:1), mp = 91-92 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 40 min, 82 mg were isolated, 83% yield. Product sensitive to $CDCl_3$ acidity. IR (ν_{max} / cm^{-1}): 1657, 1616, 1487, 1463, 1279. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.92 (s, 1H), 7.75 (d, *J* = 1.9 Hz, 1H), 7.31 (dd, J= 8.3, 1.9 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 6.52 (s, 1H), 4.97 – 4.88 (m, 1H), 4.83 (q, *J* = 9.2 Hz, 1H), 4.33 – 4.26 (m, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.77 (q, *J* = 9.5 Hz, 1H), 2.33 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 180.1, 163.7, 163.5, 153.3, 136.6, 135.8, 132.2, 127.3, 123.5, 117.6, 110.8, 86.5, 81.3, 69.5, 59.8, 45.1, 20.5, 14.5. HRMS (ESI$^+$): calcd for $C_{18}H_{18}NO_5$ $[M+H]^+$ 328.1185, found 328.1191.

Ethyl 8-(benzyloxy)-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (3c). Bright yellow amorphous solid (column chromatography), R_f = 0.41, eluent (ethyl acetate / dichloromethane 1:1), mp = 199-200 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 40 min, 87 mg were isolated, 88% yield. Product sensitive to $CDCl_3$ acidity. IR (ν_{max} / cm^{-1}): 1655, 1616, 1486, 1241. ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.94 (s, 1H), 7.51 (d, *J* = 3.1 Hz, 1H), 7.47 – 7.34 (m, 5H), 7.17 (dd, *J* = 8.9, 3.2 Hz, 1H), 6.90 (d, *J* = 8.9 Hz, 1H), 6.50 (s, 1H), 5.08 (s, 2H), 4.97 – 4.88 (m, 1H), 4.88 – 4.76 (m, 1H), 4.32 – 4.26 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.76 (q, *J* = 9.5 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 179.9, 163.7, 163.5, 154.1, 149.8, 136.6, 136.1, 128.6 (x2), 128.1, 127.6 (x2), 124.9, 124.1, 119.1, 110.5, 109.8, 86.5, 81.5, 70.6, 69.5, 59.8, 45.1, 14.5. HRMS (ESI^+): calcd for $C_{24}H_{22}NO_6$ $[M+H]^+$ 420.1447, found 420.1453.

Ethyl 8-isopropyl-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (3d). Bright yellow amorphous solid (column chromatography), R_f = 0.60, eluent (ethyl acetate / dichloromethane 1:1), mp = 84-86 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 40 min, 67 mg was isolated, 68% yield. Product sensitive to $CDCl_3$ acidity. IR (ν_{max} / cm^{-1}): 1655, 1616, 1486, 1461, 1241. ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.92 (s, 1H), 7.82 (d, *J* = 2.3 Hz, 1H), 7.37 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.53 (s, 1H), 4.98 – 4.77 (m, 2H), 4.34 – 4.25 (m, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.77 (q, *J* = 9.4 Hz, 1H), 2.92 (hept, *J* = 6.9 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.26 (s, 3H), 1.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 180.2, 163.8, 163.5, 153.5, 143.3, 135.7, 134.2, 124.8, 123.5, 117.7, 110.9, 86.5, 81.4, 69.4, 59.8, 45.1, 33.4, 23.9, 23.9, 14.5. HRMS (ESI^+): calcd for $C_{20}H_{22}NO_5$ $[M+H]^+$ 356.1498, found 356.1505.

Ethyl 8-bromo-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (3e). Bright yellow amorphous solid (column chromatography), R_f = 0.33, eluent (ethyl acetate / dichloromethane 1:1), mp = 193-194 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 38 mg were isolated, 38 % yield. Product sensitive to $CDCl_3$ acidity. IR (ν_{max} / cm^{-1}): 1657, 1618, 1488, 1459, 1247. ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.08 (d, *J* = 2.4 Hz, 1H), 7.96 (s, 1H), 7.57 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 6.57 (s, 1H), 5.01 – 4.80 (m, 2H), 4.35 – 4.26 (m, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.81 (q, *J* = 9.5 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 178.6, 163.6, 163.5, 154.1, 138.2, 136.9, 130.2, 125.2, 119.9, 115.4, 109.6, 86.8, 81.9, 69.5, 59.9, 45.1, 14.5. HRMS (ESI^+): calcd for $C_{17}H_{15}BrNO_5$ $[M+H]^+$ 392.0134, found 392.0136.

