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Studies on the Eschenmoser coupling reaction and insights on its mechanism. Application in the synthesis of Norallosedamine and other alkaloids

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ABSTRACT

The conditions of the Eschenmoser coupling reaction were studied. The formation of the α-thioiminium ion was achieved faster in the presence of an additive (NaI) and dry chloroform as the preferred solvent. The developed conditions were used for the second part of the reaction (the sulfur extrusion itself). The present protocol avoids the formation of byproducts, which were previously described as a major drawback to be overcome. Electrospray ionization tandem mass spectrometry was used to characterize some aspects (intermediates) of the first step of the reaction mechanism. Some reduction conditions were properly tested and the selected conditions were applied to the synthesis of the natural alkaloid Norallosedamine and other derivatives.

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1. Introduction

The Eschenmoser coupling reaction[1] (sulfide contraction reaction/sulfur extrusion reaction) is a general and distinct method for the preparation of β-enaminocarbonyl compounds **3** upon treating a secondary or tertiary thioamide **1** with a suitable electrophile component;[2] normally, an α-bromocarbonyl system **2** (Scheme 1). Sulfur extrusion as a method to effect carbon–carbon (C=C) bond formation was first observed by Knott[3] in his investigation of sulfur-containing chromophores. Later, a mechanism proceeding through an episulfide intermediate, followed by the extrusion of the sulfur atom, was proposed to explain his observations (see Scheme 1).[4] The sulfide contraction as a synthetic tool was developed and implemented by Albert Eschenmoser and applied in the total synthesis of Vitamin B12.[5,6] Tertiary thioamides are the substrates of preference to perform the Eschenmoser coupling reaction, especially due to the formation of a more reactive α-thioiminium intermediate. However, the possibility of byproduct formation is very likely, as described before by Eschenmoser et al.,[7] others[8,9] and us[10] (Fig. 1), mainly due to the influence of the thiolactam ring size.[11–13] In consequence, there is a need of more universal conditions for carrying out the sulfide contraction reaction using secondary or tertiary thioamides.

The Sedamine alkaloids family[14–17] (Fig. 2) is responsible for a number of therapeutic effects, e.g., control of anxiety. This class of alkaloids is extracted from both *Sedum* and *Lobelia* (Indian tobacco) species and their properties[18,19] and synthesis[20–29] have been partially reviewed.[30] These systems have long been known to exhibit interesting biological properties. *Lobelia inflata* has been used for memory enhancement. Additionally, it displays other useful properties.[31] For instance, the crude extract of Indian tobacco species has been used for treatment of respiratory illnesses such as asthma, bronchitis, and pneumonia.[32] As little is known about the biological properties of this class,[33] the development of new synthetic routes is interesting in order to allow new structure–activity relationship studies.

In relation to our interest in the Eschenmoser coupling reaction[10,34] and to our interest in biologically active heterocyclic systems,[35–39] we report in the current manuscript our study on the Eschenmoser coupling reaction conditions, the reductions tests (and conditions) to form β-aminocarbonyl compounds from Eschenmoser's adducts, a new approach to the synthesis of Norallosedamine (and other alkaloids) applying the methodology described herein, and an electrospray (tandem) mass spectrometry study on the Eschenmoser coupling reaction mechanism.

2. Results and discussion

Initially, we examined the conditions to perform the α-thioiminium salt formation using thiolactams **5a–d** and α-bromocarbonyl compound **6** (Scheme 2). The best results can be seen in

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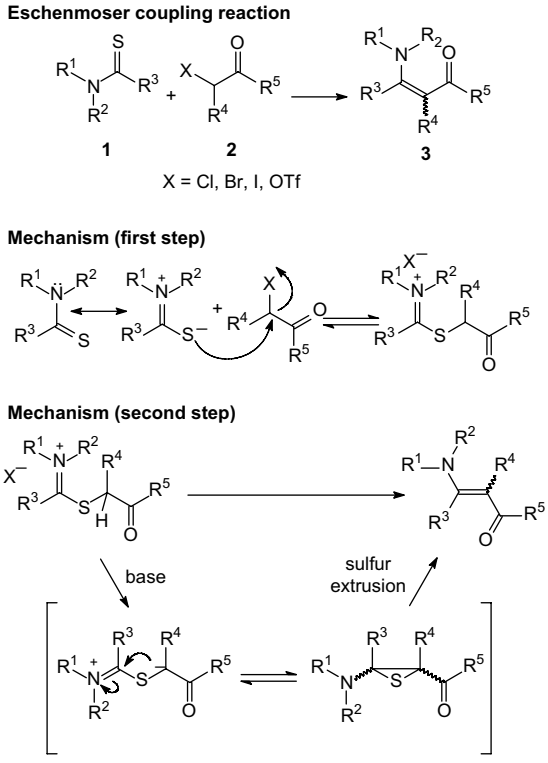


Scheme 1. Eschenmoser coupling reaction and its proposed mechanism.

Table 1 (also see Supplementary data—Tables S1 and S2—for complete data). Solvent such as benzene, diethyl ether, THF, and 1,4-dioxane gave poor conversion requiring long reaction time.

It is clear from the data in Table 1 that the use of NaI as the additive (1.1–2.0 equiv) results in a beneficial effect on the α-thioiminium salt formation, allowing a faster thiolactam consumption. Polar and aprotic solvents such as acetonitrile and chloroform gave the best results. However, it has been described that the salt formation occurs in equilibrium and it is reversible.[40] The use of chloroform gives an advantage in that the formed salt precipitates in the media avoiding the reversibility of its formation. This reversibility has been described by others.[40] Acetonitrile was capable of dissolving all tested systems (including the thioiminium salt). The use of a polar and protic solvent (ethanol) favored the bicyclic formation previously described by Eschenmoser et al.[7] (see Fig. 2) and it will be discussed in due course of the manuscript. The use of both less polar and non-polar solvents gave poor salt formation,

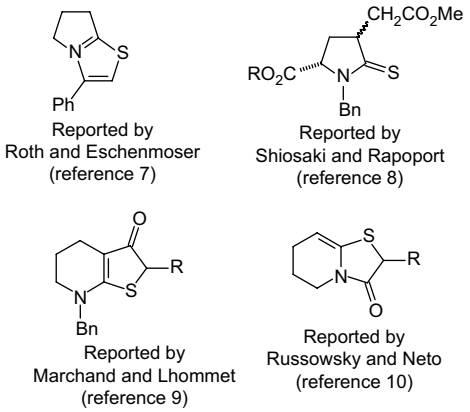


Figure 1. Examples of characterized byproducts during Eschenmoser coupling reaction.

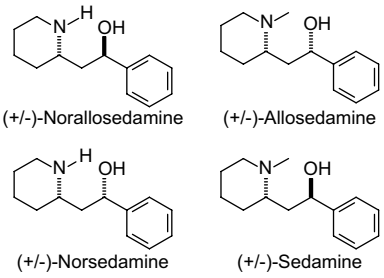


Figure 2. Sedamine alkaloid family.

requiring a long time for the reaction to take place (see Tables S1 and S2 in Supplementary data).

Despite the addition of NaI, it was not possible to observe iminium formation upon treatment of thiolactam **5d** with **6b**,**c** (Table 1, entries 12 and 15). Although it seems a simple alkylation reaction (S_N2), to the best of our knowledge, the use of thiolactam **5d** in the Eschenmoser coupling reaction to obtain tetra-substituted olefins has not been achieved so far. When **5d** is treated with iodomethane no *S*-alkylated product is formed. Methylation of thiolactam **5c** using iodomethane was reported,[41] but the same reaction using **5d** was carried out under drastic conditions: dimethylsulfate (alkylating agent) and **5d** in solventless conditions and heating.[42] Therefore, it was expected that the α-thioiminium salt formation described in Scheme 2 using the thiolactam **5d** would not be achieved. Many attempts to solve this problem were performed by us without success (see Table S3 in Supplementary data). However, initial conditions to form the α-thioiminium salt in the Eschenmoser coupling reaction was achieved (Table 1, entries 7–11 and 13–14) in a short time and with high conversion using the other thiolactams (**5a**–**c**). Electrospray (tandem) mass spectrometry experiments confirmed the importance of an appropriate solvent selection, especially to avoid the formation of byproducts, as will be discussed at the end of the current report.

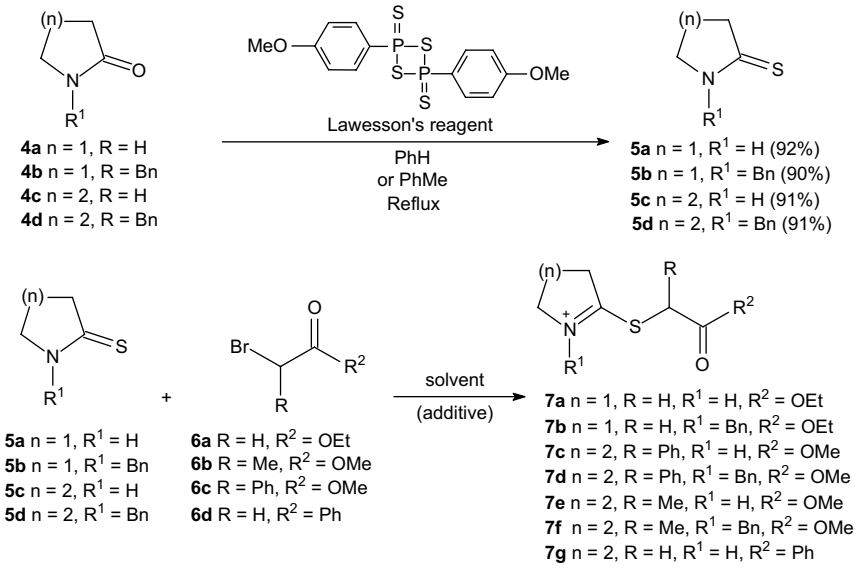
Sulfur extrusion in the Eschenmoser coupling is often a difficult transformation.[1] Some have described the use of three different solvents during the reaction course[43] and others the use of reflux conditions with xylene.[44] Nevertheless, the high boiling temperature of xylene and the inconvenience of using three solvents are drawbacks that were easily overcome by just using chloroform as solvent during all reaction courses. The second step requires the addition of thiophile and of a base, not necessarily in this order. Dual reagents (base and thiophile in the same structure) have been developed.[4,7] Although sometimes it is necessary to add first the base followed by thiophile addition[43] and, in some cases, the opposite order[45] is necessary to avoid byproduct formation.[8] We observed that actually, it depends mainly on whether a secondary or tertiary thioamide was used and on whether a mono- or disubstituted α-halocarbonyl compound was used.

First, we decided to perform the synthesis of tri-substituted β-enaminocarbonyl compounds using Eschenmoser coupling reaction (Scheme 3) and the results are summarized in Table 2.

The bromine-containing α-halocarbonyl **6e** was synthesized according to a previous report.[46,47] All compounds **8a**–**d** were synthesized in good yield using the Eschenmoser coupling reaction (64–86%) as isolated products. Compounds **8a**–**d** were equally isolated as single isomers (determined by GC analysis and confirmed using cycle-NOE experiments—Fig. 3).

The synthesis of tetra-substituted β-enaminocarbonyl compounds normally presents some drawbacks.[48] Therefore, we decided to carry out the synthesis of these derivatives as seen in Scheme 4.

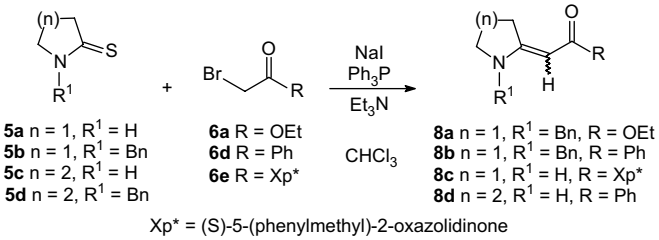
Compound **6c** was easily synthesized in two steps from an esterification reaction of phenylacetic acid followed by an



Scheme 2. Thiolactams synthesis and α-thioiminium formation.

α-bromination with NBS. The geometry of the double bond of compound **8e** was determined comparing it with previous reports from literature[49] (Table 3). All tetra-substituted β-enaminocarbonyl compounds were obtained as single isomers using the developed conditions described here. Normally, mixtures are obtained.[50] The implementation of the methodology resulted in clean conversion to the tetra-substituted alkene as a single geometric isomer, which is an improvement to the existing methods (in good yields—76% for **8e** and 69% for **8f**). Compound **8g** was obtained in only 45% yield. However, it can be obtained as a single compound by changing the reaction conditions. We have already partially described the influence of ring size (five- and six-membered ring) of thiolactams in the Eschenmoser coupling reaction in the formation of bicyclic thiazolidinones **9** or thioimines.[10] Our attempts to optimize the reaction conditions for the selective formation of **8g** are summarized in Table 4.

The geometry of the double bond for the single isomers **8f**,**g** (determined by GC analysis) was confirmed using cycle-NOE experiments (Fig. 4).



Scheme 3. Synthesis of tri-substituted β-enaminocarbonyl compounds.

Table 2
Tri-substituted β-enaminocarbonyl compounds

Entry	Thiolactam			α-Bromocarbonyl		Product			Yield (%)
	5	*n*	R^1	**6**	R	**8**	*n*	R^1	R	
1	**b**	1	Bn	**a**	OEt	**a**	1	Bn	OEt	83
2	**b**	1	Bn	**b**	Ph	**b**	1	Bn	Ph	86
3	**b**	1	Bn	**e**	(*S*)-5-(Phenylmethyl) -2-oxazolidinone	**c**	1	Bn	(*S*)-5-(Phenylmethyl) -2-oxazolidinone	80
4	**c**	2	H	**d**	Ph	**d**	2	H	Ph	64

Table 1
Conditions for α-thioiminium formation[a]

Entry	Thiolactam			Additive (equiv)	Solvent	α-Brominecarbonyl			Iminium (**7**) formation[b] (h)
	5	*n*	R^1			**6**	R	R^2	
1	**a**	1	H	—	MeCN	**a**	H	OEt	18
2	**b**	1	Bn	—	MeCN	**a**	H	OEt	24
3	**a**	1	H	—	$CHCl_3$	**a**	H	OEt	18
4	**b**	1	Bn	—	$CHCl_3$	**d**	H	Ph	22
5	**a**	1	H	NaI (2.0)	MeCN	**a**	H	OEt	16
6	**b**	1	Bn	NaI (1.5)	MeCN	**d**	H	Ph	18
7	**c**	2	H	NaI (2.0)	$CHCl_3$	**a**	H	OEt	12
8	**d**	2	Bn	NaI (1.5)	$CHCl_3$	**d**	H	Ph	18
9	**a**	1	H	NaI (1.1)	$CHCl_3$	**c**	Ph	OMe	18
10	**b**	1	Bn	NaI (1.1)	$CHCl_3$	**c**	Ph	OMe	18
11	**c**	2	H	NaI (1.1)	$CHCl_3$	**b**	Me	OMe	18
12	**d**	2	Bn	NaI (2.0)	$CHCl_3$	**c**	Ph	OMe	—
13	**c**	2	H	NaI (1.1)	$CHCl_3$	**c**	Ph	OMe	18
14	**b**	1	Bn	NaI (1.1)	$CHCl_3$	**b**	Me	OMe	18
15	**d**	2	Bn	NaI (1.1)	$CHCl_3$	**b**	Me	OMe	—
16	**c**	2	H	NaI (2.0)	$CHCl_3$	**d**	H	Ph	15

[a] Determined by GC (consumption of thiolactam).
[b] Time to iminium formation.

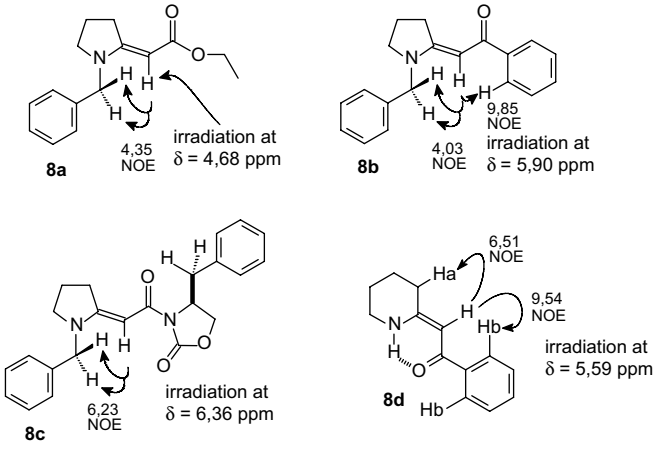
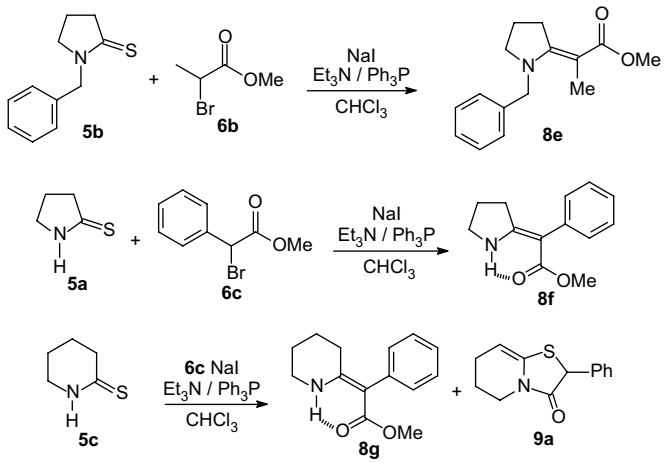


Figure 3. Cycle-NOE experiments of systems **8a**–**d**.



Scheme 4. Synthesis of tetra-substituted β-enaminocarbonyl compounds **8e**–**g**.

Table 3
Spectroscopic data for **8e**

Compound	^{13}C NMR (δ ppm)		
	C=O	N–*C*=C	C=*C*–C=O
8e *Z*[a]	167.4	159.9	86.4
8e *E*[a]	169.3	162.7	88.7
8e	169.8	163.1	88.9

[a] From literature.[49]

Table 4
Used conditions and formation of compounds **8g** and **9a**

Entry	Base (equiv)	Thiophile (equiv)	**8g** (%)	**9a** (%)	Conversion (%)
1	Et_3N (2.00)	Ph_3P (4.00)	42	20	62
2	Et_3N (2.00)	Ph_3P (2.00)	46	21	67
3	Et_3N (2.00)	Ph_3P (1.00)	45	20	65
4	Et_3N (2.00)	*n*-Bu_3P	44	16	60
5	Et_3N (2.00)	$(EtO)_3P$	—	—	—
6	DBU (2.00)	Ph_3P (2.00)	35	41	76
7	—	Ph_3P (4.00)	28	25	53
8	—	*n*-Bu_3P (4.00)	28	23	51
9	Py (2.00)	—	13	11	24
10	Et_3N (2.00)	—	6	25	31
11	DMAP (2.00)	—	27	4	31
12	DABCO (2.00)	—	32	12	44
13	DIPEA (2.00)	—	41	12	53
14	DBN (2.00)	—	41	13	54
15	TMEDA (2.00)	—	46	21	67
16	DBU (2.00)	—	60	—	60
17	KO-*t*-Bu (2.00)	—	20	35	55
18	DBU (1.10)	—	31	5	36

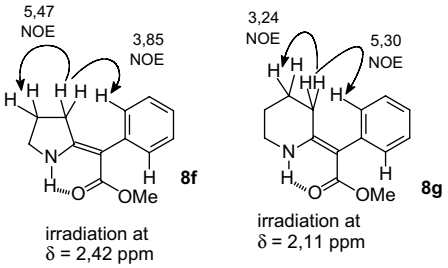
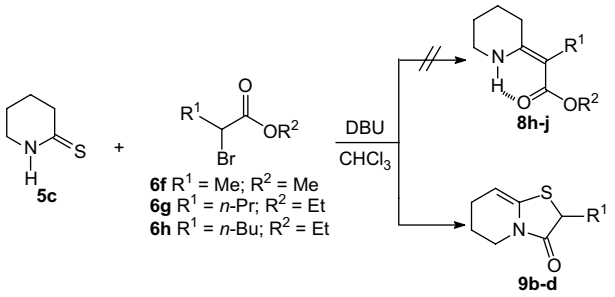


Figure 4. Cycle-NOE experiments of systems **8f**,**g**.

We clearly see that by using DBU (the strongest amine base tested) as the base and without the presence of thiophile, we can obtain compound **8g** as the only product of the Eschenmoser coupling reaction (Table 4, entry 16). Increasing the thiophile concentration, also increased byproduct formation **9a** (Table 4, entries 1–8).

In order to gain insights into the application of the described methodology, we decided to use different commercially available α-bromocarbonyl compounds to expand the methodology (Scheme 5, Table 5).

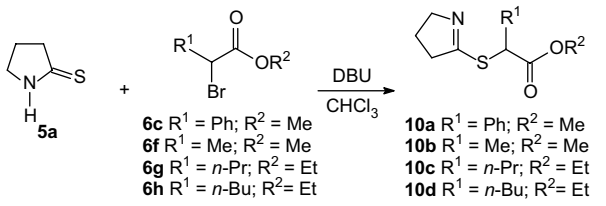


Scheme 5. Reaction of thiolactam **5c** with compounds **6f**–**h**.