Ethyl 8-chloro-9-methyl-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (3g). Bright yellow amorphous solid (column chromatography), R_f = 0.469 eluent (ethyl acetate / dichloromethane 1:1), mp = 192-193 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 59 mg were isolated, 60% yield. Product sensitive to $CDCl_3$ acidity. IR (ν_{max} / cm^{-1}): 1655, 1615, 1497, 1475, 1268. ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.89 (s, 1H), 7.86 (s, 1H), 6.83 – 6.79 (m, 1H), 6.49 (s, 1H), 4.97 – 4.78 (m, 2H), 4.29 – 4.23 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.77 (q, *J* = 9.4 Hz, 1H), 2.36 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 178.7, 163.6, 163.5, 153.5, 144.6, 136.3, 128.7, 127.2, 122.8, 120.0, 109.9, 86.8, 81.6, 69.5, 59.8, 45.1, 20.8, 14.5. HRMS (ESI^+): calcd for $C_{18}H_{17}ClNO_5$ $[M+H]^+$ 362.0795, found 362.0801.

Ethyl 9-ethoxy-10-methyl-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (3h). Bright yellow amorphous solid (column chromatography), R_f = 0.37, eluent (ethyl acetate / dichloromethane 1:1), mp = 193-194 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 41 mg were isolated, 41 % yield. Product sensitive to $CDCl_3$ acidity. IR (ν_{max} / cm^{-1}): 1653, 1611, 1518, 1497, 1267. ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.90 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 6.65 (d, *J* = 8.8 Hz, 1H), 6.54 (s, 1H), 4.98 – 4.81 (m, 2H), 4.32 (td, *J* = 9.3, 6.2 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.13 (q, *J* = 7.0 Hz, 2H), 3.82 (q, *J* = 9.3 Hz, 1H), 2.10 (s, 3H), 1.46 (t, *J* = 7.0 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 179.9, 163.8, 163.2, 162.8, 154.3, 134.7, 126.4, 117.5, 114.0, 111.0, 106.1, 86.7, 81.2, 69.3, 64.1, 59.7, 45.0, 14.8, 14.5, 8.1. HRMS (ESI^+): calcd for $C_{20}H_{22}NO_6$ $[M+H]^+$ 372.1447, found 372.1453.

Ethyl 6-oxo-1,2,6,13a-tetrahydrobenzo[7,8]chromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (3i). Bright yellow amorphous solid (column chromatography), R_f = 0.48, eluent (ethyl acetate / dichloromethane 1:1), mp = 128-129 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 44 mg were isolated, 45 % yield. Product sensitive to $CDCl_3$ acidity. IR (ν_{max} / cm^{-1}): 1652, 1617, 1489, 1463, 1239. ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.21 (d, *J* = 8.3 Hz, 1H), 7.98 (d, *J* = 8.7 Hz, 1H), 7.98 (s, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.57 – 7.50 (m, 2H), 6.76 (s, 1H), 5.03 – 4.90 (m, 2H), 4.55 – 4.43 (m, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.91 (q, *J* = 9.4 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 180.0, 163.7, 163.3, 152.7, 137.5, 129.3, 128.1, 126.2, 124.7, 122.8, 122.6, 122.2, 118.6, 110.3, 87.6, 81.6, 76.8, 69.5, 59.9, 45.2, 14.5. HRMS (ESI^+): calcd for $C_{21}H_{18}NO_5$ $[M+H]^+$ 364.1185, found 364.1188.