Table 5
Reaction of thiolactam **5c** with compounds **6f**–**h**

Entry	α-Halocarbonyl			**8h**–**j** (%)	**9b**–**d** (%)
	6f–**h**	R^1	R^2		
1	**f**	Me	Me	—	**9b** (88)
2	**g**	*n*-Pr	Et	—	**9c** (91)
3	**h**	*n*-Bu	Et	—	**9d** (94)

Instead of the desired tetra-substituted β-enamine **8h**–**j** formation, we observed a complete conversion of reactants into condensation products **9b**–**d**. At first glance, the result obtained seems to be surprising. However, the high yields obtained forming exclusively compounds **9b**–**d** (88–94% of isolated yields) can be explained in terms of the acidity of the hydrogen atoms in the intermediate thioimine analogues, as will be discussed. Nevertheless, before a more precise conclusion, the reactions were carried out using thiolactam **5a** to gain information on how the systems behaved under the developed conditions. Scheme 6 describes the reactions.



Scheme 6. Reaction of thiolactam **5a** with compounds **6e**–**h**.

The results are summarized in Table 6.

Using a five-membered thiolactam, instead thiazolidinone **9**, we obtained and characterized exclusively the intermediates thioimine **10a**–**d** in high isolated yields (89–91%). We observed the formation of **10b**, but it was shown to be a very unstable product, precluding its full spectroscopic characterization.

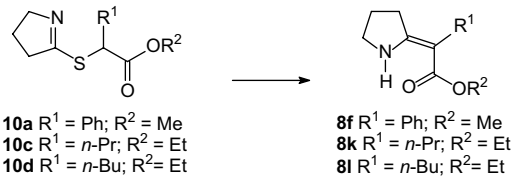
Table 6
Reaction of thiolactam **5a** with compounds **6e–h**

Entry	α-Halocarbonyl **6e–h**	R^1	R^2	**10a–d** (%)
1	**c**	Ph	Me	**a** (93)
2	**f**	Me	Me	**b** (—)
3	**g**	*n*-Pr	Et	**c** (89)
4	**h**	*n*-Bu	Et	**d** (91)

Table 7
Sulfur extrusion reaction and conditions in attempt to form systems **8f**,**k**,**l**

Entry	R^1	R^2	Steps	Intermediates **10a**,**c**,**d** (%)	Conditions	**8f**,**k**,**l** (%)
1	Ph	Me	1	Not isolated	Et_3N/Ph_3P	**8f** (69)
2	Ph	Me	1	Not isolated	DBU/Ph_3P	**8f** (77)
3	Ph	Me	2	Isolated (93%)	DBU then Ph_3P	**8f** (86)
4	Me	Me	1	Not isolated	Et_3N/Ph_3P	Decomposition
5	Me	Me	1	Not isolated	DBU/Ph_3P	Decomposition
6	Me	Me	1	Not isolated	DBU then Ph_3P	Decomposition
7	*n*-Pr	Et	1	Not isolated	Et_3N/Ph_3P	Decomposition
8	*n*-Pr	Et	1	Not isolated	DBU/Ph_3P	Decomposition
9	*n*-Pr	Et	2	Isolated (89%)	DBU then Ph_3P	Decomposition
10	*n*-Bu	Et	1	Not isolated	Et_3N/Ph_3P	Decomposition
11	*n*-Bu	Et	1	Not isolated	DBU/Ph_3P	Decomposition
12	*n*-Bu	Et	2	Isolated (91%)	DBU then Ph_3P	Decomposition

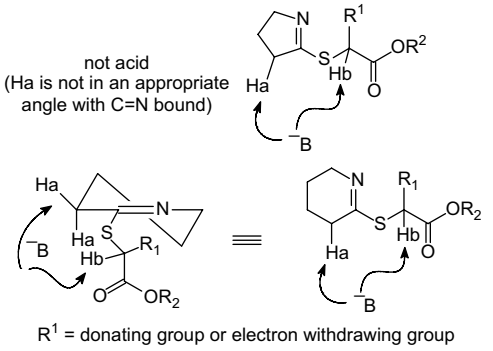
We treated thioimine intermediates under different conditions (Table 7) to obtain the respective β-enaminocarbonyl compound (Scheme 7). The presence of an electron withdrawing group in intermediate **10a** allows the hydrogen abstraction to precede the sulfur extrusion. However, the presence of electron donating groups (Me, *n*-Pr, *n*-Bu) in the other derivatives **10c**,**d** resulted in a less acidic α-proton slated for abstraction and the consequence was decomposition of the thioimine intermediates under sulfur extrusion reaction conditions. It is worth noting that when isolating **10a**, the use of triphenylphosphine alone is enough to promote the contraction of the system to form **8f** (Table 7, entry 3).



Scheme 7. Sulfur extrusion of systems **10a**,**c**,**d**.

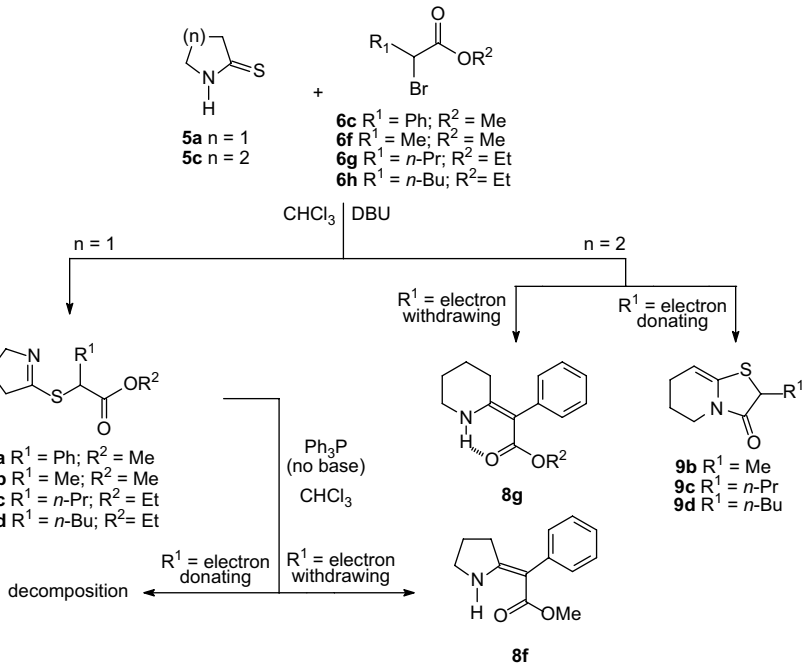
Much effort was put into trying to rationalize the main results obtained using five- and six-membered thiolactams **5a**,**c** under the developed conditions ($CHCl_3$ and DBU as base), and we had all data necessary to rationalize the observed events. In Scheme 8 we can visualize the events according to the ring size, qualitative intrinsic acid character of hydrogen atoms slated for abstraction, and conditions used to promote the Eschenmoser coupling reaction.

Once we could visualize all events and had the data relative to the developed conditions and the difference in behavior of five- and six-membered rings, we could explain the results in terms of the acidity of the hydrogen atoms in the intermediates, as seen in Scheme 9.



Scheme 9. Possible pathways to hydrogen abstraction in thioimine intermediates.

In the five-membered ring, Ha is in a position that renders the hydrogen non-acidic because of its angle relative to the C=N bond that does not favor its abstraction by the base allowing the corresponding enamine formation. On the other hand, Hb



Scheme 8. Rationalization of the obtained results using five- and six-membered thiolactams **5a**,**c** and DBU as base. Formation of thioimines **10a–d** intermediates and thiazolidinones **9b–d**.

displays a very acidic nature, especially in the situation where R^1 is an electron withdrawing group (phenyl in the case of **10a**). When R^1 is an electron donating group, the outcome is a drastic decrease in the acidity of Hb. The net result is that under the reaction conditions (strong basic media), the thioimine **10** decomposes and no sulfur extrusion takes place. In the six-membered ring, both Ha and Hb are slated for abstraction due to conformational aspects of the system (see Scheme 9, below). It is clear from our results that when R^1 is an electron withdrawing group the acidic character of Hb is considerably higher than Ha, and the expected sulfur reaction pathway takes place naturally. However, when R^1 is an electron donating group, we clearly observed a higher acidity character of Ha, and its abstraction leads to a nucleophilic enamine, which undergoes spontaneous cyclization forming, in an exclusive manner, the corresponding bicyclic thiazolidinones **9**. As a consequence, thioimine intermediates with the six-membered ring are not observed, only byproducts **9**.

Once we could tune the synthesis of some β-enaminocarbonyl compounds, we decided to investigate the partial and/or total reduction of those systems. Both catalytic hydrogenations and hydride reductions were tested under different conditions (Scheme 10, Table 8).

Many other methods were tested without success to partial and/or total reduction of β-enaminocarbonyl compounds (see Table S4 in Supplementary data to access all experiments). It is noteworthy that partial reduction (C=C only) occurs preferentially in all cases. And, as will be discussed, in only one case the total reduction (C=C and C=O reductions) takes place under the tested conditions.

The reduction using borohydrides was shown to be a good methodology to access β-aminocarbonyl compounds **11**. All reactions were fast and clean. The use of $NaBH_4$ and AcOH was very effective in reducing β-enaminocarbonyl compounds[51,52] derived from tertiary thioamide (R^1=Bn) yet ineffective toward secondary thioamide derivatives. Indeed, for tertiary thioamide derivatives, it was shown to be the best method tested (Table 8, entries 1, 5, and 9). On the other hand, commercially available $NaBH(OAc)_3$ was the least effective for promoting C=C reduction (Table 8, entries 3, 7, 11, 14, 19, 29, and 30), despite the fact that it could also reduce secondary thioamide derivatives. $NaBH_3CN$/HCl was shown to be a good combination for partial reduction of the tested systems. In all cases the yields were very good (Table 8, entries 2, 6, 10, 13, 18, 21, and 28).

Catalytic hydrogenations were equally tested using all β-enaminocarbonyl derivatives **8a–g**. When we used Pd-containing catalysts under many different conditions (see Table S4 in Supplementary data), no partial hydrogenation could be observed. Nevertheless, the use of platinum derivatives showed these to be a very good choice for selective reduction of the C=C double bond. Using PtO_2 and catalytic amounts of acetic acid, no reductions were observed. However, using catalytic amounts of a stronger acid ($HClO_4$) and small H_2 pressure (1–3 atm) we could observe partial reduction (C=C reduction) in all tested compounds **8a–g** (Table 8, entries 4, 8, 12, 16, 20, 23–27, 32, and 33).

It is important to note that the use of borohydrides led to a higher stereoselectivity during the reduction of the C=C double bond than hydrogenations. A possible explanation to the described selection may have its origin in the mechanism of the reduction, as proposed in the great work of Palmieri et al.[51,52] The proposed mechanism previously reported by this group explains the selectivity, however it has some aspects that differ in kind to our proposition (see Scheme 11 for a plausible catalytic cycle).

It is believed that the mixture $NaBH_4$ and acetic acid leads to an in situ generation of the reducing agent $NaH(OAc)_3$ that reduces an iminium–enol intermediate. The reduction leads preferentially to *erythro* derivatives, as seen in Scheme 11.

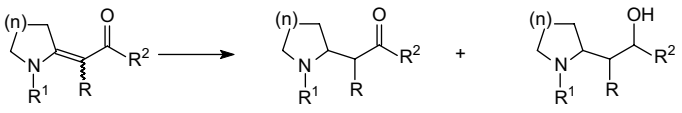
It is important to highlight that the proposition seen in Scheme 11 can explain either catalytic amounts of acid acting in the system to form the iminium–enol intermediate slated for reduction and cases where the chosen acid act as solvent (media) and reagent, as described in the case of the reducing system $NaBH_4$/AcOH.

Under catalytic acid conditions using different borohydrides, the reduction can be explained as follows: first, the tautomeric iminium–enol specie is formed by protonation. The available borate complexes in the oxygen and the hydride is transferred reducing the C=N double bond in the iminium carbon. After, a protonation in the enol carbon takes place, restoring the C=O double bond and releasing both the reduced β-aminocarbonyl compound and the acid, allowing a new catalytic cycle to start.

The reduction of compound **8c** is of special importance, mainly due to a presence of a chiral inductor in the ester moiety ((*S*)-5-phenylmethyl-2-oxazolidinone). In all cases (Table 8, entries 9–12) we observed a 1:1 mixture of diastereoisomers in the reduced β-aminocarbonyl compound **11c**. The results associated with the previous knowledge of cycle-NOE experiments performed in its precursor (**8c**) indicate that the stereogenic center is far from the double bond, resulting in no chiral induction during the reduction (see Fig. 3).

Reducing compounds **8f** and **8g** we obtain, respectively, a five- and six-membered ring (the five-membered analogue and methylphenidate), which is an indirect catecholamine agonist,[53] and is the drug treatment of choice for attention deficit/hyperactivity disorder,[54] one of the most common behavioral disorders in children and which affects 5–10% of the general population.[55]

Compound **11f** had its stereochemistry determined by comparing its NMR data with a previous report in literature.[56] However, the most important is compound **11g**, which suffers



β-enaminocarbonyl β-aminocarbonyl γ-aminoalcohol

β-enaminocarbonyl	β-aminocarbonyl	γ-aminoalcohol
8a n = 1, R^1 = Bn, R = H, R^2 = OEt	**11a** n = 1, R^1 = Bn, R = H, R^2 = OEt	**12a** n = 1, R^1 = Bn, R = H, R^2 = H
8b n = 1, R^1 = Bn, R = H, R^2 = Ph	**11b** n = 1, R^1 = Bn, R = H, R^2 = Ph	**12b** n = 1, R^1 = Bn, R = H, R^2 = Ph
8c n = 1, R^1 = Bn, R = H, R^2 = Xp*	**11c** n = 1, R^1 = Bn, R = H, R^2 = Xp*	**12c** n = 1, R^1 = Bn, R = H, R^2 = H
8d n = 2, R^1 = H, R = H, R^2 = Ph	**11d** n = 2, R^1 = H, R = H, R^2 = Ph	**12d** n = 2, R^1 = H, R = H, R^2 = Ph
8e n = 1, R^1 = Bn, R = Me, R^2 = OMe	**11e** n = 1, R^1 = Bn, R = Me, R^2 = OMe	**12e** n = 1, R^1 = Bn, R = Me, R^2 = H
8f n = 1, R^1 = H, R = Ph, R^2 = OMe	**11f** n = 1, R^1 = H, R = Ph, R^2 = OMe	**12f** n = 1, R^1 = H, R = Ph, R^2 = H
8g n = 2, R^1 = H, R = Ph, R^2 = OMe	**11g** n = 2, R^1 = H, R = Ph, R^2 = OMe	**12g** n = 2, R^1 = H, R = Ph, R^2 = H

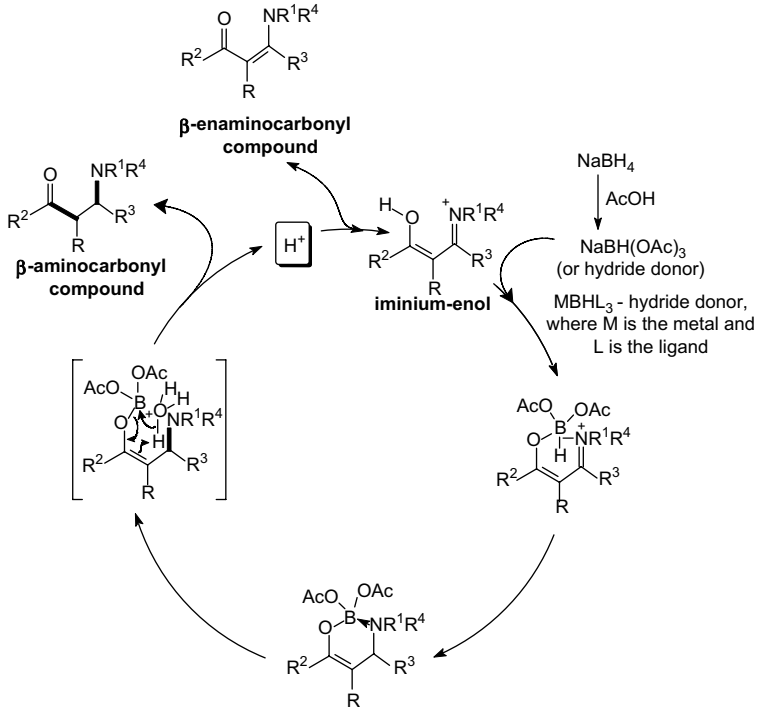
Xp* = (S)-5-(phenylmethyl)-2-oxazolidinone

Scheme 10. Reduction of β-enaminocarbonyl compounds **8a–g**.

Table 8
β-Enaminocarbonyl compounds (**8a–g**) reductions and conditions

Entry	**8**					Conditions	**11** (%)	**12** (%)	*erythro*:*threo*[b] (**11**)
		n	R^1	R	R^2				
1	**a**	1	Bn	H	OEt	$NaBH_4$/AcOH	88	—	—
2	**a**	1	Bn	H	OEt	$NaBH_3CN$/HCl[a]	75	—	—
3	**a**	1	Bn	H	OEt	$NaBH(OAc)_3$	71	—	—
4	**a**	1	Bn	H	OEt	PtO_2 (1 atm H_2)/$HClO_4$[a]	85	—	—
5	**b**	1	Bn	H	Ph	$NaBH_4$/AcOH	89	—	—
6	**b**	1	Bn	H	Ph	$NaBH_3CN$/HCl[a]	72	—	—
7	**b**	1	Bn	H	Ph	$NaBH(OAc)_3$	72	—	—
8	**b**	1	Bn	H	Ph	PtO_2 (1 atm H_2)/$HClO_4$[a]	86	—	—
9[c]	**c**	1	Bn	H	Xp*	$NaBH_4$/AcOH	99	—	—
10[c]	**c**	1	Bn	H	Xp*	$NaBH_3CN$/HCl[a]	74	—	—
11[c]	**c**	1	Bn	H	Xp*	$NaBH(OAc)_3$	73	—	—
12[c]	**c**	1	Bn	H	Xp*	PtO_2 (1 atm H_2)/$HClO_4$[a]	88	—	—
13	**d**	2	H	H	Ph	$NaBH_3CN$/HCl[a]	75	—	—
14	**d**	2	H	H	Ph	$NaBH(OAc)_3$	71	—	—
15	**d**	2	H	H	Ph	$NaBH_4$/EtOH	9	60	—
16	**d**	2	H	H	Ph	PtO_2 (1 atm H_2)/$HClO_4$[a]	87	—	—
17	**e**	1	Bn	Me	OMe	$NaBH_4$/AcOH	92	—	97:3
18	**e**	1	Bn	Me	OMe	$NaBH_3CN$/HCl[a]	98	—	95:5
19	**e**	1	Bn	Me	OMe	$NaBH(OAc)_3$	71	—	95:5
20	**e**	1	Bn	Me	OMe	PtO_2 (1 atm H_2)/$HClO_4$[a]	81	—	85:15
21	**f**	1	H	Ph	OMe	$NaBH_3CN$/HCl[a]	70	—	99:1
22	**f**	1	H	Ph	OMe	$NaBH(OAc)_3$	62	—	99:1
23	**f**	1	H	Ph	OMe	PtO_2 (30 atm H_2)/$HClO_4$[a]—24 h	35	—	99:1
24	**f**	1	H	Ph	OMe	PtO_2 (50 atm H_2)/$HClO_4$[a]—24 h	60	—	99:1
25	**f**	1	H	Ph	OMe	PtO_2 (70 atm H_2)/$HClO_4$[a]—24 h	68	—	99:1
26	**f**	1	H	Ph	OMe	PtO_2 (100 atm H_2)/$HClO_4$[a]—18 h	91	—	99:1
27	**f**	1	H	Ph	OMe	PtO_2 (130 atm H_2)/$HClO_4$[a]—18 h	99	—	99:1
28	**g**	2	H	Ph	OMe	$NaBH_3CN$/HCl[a]	90	—	96:4
29	**g**	2	H	Ph	OMe	$NaBH(OAc)_3$	89	—	96:4
30	**g**	2	H	Ph	OMe	$NaBH(OAc)_3$/AcOH	72		93:7
31	**g**	2	H	Ph	OMe	Mg/MeOH—reflux	40	—	85:15
32	**g**	2	H	Ph	OMe	PtO_2 (3 atm H_2)/$HClO_4$[a]	45		80:20
33	**g**	2	H	Ph	OMe	PtO_2 (5 atm H_2)/$HClO_4$[a]	90		80:20

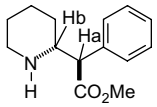
Xp*=(*S*)-5-(phenylmethyl)-2-oxazolidinone.
[a] Catalytic amounts of acid.
[b] Determined by GC analysis.
[c] Diastereoisomeric ratio determined by GC (≈1:1 in all cases).