***Ethyl 6-oxo-1,2,6,13a-tetrahydrobenzo[5,6]chromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate* (3j).** Bright yellow amorphous solid (column chromatography), R_f = 0.38, eluent (ethyl acetate / dichloromethane 1:1), mp = 91-92 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 70 mg were isolated, 71 % yield. Product sensitive to $CDCl_3$ acidity. IR (ν_{max} / cm^{-1}): 1657, 1616, 1486, 1463, 1279. ^1H NMR (300 MHz, $CDCl_3$): δ_H 9.39 (dd, *J* = 8.7, 1.0 Hz, 1H), 7.97 (s, 1H), 7.94 (d, *J* = 9.0 Hz, 1H), 7.77 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.65 (ddd, *J* = 8.6, 6.9, 1.5 Hz, 1H), 7.45 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.06 (d, *J* = 8.9 Hz, 1H), 6.51 (s, 1H), 4.98 – 4.89 (m, 1H), 4.84 (q, *J* = 9.0, 8.4 Hz, 1H), 4.34 – 4.27 (m, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.78 (q, *J* = 9.4 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 180.5, 163.8, 163.2, 156.1, 137.1, 131.8, 130.0, 129.2, 128.3, 126.6, 125.1, 118.3, 116.2, 111.7, 86.4, 81.4, 76.7, 69.5, 59.8, 45.0, 14.5. HRMS (ESI^+): calcd for $C_{21}H_{18}NO_5$ $[M+H]^+$ 364.1185, found 364.1192.

Ethyl 6-oxo-2,3,6,11a-tetrahydro-1H-chromeno[3,2-e]imidazo[1,2-a]pyridine-4-carboxylate (3k). Bright yellow amorphous solid (column chromatography), R_f = 0.16, eluent (ethyl acetate / dichloromethane 1:1), mp = 183-184 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 78 mg were isolated, 67% yield. Product sensitive to $CDCl_3$ acidity. IR (ν_{max} / cm^{-1}): 1648, 1607, 1558, 1501, 1478, 1462, 1360. ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.98 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.95 (s, 1H), 7.86 (bs, 1H), 7.45 (ddd, *J* = 8.6, 7.2, 1.8 Hz, 1H), 7.08 (td, *J* = 7.6, 1.1 Hz, 1H), 6.94 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.31 (s, 1H), 4.30 – 4.22 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.91 (t, *J* = 8.5 Hz, 2H),

3.75 – 3.57 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 179.7, 166.8, 159.0, 155.7, 135.2, 134.8, 127.5, 124.3, 122.2, 117.7, 108.2, 86.2, 80.5, 59.6, 46.3, 42.8, 14.6. HRMS (ESI$^+$): calcd for $C_{17}H_{17}N_2O_4$ $[M+H]^+$ 313.1188, found 313.1194.

4-Benzoyl-2,3-dihydro-1H-chromeno[3,2-e]imidazo[1,2-a]pyridin-6(11aH)-one (3l). Bright yellow amorphous solid (column chromatography), R_f = 0.25, eluent (ethyl acetate / dichloromethane 1:1), mp = 219-221 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 50 min, 79 mg were isolated, 69% yield. Product sensitive to $CDCl_3$ acidity. IR (ν_{max} / cm^{-1}): 1726, 1643, 1553, 1469, 1463, 1362. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 9.42 (s, 1H), 7.96 (dd, J = 7.8, 1.8 Hz, 1H), 7.76 (s, 1H), 7.56 – 7.39 (m, 6H), 7.10 (td, J = 7.5, 1.1 Hz, 1H), 6.98 (dd, J = 8.3, 1.0 Hz, 1H), 6.32 (s, 1H), 4.32 (td, J = 9.6, 6.5 Hz, 1H), 4.12 – 3.89 (m, 2H), 3.85 – 3.56 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 191.4, 179.9, 160.2, 155.9, 139.5, 136.7, 135.1, 130.3, 128.4 (x2), 127.9 (x2), 127.6, 124.1, 122.5, 117.7, 109.2, 91.6, 85.4, 45.9, 43.1. HRMS (ESI$^+$): calcd for $C_{21}H_{17}N_2O_3$ $[M+H]^+$ 345.1239, found 345.1240.