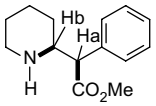
Scheme 11. Proposed mechanism to acid-catalyzed hydride reduction. (Based on previous literature reports.[51,52])

epimerization[57] leading to *threo*-isomer, which is commercially available as Ritalin®. This specific drug is sold as the racemate and it is synthesized using the *erythro*-epimer.[34] The data for both isomers are available in the literature[56,58] allowing an easy attribution for the formed β-aminocarbonyl **11g** as seen in Tables 9 and 10.

Table 9
^{1}H NMR of compound **11g**



threo-methylphenidate

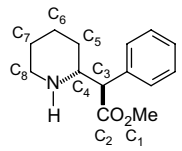


erythro-methylphenidate

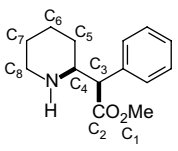
Methylphenidate	^{1}H NMR (δ=ppm and J=Hz)		
threo[a]	7.29 (m, 5H)	3.44 (d, 1Ha, J=9.9)	2.69 (dt, 1Hb, J=3.0 e 12.0)
erythro[a]	7.42–7.20 (m, 5H)	3.48 (d, 1Ha, J=10.2)	2.93 (d, 1Hb, J=12.3)
11g	7.44–7.28 (m, 5H)	3.48 (d, 1Ha, J=10.1)	2.92 (d, 1Hb, J=12.4)

[a] Data from literature.[56,58]

Table 10
^{13}C NMR of compound **11g**



threo-methylphenidate



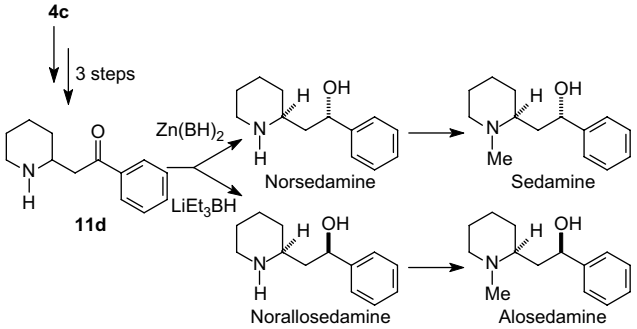
erythro-methylphenidate

Methylphenidate	^{13}C NMR (δ=ppm)							
	C_2	C_1	C_3	C_4	C_8	C_5	C_6	C_7
threo[a]	173.8	58.8	58.7	51.9	46.8	29.9	26.1	24.3
erythro[a]	173.1	59.0	58.3	51.9	47.0	31.0	25.7	24.4
11g	172.9	59.2	58.1	51.8	46.9	30.9	25.6	24.5

[a] Data from literature.[56,58]

Tables 9 and 10 clearly show that the reduction of compound **8g** leads directly to *erythro*-isomer, independent of the chosen reducing agent.

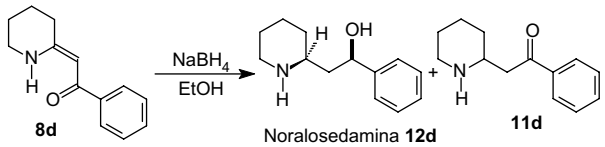
Studying the reduction of β-enaminocarbonyl **8d** we envisioned the possibility of a formal synthesis of the Sedamine alkaloid family and the total synthesis of one stereoisomer from this family by the total reduction of compound **8d**. The partial reduction of the molecule would lead directly to β-aminocarbonyl compound **11d**, which is the formal synthesis of all four isomers (Scheme 12).[59,60]



Scheme 12. Formal synthesis of four Sedamine alkaloid family isomers.

The methods described here allow us to a directly obtain of the desired intermediate **11d**. The reduction of **8d** using the reducing systems $NaBH_3CN$/HCl and $NABH(OAc)_3$ led directly to **11d**, marking the formal synthesis of Sedamine derivatives (Table 8, entries 13 and 14). Nevertheless, in this case, the use of catalytic hydrogenation (PtO_2/$HClO_4$ and H_2 1 atm—Table 8, entry 16) gave a better yield (87%) of the desired intermediate.

Due to our interest in studying the reduction of β-enaminocarbonyl systems, we decided to investigate the total reduction of molecule **8d**. Since all methods led only to partial reduction of tested compounds, we decided to use $NaBH_4$/EtOH as the reducing system. The combination resulted in the total reduction of β-enaminocarbonyl with the formation of only one isomer: Norallosedamine **12d** (γ-aminoalcohol) in a good yield (Scheme 13, Table 8, entry 15). We could also observe in 9% yield the β-aminocarbonyl **11d** (Table 8, entry 15).



Scheme 13. Synthesis of Norallosedamine.

The developed method allowed the synthesis of the natural alkaloid in only three steps with good overall yield. The stereochemistry of compound **12d** was confirmed comparing the NMR data previously reported to Sedamine alkaloids[59,61–63] (Table 11).

The data confirms the stereochemistry attributed to compound **12d** was correctly assigned to the natural alkaloid Norallosedamine.

Finally, we present the results using electrospray (tandem) mass spectrometry to study the Eschenmoser coupling reaction's first step. To gain insights into the mechanism of the reaction we monitored it online by electrospray ionization (tandem) mass spectrometry.[64,65] Note that ESI-MS and ESI-MS/MS have been shown to be a suitable technique to study reaction mechanisms via the interception and structural characterization of key ionic intermediates.[66–69] Our group has used successfully this fast and sensitive technique in the study of other reactions.[37,39] The gentle transfer to the gas phase allowed us to have a good idea of how the species are behaving during Eschenmoser coupling reaction.

First, we tested the reaction using mixtures of thiolactam **5a** and α-halocarbonyl compound **6d** in a polar and protic solvent (MeOH—Fig. 5A). A second experiment was performed with a polar and aprotic solvent (MeCN—Fig. 5B) in order to analyze how the reaction behaves under different solvents influence.

It is important to point out that in a polar and protic solvent (MeOH) we could observe the presence of a m/z 202 ion that was attributed as a byproduct previously described by Eschenmoser et al..[7] ESI(+)MS/MS of the signal (Fig. 5C) shows its fragmentation pattern and it is coherent with the proposed structure exhibiting signals of m/z 174, 134, 105, and 91. The structures of these signals are seen in Figure 5. On the other hand, when using a polar and

Table 11
Data for Sedamine derivatives

Compound	^{1}H NMR δ (ppm), HO–C–*H*	J (Hz), HO–C–*H*	^{13}C NMR δ (ppm)
Norallosedamine[a]	5.05	dd, J=7.4 and 3.8	71.6
Norsedamine[a]	4.92	dd, J=10.8 and 2.7	75.5
Allosedamine[a]	5.13	dd, J=10.5 and 3.3	71.8
Sedamine[a]	4.90	dd, J=10.6 and 2.8	75.0
12d	5.02	dd, J=8.6 and 4.2	71.3

[a] Data from literature.[59,61–63]

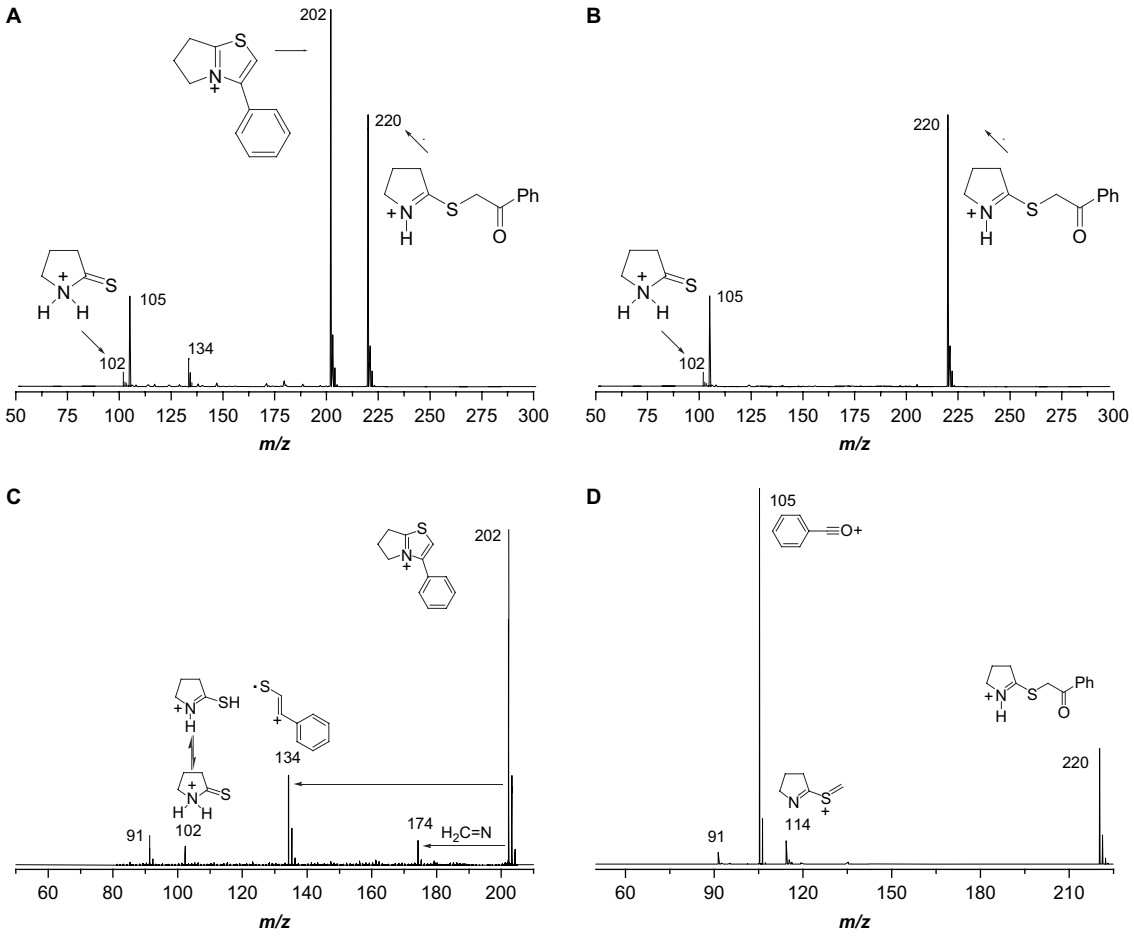


Figure 5. ESI(+)MS and ESI(+)MS/MS of the Eschenmoser coupling reaction first step. (A) ESI(+)/MS of a mixture of thiolactam **5a** and α-halocarbonyl **6d** in methanol solution. (B) ESI(+)/MS of a mixture of thiolactam **5a** and α-halocarbonyl **6d** in MeCN solution. (C) ESI(+)MS/MS of ion of *m*/*z* 202. (D) ESI(+)MS/MS of ion of *m*/*z* 220.

aprotic solvent, no signal of *m*/*z* 202 was observed. The main signal (*m*/*z* 220—Fig. 5B) was structurally characterized and its ESI(+)MS/MS was collected (Fig. 5D). The set of fragmentation displays signal of *m*/*z* 114, 105, and 91, that were attributed to the species seen in Figure 5D. The mass experiments clearly show that to perform the thioiminium ion formation in the first step, a polar and aprotic solvent is preferred.

In summary, we demonstrate that the Eschenmoser coupling reaction is an efficient and elegant method for the construction of β-enaminocarbonyl systems. In the first step, the use of a polar and aprotic solvent avoids byproduct formation and the use of an additive (NaI) consistently reduces the required time for thioiminium formation. Electrospray (tandem) mass spectrometry experiments confirm the importance of an appropriate solvent selection to thioiminium formation without byproduct formation. The use of a strong base (such as DBU) to form tetra-substituted derivatives helps the proton abstraction and the sulfur extrusion itself. Reducing systems such as $NaBH_4$/AcOH and PtO_2/H_2 resulted in β-aminocarbonyl (partially reduced) compounds in high yields. The developed methodology allowed the synthesis of methylphenidate analogue, Ritalin®, and Norallosedamine. Thus, it opens up a new avenue for other alkaloid syntheses.

3. Experimental

3.1. General

All commercial chemicals were purchased from Acros or Aldrich and used without further purification. All air/wet sensible reactions were carried out under an argon or nitrogen atmosphere in oven-dried resealable Schlenk tubes. All new compounds were fully characterized after purification. NMR spectra were recorded on Varian Inova 300 MHz or Varian Gemini 200 MHz spectrometers. Infrared spectra were registered on a Bomem B-102 spectrometer. Melting points were measured on a 12000 PL-DSC apparatus at a heating rate of 5 °C/min or in an Electrothermal IA9000 Melting Point apparatus.

3.2. General procedure for the synthesis of thiolactams derivatives 5a–d

To a 50 mL flask were added 2.5 mmol of lactams **4a**–**d**, 20 mL of benzene or toluene, and 1.25 mmol of Lawesson's reagent. The reaction was refluxed for 4 h and the solvent was removed under reduced pressure. The crude products were purified by chromatography column eluted with *n*-hexane/ethyl acetate mixtures.

*3.2.1. Thiolactam **5a***

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 9.24–9.12 (br, 1H), 3.68 (t, *J*=7.3 Hz, 2H), 2.92 (t, *J*=7.9 Hz, 2H), 2.22 (qt, *J*=7.6 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 205.2, 49.6, 43.2, 22.6. FTIR (KBr, cm^{-1}): 2946, 2884, 1535, 1294, 1113. Mp=114.6–115.8; literature[7] 114.0–116.0. Anal. Calcd for C_4H_7NS: C, 47.49; H, 6.97; N, 13.85. Found: C, 47.52; H, 6.99; N, 13.95.

*3.2.2. Thiolactam **5b***

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 7.30 (s, 5H), 4.98 (s, 2H), 3.59 (t, *J*=7.3 Hz, 2H), 3.10 (t, *J*=7.9 Hz, 2H), 2.00 (qt, *J*=7.6 Hz, 2H). ^{13}C

NMR (50 MHz, $CDCl_3$): δ ppm 201.5, 131.9, 128.6, 128.1, 127.8, 53.8, 51.1, 41.8, 19.3. FTIR (KBr, cm^{-1}): 3021, 2985, 1592, 1511, 1303. Mp=70.2–71.8; literature[70] 70.0–71.0. Anal. Calcd for $C_{11}H_{13}NS$: C, 69.07; H, 6.85; N, 7.32. Found: C, 69.10; H, 7.01; N, 7.40.

3.2.3. Thiolactam ***5c***

^1H NMR (200 MHz, $CDCl_3$): δ ppm 9.60–9.06 (br, 1H), 3.36–3.2 (m, 2H), 2.93–2.87 (m, 2H), 1.90–1.70 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 200.8, 43.7, 38.4, 19.9, 19.3. FTIR (KBr, cm^{-1}): 2859, 1571, 1321, 1114. Mp=92.1–92.8; literature[71] 87–93. Anal. Calcd for C_5H_9NS: C, 52.13; H, 7.87; N, 12.16. Found: C, 52.19; H, 7.94; N, 12.23.

3.2.4. Thiolactam ***5d***

^1H NMR (200 MHz, $CDCl_3$): δ ppm 7.31 (s, 5H), 5.32 (s, 2H), 3.34 (t, *J*=7.9 Hz, 2H), 3.08 (t, *J*=6.1 Hz, 2H), 1.88–1.63 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 200.4, 135.2, 128.4, 127.4, 57.1, 49.0, 41.6, 22.0, 20.3. FTIR (KBr, cm^{-1}): 3023, 2956, 1592, 1508, 1299. Mp=67.7–69.1; literature[72] 68.0–69.0. Anal. Calcd for $C_{12}H_{15}NS$: C, 70.20; H, 7.36; N, 6.82. Found: C, 70.14; H, 7.23; N, 6.77.

3.3. α-Halocarbonyl compound 6c

In a 100 mL flask were added methyl phenylacetate (6.17 g; 41.1 mmol), 30 mL of CCl_4, NBS (8.1 g; 45.3 mmol), and benzoyl peroxide 70% (0.1 g; 0.41 mmol). The reaction was refluxed for 4 h. The formed succinimide was filtered off and the crude product was distilled at 1 mmHg/115 °C affording methyl-α-bromophenylacetate **6c** in 84% yield as a colorless liquid.

^1H NMR (200 MHz, $CDCl_3$): δ ppm 7.56–7.52 (m, 2H), 7.37–7.34 (m, 3H), 5.36 (s, 1H), 3.78 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 168.7, 135.6, 129.2, 128.8, 128.6, 53.3, 46.5. FTIR (neat, cm^{-1}): 3023, 2859, 1731, 1594, 1464, 1368. Anal. Calcd for $C_9H_9BrO_2$: C, 47.19; H, 3.96. Found: C, 47.24; H, 3.99.

3.4. α-Halocarbonyl compound 6e

Under inert atmosphere conditions, (*S*)-4-benzyl-2-oxazolidinone (1.0 g, 5.64 mmol) was dissolved in dry THF (18 mL) and the solution was cooled at −78 °C. To this solution was added a solution of *n*-BuLi 2 M (2.82 mL) and α-bromoacetylbromide (0.55 mL, 6.20 mmol). The reaction was stirred for 10 min at −78 °C and 30 min at room temperature. After, the solvent was removed under reduced pressure. The crude product was dissolved in CH_2Cl_2 and washed with aqueous saturated ammonium chloride solution. The organic phase was dried, filtered off, and the solvent removed. The product was purified by chromatography column eluted with *n*-hexane/ethyl acetate mixture to afford **6c** in 86% yield.

^1H NMR (200 MHz, $CDCl_3$): δ ppm 7.39–7.20 (m, 5H), 4.76–4.64 (m, 1H), 4.53 (s, 2H), 4.32–4.20 (m, 2H), 3.32 (dd, *J*=3.2 and 14.0 Hz, 1H), 2.80 (dd, *J*=9.5 and 14.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 165.8, 152.9, 134.7, 129.3, 128.9, 127.4, 66.6, 55.3, 37.4, 28.3. $[\alpha]_D$ −75.1 (*c* 2.30, CH_2Cl_2); literature[46] (enantiomer) +75.4 (*c* 2.30, CH_2Cl_2). Anal. Calcd for $C_{12}H_{12}BrNO_3$: C, 48.34; H, 4.06; N, 4.70. Found: C, 48.28; H, 4.13; N, 4.78.

3.5. General procedure for the synthesis of tri-substituted β-enaminocarbonyl compounds 8a–d

In a 50 mL flask, in an argon atmosphere, thiolactams **5a–d** (0.79 mmol) was dissolved in 2 mL of dry chloroform. To the solution were added dry NaI (0.87 mmol) and the α-halo compounds **6a**, **6d** or **6e**. The reaction was stirred for 18 h at room temperature. After this period were added triphenylphosphine (1.58 mmol) and triethylamine (1.58 mmol) in this order to the protected nitrogen compounds. To the unprotected compounds the additions were performed in the inverse order. The reaction system was stirred for 24 h and the volatiles were removed under reduced pressure. The products were purified by a chromatography column eluted with *n*-hexane/ethyl acetate gradient.

3.5.1. β-Enaminocarbonyl compound ***8a***

^1H NMR (200 MHz, $CDCl_3$): δ ppm 7.32–7.15 (m, 5H), 4.68 (s, 1H), 4.34 (s, 2H), 4.08 (q, *J*=7.1 Hz, 2H), 3.33 (t, *J*=6.9 Hz, 2H), 3.22 (t, *J*=7.8 Hz, 2H), 1.95 (qt, *J*=7.5 Hz, 2H), 1.22 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 164.9, 135.8, 128.5, 127.2, 126.9, 78.2, 58.0, 52.2, 49.8, 32.4, 20.9, 14.5. FTIR (KBr, cm^{-1}): 3013, 2918, 1657, 1592, 1085, 1027. Mp=61.8–62.9; literature[70] 62.0–63.0. Yield 83%. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.51; H, 7.90; N, 5.79.

3.5.2. β-Enaminocarbonyl compound ***8b***

^1H NMR (200 MHz, $CDCl_3$): δ ppm 7.85–7.20 (m, 10H), 5.90 (s, 1H), 4.51 (s, 2H), 3.53–3.40 (m, 4H), 2.05 (qt, *J*=7.4 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 187.9, 167.4, 141.9, 135.5, 130.2, 128.9, 127.9, 127.7, 127.1, 86.8, 52.6, 50.3, 33.8, 20.9. FTIR (KBr, cm^{-1}): 3022, 2949, 2870, 1620, 1576, 1543, 1475, 1219. Mp=57.1–58.3. Yield 86%. Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 7.81; N, 5.71. Found: C, 82.33; H, 7.89; N, 5.79.