Phenyl 6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (3m). Bright yellow amorphous solid (column chromatography), R_f = 0.44, eluent (ethyl acetate / dichloromethane 1:1), mp = 123-124 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 40 min, 71 mg were isolated, 81% yield. Product sensitive to $CDCl_3$ acidity. IR (ν_{max} / cm^{-1}): 1661, 1613, 1522, 1500, 1469, 1284, 1266. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.06 (s, 1H), 7.98 (dd, J = 7.8, 1.8 Hz, 1H), 7.52 (ddd, J = 8.6, 7.5, 1.8 Hz, 1H), 7.40 – 7.33 (m, 2H), 7.20 (t, J = 7.4 Hz, 1H), 7.15 – 7.08 (m, 3H), 6.98 (d, J = 8.2 Hz, 1H), 6.57 (s, 1H), 4.90 (td, J = 9.1, 5.3 Hz, 1H), 4.81 (q, J = 9.1 Hz, 1H), 4.29 (td, J = 9.4, 6.2 Hz, 1H), 3.79 (q, J = 9.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 179.9, 164.1, 162.1, 155.4, 150.9, 135.8, 135.5, 129.2 (x2), 127.6, 125.3, 123.8, 122.7, 122.0 (x2), 117.9, 111.2, 86.4, 80.6, 69.7, 45.2. HRMS (ESI$^+$): calcd for $C_{21}H_{16}NO_5$ $[M+H]^+$ 362.1028, found 362.1033.

(1S, 11aS)-Ethyl 1-methyl-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (3n). Bright yellow amorphous solid (column chromatography), R_f = 0.40, eluent (ethyl acetate / dichloromethane 1:1), mp = 71-72 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 87 mg were isolated, 84% yield. Product sensitive to $CDCl_3$ acidity. IR (ν_{max} / cm^{-1}): 1658, 1610, 1509, 1460, 1280. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.97 (dd, J = 7.8, 1.8 Hz, 1H), 7.93 (s, 1H), 7.50 (ddd, J = 8.4, 7.2, 1.8 Hz, 1H), 7.10 (ddd, J = 8.1, 7.3, 1.1 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 6.65 (s, 1H), 4.91 (t, J = 8.5 Hz, 1H), 4.66 – 4.54 (m, 1H), 4.48 (dd, J = 8.8, 5.8 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 1.47 (d, J = 6.3 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 180.3, 163.8, 162.9, 155.2, 135.8, 135.6, 127.6, 123.9, 122.6, 117.8, 110.5, 83.4, 81.5, 76.0, 59.8, 51.4, 15.2, 14.5. HRMS (ESI$^+$): calcd for $C_{18}H_{18}NO_5$ $[M+H]^+$ 328.1185, found 328.1190.

(1R)-Ethyl 1-ethyl-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (3o). Bright yellow amorphous solid (column chromatography), R_f = 0.49, eluent (ethyl acetate / dichloromethane 1:1), mp = 61-62 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 83 mg were isolated, 77% yield. Product sensitive to $CDCl_3$ acidity. IR (ν_{max} / cm^{-1}): 1659, 1613, 1508, 1458, 1282. Major

diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.97 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.94 (s, 1H), 7.49 (ddd, *J* = 8.7, 7.2, 1.8 Hz, 1H), 7.13 – 7.06 (m, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.62 (s, 1H), 4.85 (t, *J* = 8.9 Hz, 1H), 4.60 (dd, *J* = 9.0, 5.4 Hz, 1H), 4.56 – 4.39 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.10 – 1.87 (m, 1H), 1.80 – 1.68 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 180.4, 163.8, 163.3, 155.2, 135.8, 135.6, 127.7, 124.0, 122.6, 117.8, 110.4, 83.7, 81.3, 73.6, 59.8, 56.1, 21.3, 14.5, 8.0. HRMS (ESI$^+$): calcd for $C_{19}H_{20}NO_5$ $[M+H]^+$ 342.1375, found 342.1348.

(1S)-Ethyl 1-isopropyl-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (3p). Bright yellow amorphous solid (column chromatography), R_f = 0.52, eluent (ethyl acetate / dichloromethane 1:1), mp = 65-66 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 75 mg were isolated, 67% yield. Product sensitive to $CDCl_3$ acidity. IR (ν_{max} / cm^{-1}): 2963, 1660, 1614, 1509, 1459, 1284. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.01 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.97 (s, 1H), 7.55 – 7.47 (m, 1H), 7.16 – 7.09 (m, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.63 (s, 1H), 4.80 – 4.62 (m, 2H), 4.56 – 4.48 (m, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.42 (hept, *J* = 6.9, 3.3 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 180.4, 163.8, 163.4, 155.3, 135.9, 135.6, 127.8, 124.0, 122.6, 117.8, 110.4, 83.9, 81.1, 70.0, 59.8, 59.7, 24.7, 18.0, 14.5, 14.2. HRMS (ESI$^+$): calcd for $C_{20}H_{22}NO_5$ $[M+H]^+$ 356.1498, found 356.1507.