3.5.3. β-Enaminocarbonyl compound ***8c***

^1H NMR (300 MHz, $CDCl_3$): δ ppm 7.40–7.22 (m, 10H), 6.36 (s, 1H), 4.73–4.68 (m, 1H), 4.47 (s, 2H), 4.06–3.96 (m, 2H), 3.44 (t, *J*=7.0 Hz, 2H), 3.34 (dd, *J*=16.0 and 14.0 Hz, 1H), 2.75 (dd, *J*=12.0 and 10.0 Hz, 1H), 2.01 (qt, *J*=7.5 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 167.7, 165.3, 154.2, 136.2, 135.4, 129.5, 128.7, 128.6, 127.8, 127.7, 126.8, 79.7, 65.3, 55.3, 52.5, 50.5, 38.6, 33.8, 20.8. FTIR (KBr, cm^{-1}): 3019, 2944, 2861, 1642, 1592, 1205. $[\alpha]_D$ +10.1 (*c* 1.01, ethanol). Mp=153.2–154.4. Yield 80%. Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.19; H, 6.40; N, 9.87.

3.5.4. β-Enaminocarbonyl compound ***8d***

^1H NMR (200 MHz, $CDCl_3$): δ ppm 11.78–1.59 (br, 1H), 7.92–7.78 (m, 7H), 7.42–7.31 (m, 4H), 5.59 (s, 1H), 3.46–3.28 (m, 2H), 2.50 (t, *J*=6.1 Hz, 2H), 1.91–1.68 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 187.0, 165.7, 140.6, 130.1, 128.0, 126.7, 90.3, 41.0, 28.9, 22.2, 19.3. FTIR (KBr, cm^{-1}): 3042, 2928, 1606, 1528, 1335, 1289. Mp=96.4–97.5. Yield 64%. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.67; H, 7.61; N, 7.05.

3.6. General procedure for the synthesis of tetra-substituted enaminocarbonyl compounds 8e–g and compound 9a

In a 50 mL flask, under argon atmosphere, to a solution of compound **5a–c** (2.62 mmol) in dry chloroform (6 mL) were added NaI (2.62 mmol) and compound **6b** (7.86 mmol). The reaction was stirred for 24 h at room temperature. After this period the reaction temperature was raised to reflux and a solution of triphenylphosphine (5.24 mmol) and triethylamine (5.24 mmol) in dry chloroform (6 mL) was added dropwise. The system was kept at this temperature and under stirring for 18 h. The solvent was removed and compounds **8e**, **8f** or **8g** (also compound **9a** obtained as undesired product) were obtained pure after purification by chromatography column eluted with *n*-hexane/ethyl acetate gradient.

3.6.1. β-Enaminocarbonyl compound ***8e***

^1H NMR (200 MHz, $CDCl_3$): δ ppm 7.31–7.18 (m, 5H), 4.97 (s, 1H), 3.68 (s, 3H), 3.29 (t, *J*=7.1 Hz, 2H), 3.12 (t, *J*=7.1 Hz, 2H), 1.96–1.88 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 170.3, 163.9, 138.2, 129.3, 127.2, 126.9, 89.6, 54.6, 52.3, 50.1, 34.8, 21.8, 14.7. FTIR (KBr, cm^{-1}): 3015, 2978, 2943, 1674, 1577, 1427, 1275. Mp=62.1–62.8. Yield 76%. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.50; H, 7.89; N, 5.78.

*3.6.2. β-Enaminocarbonyl compound **8f***

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 8.61–8.42 (br, 1H), 7.28–7.15 (m, 5H), 3.60 (s, 3H), 3.58 (t, *J*=7.5 Hz, 2H), 1.90 (qt, *J*=7.1 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 169.9, 165.5, 138.2, 131.4, 127.6, 125.7, 92.5, 50.5, 47.3, 32.2, 22.1. FTIR (KBr, cm^{-1}): 3044, 2925, 1581, 1489, 1238. Mp=113.5–114.5. Yield 90%. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.97; H, 7.04; N, 6.55.

*3.6.3. β-Enaminocarbonyl compound **8g***

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 9.82–9.63 (br, 1H), 7.34–7.10 (m, 5H), 3.55 (s, 3H), 3.40–3.33 (m, 2H), 2.11 (t, *J*=6.5 Hz, 3H), 1.74 (qt, *J*=5.8 Hz, 2H), 1.63–1.54 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 170.2, 161.3, 138.1, 132.2, 127.8, 125.9, 94.4, 50.4, 41.3, 27.7, 22.2, 19.0. FTIR (KBr, cm^{-1}): 3043, 2926, 1581, 1485, 1257. Mp=114.1–115.0. Yield 60%. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.78; H, 7.48; N, 6.13.

*3.6.4. Thiazolidinone compound **9a***

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 7.38 (m, 5H), 5.03 (s, 1H), 4.92 (t, *J*=4.3 Hz, 1H), 3.71 (m, 2H), 2.28 (m, 2H), 1.9 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 10.8, 137.4, 129.1, 128.7, 128.2, 128.1, 98.1, 51.0, 42.0, 22.5, 20.4. FTIR (neat, cm^{-1}): 3061, 2928, 2849, 1696, 1645, 1387, 1253. Anal. Calcd for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06. Found: C, 67.55; H, 5.74; N, 6.13.

3.7. General procedure for the synthesis of compounds 9b–d

To a solution of thiolactam **5c** (0.87 mmol) in dry chloroform (5 mL) was added α-bromoesters **6f–h** (0.96 mmol) and the reaction was stirred for 24 h at room temperature. After this period, DBU (1.83 mmol) was added and the stirring was kept for an additional 20 h. After this period, the reaction was warmed to reflux temperature for 1 h and the solvent removed. The crude product was purified by chromatography column eluted with *n*-hexane/ethyl acetate gradient.

*3.7.1. Thiazolidinone compound **9b***

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 4.82 (t, *J*=4.1 Hz, 1H), 4.01 (q, *J*=7.3 Hz, 1H), 3.72–3.52 (m, 2H), 2.25–2.13 (m, 2H), 1.93–1.83 (m, 2H), 1.57 (d, *J*=7.5 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 172.8, 130.9, 97.9, 41.9, 41.8, 22.9, 20.8, 19.9. Yield 88%. Unstable to perform elementary analysis.

*3.7.2. Thiazolidinone compound **9c***

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 4.82 (t, *J*=4.3 Hz, 1H), 3.97 (dd, *J*=3.7 and 9.3 Hz, 1H), 3.67–3.57 (m, 2H), 2.20–1.27 (m, 4H), 0.94 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 172.1, 131.2, 97.3, 47.6, 41.5, 35.8, 22.3, 20.2, 20.1, 13.4. Yield 91%. Anal. Calcd for $C_{10}H_{15}NOS$: C, 60.88; H, 7.66; N, 7.10. Found: C, 60.97; H, 7.75; N, 7.20.

*3.7.3. Thiazolidinone compound **9d***

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 4.81 (t, *J*=4.2 Hz, 1H), 3.96 (dd, *J*=3.7 and 9.3 Hz, 1H), 3.65–3.60 (m, 2H), 2.24–1.26 (m, 5H), 0.91 (t, *J*=6.6 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 171.9, 131.1, 97.1, 47.7, 41.4, 33.4, 28.9, 22.3, 22.0, 20.1, 13.7. Yield 94%. Anal. Calcd for $C_{11}H_{17}NOS$: C, 62.52; H, 8.11; N, 6.63. Found: C, 62.63; H, 8.20; N, 6.71.

3.8. General procedure for the synthesis of thioimines 10a–d

To a solution of thiolactam **5a** (0.99 mmol) in dry chloroform (5 mL) was added α-bromoesters **6c–h** (1.09 mmol) and the reaction was kept under stirring for 24 h. After this period, DBU (2.08 mmol) was added and the reaction was stirred for 20 h more at room temperature. The temperature was raised to reflux after this period and kept in this condition an additional hour. The solvent was removed and the crude products purified by chromatography column eluted with *n*-hexane/ethyl acetate gradient.

*3.8.1. Thioimine compound **10a***

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 7.55–7.27 (m, 5H), 5.55 (s, 1H), 3.89–3.81 (m, 2H), 3.72 (s, 3H), 2.66–2.56 (m, 2H), 1.99 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 170.9, 170.7, 134.8, 128.8, 128.4, 128.3, 60.7, 52.9, 52.1, 37.9, 23.5. FTIR (neat, cm^{-1}): 3063, 2951, 1740, 1693, 1594. Yield 93%. Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.37; H, 7.22; N, 5.28. Found: C, 63.44; H, 7.31; N, 5.36.

*3.8.2. Thioimine compound **10c***

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 4.42 (t, *J*=7.3 Hz, 1H), 4.20 (q, *J*=7.1 Hz, 2H), 3.83 (t, *J*=7.2 Hz, 2H), 2.60 (t, *J*=7.4 Hz, 2H), 2.06–1.78 (m, 4H), 1.45 (st, *J*=7.2 Hz, 2H), 1.27 (t, *J*=7.1 Hz, 3H), 0.94 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 172.2, 170.6, 61.3, 60.7, 47.2, 38.3, 34.1, 23.5, 20.4, 14.1, 13.7. FTIR (neat, cm^{-1}): 3023, 2859, 1731, 1594, 1464, 1368. Yield 89%. Anal. Calcd for $C_{12}H_{23}NO_2S$: C, 58.74; H, 9.45; N, 5.71. Found: C, 58.81; H, 9.53; N, 5.80.

*3.8.3. Thioimine compound **10d***

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 4.40 (t, *J*=7.3 Hz, 1H), 4.20 (q, *J*=7.3 Hz, 2H), 3.83 (t, *J*=7.2 Hz, 2H), 2.60 (t, *J*=7.4 Hz, 2H), 2.06–1.80 (m, 4H), 1.42–1.34 (m, 4H), 1.27 (t, *J*=7.1 Hz, 3H), 0.90 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 171.9, 170.2, 61.0, 60.5, 47.1, 38.1, 31, 28.9, 23.5, 22.1, 13.9, 13.6. FTIR (neat, cm^{-1}): 2957, 2865, 1736, 1594, 1464. Yield 91%. Anal. Calcd for $C_{13}H_{25}NO_2S$: C, 60.19; H, 9.71; N, 5.40. Found: C, 60.27; H, 9.81; N, 5.49.

3.9. General procedure for the synthesis of β-enaminocarbonyl compound 8f from compound 10a

In a 50 mL flask, under argon atmosphere, to a solution of compounds **10a** and **10c**,**d** (2.62 mmol) in dry chloroform (6 mL) were added base (5.24 mmol) (Et_3N or DBU) and triphenylphosphine (5.24 mmol). The reaction was stirred for 18 h at reflux temperature. The solvent was removed and compound **8f** was obtained pure after purification by chromatography column eluted with *n*-hexane/ethyl acetate gradient.