(1R)-Ethyl 1-((methylthio)methyl)-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (3q). Bright yellow amorphous solid (column chromatography), R_f = 0.51, eluent (ethyl acetate / dichloromethane 1:1), mp = 68-69 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 81 mg were isolated, 69% yield. Product sensitive to $CDCl_3$ acidity. IR (ν_{max} / cm^{-1}): 2977, 1658, 1612, 1509, 1460, 1282. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.01 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.95 (s, 1H), 7.52 (ddd, *J* = 8.6, 7.3, 1.8 Hz, 1H), 7.17 – 7.10 (m, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.72 (s, 1H), 5.03 – 4.87 (m, 1H), 4.82 (dd, *J* = 9.3, 4.9 Hz, 1H), 4.77 – 4.66 (m, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.02 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.81 (dd, *J* = 13.5, 8.1 Hz, 1H), 2.21 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 180.2, 163.7, 163.1, 155.1, 135.8, 135.7, 127.8, 124.0, 122.7, 117.7, 110.7, 84.0, 81.6, 74.1, 59.9, 54.5, 33.2, 16.1, 14.5. HRMS (ESI$^+$): calcd for $C_{19}H_{20}NO_5S$ $[M+H]^+$ 374.1057, found 374.1062.

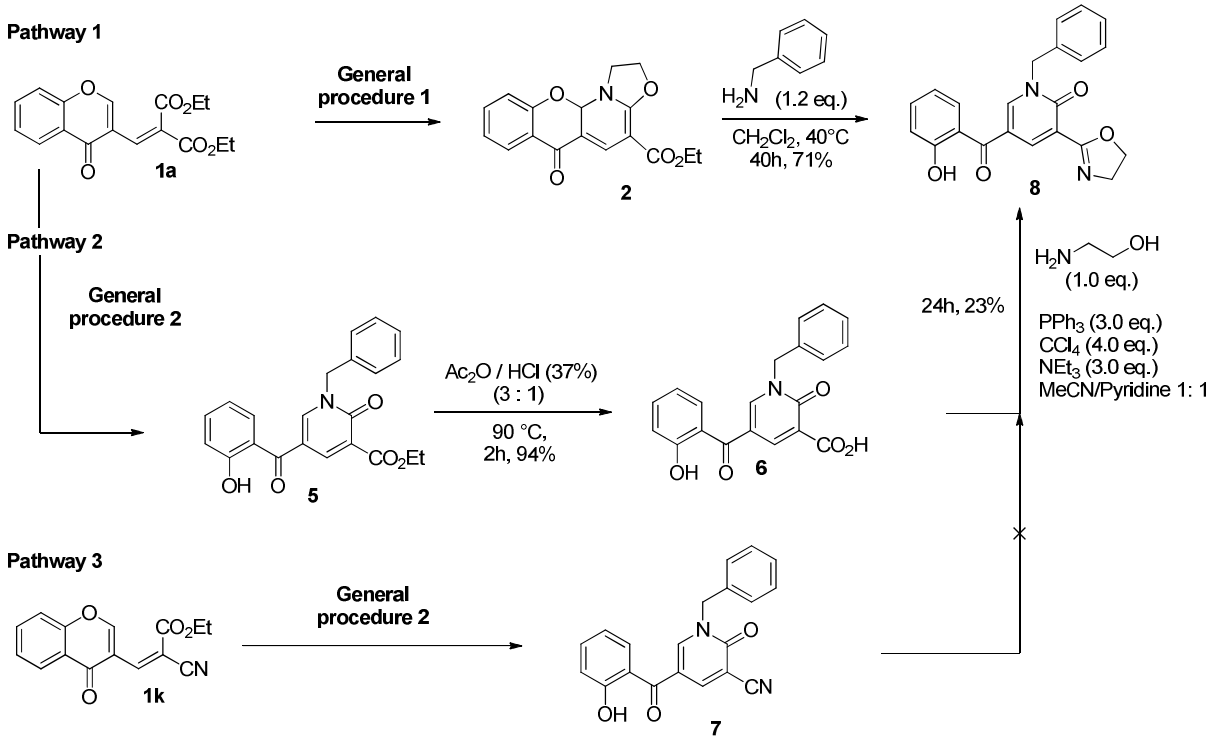
(1S,11aS)-ethyl 1-benzyl-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (3r). Bright yellow amorphous solid (column chromatography), R_f = 0.55, eluent (ethyl acetate / dichloromethane 1:1), mp = 83-84 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 97 mg were isolated, 75% yield. Product sensitive to $CDCl_3$ acidity. IR (ν_{max} / cm^{-1}): 1657, 1617, 1488, 1460, 1279. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.96 (s, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.48 – 7.40 (m, 4H), 7.38 – 7.32 (m, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.15 (s, 1H), 5.44 (dd, *J* = 9.1, 5.4 Hz, 1H), 5.17 (t, *J* = 9.2 Hz, 1H), 4.82 (dd, *J* = 9.3, 5.4 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 180.4, 163.9, 162.9, 155.3, 135.6, 135.4, 134.2, 130.0, 129.8 (x2), 127.6, 127.5 (x2), 123.9, 122.5, 117.8, 111.2, 83.9, 81.4, 76.9, 59.9, 59.6, 14.6. HRMS (ESI$^+$): calcd for $C_{23}H_{20}NO_5$ $[M+H]^+$ 390.1341, found 390.1346.