*3.9.1. β-Enaminocarbonyl compound **8f***

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 8.61–8.42 (br, 1H), 7.28–7.15 (m, 5H), 3.60 (s, 3H), 3.58 (t, *J*=7.5 Hz, 2H), 1.90 (qt, *J*=7.1 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 169.9, 165.5, 138.2, 131.4, 127.6, 125.7, 92.5, 50.5, 47.3, 32.2, 22.1. FTIR (KBr, cm^{-1}): 3044, 2925, 1581, 1489, 1238. Mp=113.5–114.5. See Table 7 for the yield. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.97; H, 7.04; N, 6.55.

3.10. Reductions of β-enaminocarbonyl compounds 8a–g

3.10.1. Method A: $NaBH_4$/AcOH

To a solution of $NaBH_4$ (7.56 mg, 0.2 mmol) in glacial acetic acid (10 mL) was added β-enaminocarbonyl compound (0.40 mmol) at 0 °C. The solution was stirred for 30 min at room temperature. After, CH_2Cl_2 (30 mL) was added and the organic phase was washed with saturated sodium carbonate, dried, and filtered off. The solvent was removed and the crude products purified by chromatography column eluted with *n*-hexane/ethyl acetate gradient.

3.10.2. Method B: $NaCNBH_3$/HCl

To a solution of β-enaminocarbonyl compound (0.22 mmol), $NaBH_3CN$ (0.33 mmol) and bromo-cresol 1% m/m (as the indicator) in MeCN (2 mL) were added dropwise a methanolic solution of HCl (1 M). The addition was stopped when the solution became yellow.

The reaction was stirred for 30 min at room temperature. After this period dichloromethane (10 mL) was added and the organic layer was neutralized with an aqueous solution of $NaHCO_3$, separated, dried over $MgSO_4$, and the solvent removed. The crude product was purified by chromatography column eluted with *n*-hexane/ethyl acetate gradient.

3.10.3. Method C: $NaBH(OAc)_3$

To a solution of β-enaminocarbonyl compound (0.22 mmol) in dry MeCN (3 mL) was added $NaBH(OAc)_3$ (0.66 mmol). The reaction was stirred for 24 h at room temperature. Acetonitrile was removed under reduced pressure and the system was dissolved in CH_2Cl_2 (10 mL). The organic phase was neutralized using an aqueous saturated solution of NH_4Cl, dried over $MgSO_4$, and the solvent removed. The crude product was purified by chromatography column eluted with *n*-hexane/ethyl acetate gradient.

3.10.4. Method D: $PtO_2/HClO_4$

In a 50 mL Schlenk were added the β-enaminocarbonyl compound (0.40 mmol), methanol (10 mL) PtO_2 (1 mol %), and an aqueous solution of $HClO_4$ (70%) (30 μL). The system was degassed, charged with H_2 (1 atm) and stirred for 24 h. The organic phase was filtered off, neutralized using an aqueous solution of Na_2CO_3 and the solvent was removed to afford the desired product in a good purity without any additional purification process.

3.10.5. Method E: $NaBH_4/EtOH$

To a solution of β-enaminocarbonyl compound (0.74 mmol) in ethanol (5 mL) was added sodium borohydride (1.48 mmol). The reaction was kept under stirring for 1 h at room temperature and additional 48 h at reflux. After, HCl (2 N solution in water) was added and the organic compounds extracted with CH_2Cl_2. The organic layer was dried, filtered, and the solvent removed. The crude oil was purified by chromatography column eluted with *n*-hexane/ethyl acetate gradient.

3.10.6. Method F: Mg/MeOH

To a solution of β-enaminocarbonyl compound (0.22 mmol) in dry methanol (5 mL), magnesium (2.20 mmol) was carefully added under stirring. The reaction was warmed to reflux temperature and kept for 72 h. The solvent was removed and the crude oil was dissolved in CH_2Cl_2 (5 mL). The organic phase was washed two times with 2 N HCl solution, dried over $MgSO_4$, and the solvent was removed to afford a crude product. The purification was made by chromatography column eluted with *n*-hexane/ethyl acetate gradient.

3.11. β-Aminocarbonyl compound 11a

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 7.35–7.22 (m, 5H), 4.13 (q, *J*=7.1 Hz, 2H), 4.02 (d, *J*=13.2 Hz, 1H), 3.37 (d, *J*=12.9 Hz, 1H), 3.39–2.93 (m, 2H), 2.70 (dd, *J*=8.8 and 15.0 Hz, 1H), 2.40 (dd, *J*=8.8 and 15.0 Hz, 1H), 2.31–2.22 (m, 1H), 2.14–2.02 (m, 1H), 1.82–1.59 (m, 3H), 1.25 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 172.2, 138.8, 128.9, 128.2, 126.9, 60.8, 60.2, 58.5, 53.8, 39.6, 30.8, 22.1, 14.2. FTIR (neat, cm^{-1}): 3029, 2964, 2929, 1734, 1454, 1244. Yield: 88% (method A), 75% (method B), 71% (method C), 85% (method D). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.91; H, 8.67; N, 5.73.

3.12. β-Aminocarbonyl compound 11b

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 7.94–7.90 (m, 2H), 7.60–7.21 (m, 2H), 4.00 (d, *J*=12.9 Hz, 1H), 3.43 (d, *J*=12.9 Hz, 1H), 3.36 (t, *J*=6.2 Hz, 2H), 3.22–2.93 (m, 3H), 2.33–2.07 (m, 2H), 1.84–1.78 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 199.4, 137.1, 133.0, 128.9, 128.5, 128.4, 128.2, 128.1, 127.0, 60.7, 58.9, 53.9, 43.9, 31.3, 22.3. FTIR (neat, cm^{-1}): 3060, 3028, 2927, 1684, 1450, 1367, 1207. Yield: 89% (method A), 72% (method B), 72% (method C), 86% (method D). Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.77; H, 7.69; N, 5.11.

3.13. β-Aminocarbonyl compound 11c

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 7.32–7.17 (m, 10H), 4.73–4.51 (m, 1H), 4.14–3.99 (m, 3H), 3.47–3.24 (m, 3H), 3.07–2.87 (m, 2H), 2.80–2.73 (m, 1H), 2.23–2.12 (m, 1H), 1.74–1.62 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 171.9, 171.8, 153.2, 139.6, 139.5, 135.2, 129.2, 128.8, 128.6, 128.5, 128.0, 127.2, 126.6, 66.0, 65.9, 60.3, 60.2, 58.7, 58.6, 55.0, 53.8, 53.7, 40.9, 40.8, 37.8, 31.1, 30.9, 22.3. FTIR (neat, cm^{-1}): 3028, 2922, 2794, 1784, 1697, 1452, 1387, 1354, 1211. Yield: 99% (method A), 74% (method B), 73% (method C), 88% (method D). Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 73.06; H, 6.99; N, 7.48.

3.14. β-Aminocarbonyl compound 11d

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 7.96 (m, 2H), 7.81–7.52 (m, 3H), 5.18–5.06 (br, 1H), 3.17–3.02 (m, 3H), 2.82–2.54 (m, 1H), 1.87–1.74 (m, 1H), 1.69–1.58 (m, 2H), 1.31.52–1.20 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 199.2, 137.0, 133.5, 128.9, 128.3, 53.0, 46.4, 44.7, 31.9, 25.3, 24.4. FTIR (neat, cm^{-1}): 3060, 2929, 1682, 1448, 1292. Yield: 75% (method B), 87% (method D), 9% (method E). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.88; H, 8.51; N, 6.97.

3.15. β-Aminocarbonyl compound 11e

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 7.34–7.21 (m, 5H), 4.12 (d, *J*=12.9 Hz, 1H), 3.69 (s, 3H), 3.19 (d, *J*=12.9 Hz, 1H), 2.90–2.69 (m, 3H), 2.11 (dd, *J*=8.6 and 17.3 Hz, 1H), 1.95–1.81 (m, 2H), 1.70–1.26 (m, 2H), 1.22 (d, *J*=6.7 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 175.7, 139.9, 128.5, 128.0, 126.6, 66.5, 59.2, 54.3, 51.2, 42.1, 27.1, 22.5, 14.0. FTIR (neat, cm^{-1}): 3026, 2949, 2875, 1736, 1689, 1454, 1196. Yield: 92% (method A), 98% (method B), 71% (method C), 81% (method D). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.88; H, 8.61; N, 5.70.

3.16. Methylphenidate analogue 11f

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 7.36–7.26 (m, 5H), 6.28–6.05 (br, 1H), 4.14 (s, 1H), 3.69 (s, 3H), 3.43–3.40 (m, 3H), 2.35–1.87 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 217.4, 133.5, 128.9, 128.8, 128.5, 62.8, 52.8, 46.8, 28.4, 23.4. FTIR (neat, cm^{-1}): 3022, 2935, 1735, 1453, 1161. Yield: 70% (method B), 62% (method C), 99% (method D, 130 atm of H_2 pressure). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.30; H, 7.90; N, 6.47.

3.17. Methylphenidate 11g

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 7.44–7.28 (m, 5H), 3.64 (s, 3H), 3.48 (d, *J*=10.1 Hz, 1H), 3.16–3.06 (m, 1H), 2.92 (d, *J*=12.4 Hz, 1H), 2.50 (dt, *J*=3.1 and 11.1 Hz, 1H), 1.83–1.23 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 172.9, 135.6, 128.8, 128.6, 127.9, 59.2, 58.1, 51.8, 46.9, 30.9, 25.6, 24.5. FTIR (neat, cm^{-1}): 3022, 2935, 1735, 1453, 1161. Yield: 90% (method B), 89% (method C), 90% (method D, 5 atm of H_2 pressure), 40% (method F). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.10; H, 8.24; N, 6.03.

3.18. Norallosedamine 12d

In a 25 mL sealed flask, to a solution of compound **8d** (0.74 mmol) in EtOH (5 mL) were added 1.48 mmol of $NaBH_4$. The

reaction was stirred for 48 h at reflux temperature. A solution of HCl (2 N) was added to neutralize the media. The mixture was extracted with CH_2Cl_2. The organic solvent was separated and removed and compound **12d** was obtained pure after purification by chromatography column eluted with *n*-hexane/ethyl acetate/methanol gradient.

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 7.39–7.16 (m, 5H), 5.02 (dd, J=8.6 and 4.2 Hz, 1H), 3.21–2.73 (m, 2H), 2.89–2.71 (m, 1H), 2.46–2.32 (m, 1H), 2.30–1.98 (m, 3H), 1.75–1.59 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 143.9, 128.6, 127.7, 125.4, 71.2, 56.9, 52.9, 39.9, 26.6, 22.8, 20.4. Mp=91.4–92.9; literature 92.0–93.0. Yield: 60% Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.11; H, 9.39; N, 6.88.

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Supplementary data

Supplementary data including Tables and NMR spectra is available for the current article. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.01.081.

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