(1S)-Ethyl 6-oxo-1-phenyl-1,2,6,11a-tetrahydrochromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (3s). Bright yellow amorphous solid (column chromatography), R_f = 0.57, eluent (ethyl acetate / dichloromethane 1:1), mp = 65-66 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 99 mg were isolated, 77% yield. Product sensitive to $CDCl_3$ acidity. IR (ν_{max} / cm^{-1}): 1661, 1615, 1509, 1460, 1279. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.02 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.97 (s, 1H), 7.58 – 7.49 (m, 1H), 7.41 – 7.30 (m, 3H), 7.23 (d, *J* = 6.7 Hz, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.76 (s, 1H), 4.82 – 4.73 (m, 1H), 4.73 – 4.60 (m, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.38 (dd, *J* = 13.7, 4.1 Hz, 1H), 2.79 (dd, *J* = 13.6, 9.0 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 180.3, 163.7, 163.1, 155.2, 135.8, 135.7, 134.3, 129.3, 129.2, 129.1, 129.0, 127.8, 127.7, 124.0, 122.7, 117.8, 110.7, 83.9, 81.6, 73.7, 59.8, 56.3, 35.1, 14.5. HRMS (ESI^+): calcd for $C_{24}H_{22}NO_5$ $[M+H]^+$ 404.1498, found 404.1503.

Ethyl 1,1-dimethyl-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (3t). Bright yellow amorphous solid (column chromatography), R_f = 0.47, eluent (ethyl acetate / dichloromethane 1:1), mp = 188-189 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 56 mg were isolated, 52% yield. Product sensitive to $CDCl_3$ acidity. IR (ν_{max} / cm^{-1}): 1653, 1607, 1488, 1459, 1278. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.98 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.91 (s, 1H), 7.50 (ddd, *J* = 8.7, 7.3, 1.8 Hz, 1H), 7.16 – 7.07 (m, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.71 (s, 1H), 4.54 (d, *J* = 8.7 Hz, 1H), 4.45 (d, *J* = 8.7 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.73 (s, 3H), 1.52 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 180.5, 163.9, 163.5, 155.5, 135.6, 127.7, 124.1, 122.6, 117.9, 111.3, 84.5, 81.8, 81.1 (x2), 61.8, 59.8, 27.1, 22.3, 14.5. HRMS (ESI^+): calcd for $C_{19}H_{20}NO_5$ $[M+H]^+$ 342.1341, found 342.1348.

(2S)-Ethyl 2-methyl-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (3v). Bright yellow amorphous solid (column chromatography), R_f = 0.52, eluent (ethyl acetate / dichloromethane 1:1), mp = 78-79 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 36 mg were isolated, 35% yield. Product sensitive to $CDCl_3$ acidity. IR (ν_{max} / cm^{-1}): 1658, 1609, 1516, 1489, 1460, 1279. Diastereoisomer 1: ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.97 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.94 (s, 1H), 7.49 (ddd, *J* = 8.6, 7.3, 1.8 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.3, 1.1 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.53 (s, 1H), 5.35 – 5.16 (m, 1H), 4.37 (t, *J* = 8.9 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.87 (d, *J* = 8.5 Hz, 1H), 1.69 (t, *J* = 6.5 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 179.9, 163.7, 163.3, 155.3, 136.2, 135.6, 127.6, 123.9, 122.6, 117.8, 110.4, 86.7, 81.4, 79.4, 59.7, 51.7, 20.0, 14.5. Diastereoisomer 2: ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.97 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.95 (s, 1H), 7.49 (ddd, *J* = 8.6, 7.3, 1.8 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.3, 1.1 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.53 (s, 1H), 5.35 – 5.16 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.87 (d, *J* = 8.5 Hz, 1H), 3.36 (t, *J* = 9.4 Hz, 1H), 1.69 (t, *J* = 6.5 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 180.0, 163.7, 163.1, 155.3, 136.1, 135.6, 127.6, 123.9, 122.6, 117.8, 110.2, 86.4, 81.3, 79.1, 59.7, 50.9, 20.5, 14.5. HRMS (ESI^+): calcd for $C_{18}H_{18}NO_5$ $[M+H]^+$ 328.1185, found 328.1186.

IV. Synthetic pathways for the access of 3-dihydrooxazolopyridin-2-one (8).



Ethyl 1-benzyl-5-(2-hydroxybenzoyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (5). Synthetized according to general procedure 2 using 1,05 eq. of benzylamine and 1.0 eq. of **1a**. Pale orange powder (precipitation in cold diethyl ether), R_f = 0.36, eluent (ethyl acetate / cyclohexane 1:1), mp = 120-122 °C, 0.50 g scale reaction (in 5 mL of CH_2Cl_2) for 1h, 0.57 g was isolated, 95% yield. IR (ν_{max} / cm^{-1}): 3444, 1727, 1650, 1624, 1540, 1340, 1238. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.53 (d, *J* = 2.6 Hz, 1H), 8.15 (d, *J* = 2.7 Hz, 1H), 7.52 (ddd, *J* = 8.5, 7.3, 1.6 Hz, 1H), 7.43 – 7.35 (m, 6H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.90 – 6.83 (m, 1H), 5.25 (s, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 194.3, 164.1, 162.6, 158.7, 146.2, 143.6, 136.4, 134.8, 131.4, 129.3 (x2), 128.9, 128.8 (x2), 120.4, 119.0, 118.9, 118.6, 115.9, 61.7, 53.3, 14.3. HRMS (ESI^+) calcd for $C_{22}H_{20}NO_5$ $[M+H]^+$ 378.1341, found 378.1336.

1-Benzyl-5-(2-hydroxybenzoyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (6). A solution of **5** (1.14 g, 3.02 mmol) in 6 mL of Ac_2O/ HCl (37%) was heated to 90 °C. After complete consumption of starting material (2 h) the reaction media was allowed to cool at room temperature. The formed precipitate was filtrated and washed with cyclohexane to yield pure compound **6** as a white powder. R_f = 0.36, eluent (ethyl acetate / cyclohexane 1:1), mp = 201-203 °C, 1.01 g was isolated, 94% yield. IR (ν_{max} / cm^{-1}): 3418, 2958, 1722, 1610, 1467, 1439. ^{1}H NMR (300 MHz, DMSO-d_6) : δ_H 10.39 (s, 1H), 8.92 (d, *J* = 2.6 Hz, 1H), 8.50 (d, *J* = 2.6 Hz, 1H), 7.50 – 7.32 (m, 7H), 7.10 – 6.90 (m, 2H), 5.40 (s, 2H). ^{13}C NMR (75 MHz, DMSO): δ_C 191.4, 164.8, 163.0, 156.3, 149.1, 144.8, 135.9, 133.9, 130.7, 129.2 (x2), 128.5 (x3), 124.8, 119.9, 118.9, 117.2, 117.1, 53.6. HRMS (ESI^+) calcd for $C_{20}H_{16}NO_5$ $[M+H]^+$ 350.1028, found 350.1034.

1-Benzyl-5-(2-hydroxybenzoyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (7). Synthetized according to general procedure 2 using 1,05 eq. of benzylamine and 1.0 eq. of **1k**. White powder (column chromatography), R_f = 0.38, eluent (ethyl acetate / cyclohexane 1:1), mp = 89-91

°C, 400 mg scale reaction (in 4 mL of EtOH) for 2h, 211 mg was isolated, 43% yield. IR (ν_{max} / cm^{-1}): 3054, 2230, 1731, 1660, 1622, 1541, 1337, 1251. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 11.19 (s, 1H), 8.22 (d, *J* = 2.6 Hz, 1H), 8.18 (d, *J* = 2.6 Hz, 1H), 7.55 (ddd, *J* = 8.6, 7.2, 1.7 Hz, 1H), 7.46 – 7.37 (m, 5H), 7.36 – 7.31 (m, 1H), 7.08 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.93 – 6.86 (m, 1H), 5.25 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 193.1, 162.6, 158.9, 146.6, 146.5, 137.0, 133.9, 131.1, 129.5 (x2), 129.3, 128.9 (x2), 119.3, 119.1, 118.1, 116.6, 114.6, 105.3, 53.8. HRMS (ESI^+) calcd for $C_{20}H_{15}N_2O_3$ $[M+H]^+$ 331.1083, found 331.1106.

1-Benzyl-3-(4,5-dihydrooxazol-2-yl)-5-(2-hydroxybenzoyl)pyridin-2(1H)-one (8). **Pathway 1:** To a solution of **3a** (120 mg, 0.38 mmol) in dichloromethane (3 mL) was added benzylamine (46 µL, 0.42 mmol) and the reaction mixture was heated to reflux. After complete consumption of starting material (40h) the reaction was allowed to cool at room temperature and was concentrated under vacuum. Selective precipitation in cold diethyl ether afforded pure compound **8** as a white powder. R_f = 0.14, eluent (ethyl acetate / dichloromethane 9:1), mp = 175-177 °C, 102 mg were isolated, 71% yield. **Pathway 2:** To a solution of **5** (300 mg, 0.84 mmol), ethanolamine (50 µL, 0.84 mmol), Et_3N (0.35 mL, 2.52 mmol) and CCl_4 (0.33 mL, 3.36 mmol) in MeCN/pyridine (2 mL, 1: 1) was added dropwise a solution of PPh_3 (511 mg, 2.52 mmol) in MeCN/pyridine (2 mL, 1: 1). The mixture was stirred at room temperature for 18h and the latter was concentrated under reduced pressure. The residue was then dissolved in diethyl ether and basified to pH 8-9 with concentrated aqueous NH_4OH solution. The organic layer was separated and the organic phase was extracted with diethyl ether (three times). The combined extracts were dried ($MgSO_4$) and evaporated. Purification by column chromatography afforded pure compound **8** as a white powder. R_f = 0.14, eluent (ethyl acetate / dichloromethane 9:1), mp = 175-177 °C, 42 mg were isolated, 23% yield. IR (ν_{max} / cm^{-1}): 1673, 1632, 1541, 1291, 1247. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 11.37 (s, 1H), 8.41 (d, *J* = 2.7 Hz, 1H), 8.12 (d, *J* = 2.7 Hz, 1H), 7.49 (ddd, *J* = 8.6, 7.2, 1.7 Hz, 1H), 7.46 – 7.34 (m, 6H), 7.05 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.86 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 5.24 (s, 2H), 4.36 (td, *J* = 9.4, 1.3 Hz, 2H), 4.13 (td, *J* = 9.4, 1.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 194.5, 162.5, 160.8, 158.7, 144.8, 141.4, 136.4, 135.0, 131.5, 129.2 (x2), 128.9 (x2), 128.8, 119.0, 118.8, 118.6, 117.7, 116.1, 67.0, 55.8, 53.5. HRMS (ESI^+) calcd for $C_{22}H_{19}N_2O_4$ $[M+H]^+$ 375.1345, found 375.1347.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge via the internet at http://pubs.acs.org.

-Single crystal X-ray diffraction data for compound **3l** CCDC 1477526 (CIF)

-Experimental procedures, products characterization data including ^{1}H and ^{13}C NMR spectra and Quantum chemical calculation details.

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Notes

The authors declare no competing financial interest.

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(35) For complete computational details see SI section.

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