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Article

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An access to 2,6-disubstituted piperidines : control of the diastereoselectivity, scope and limitations. Applications to the stereoselective synthesis of (-)-Solenopsine A and alkaloid (+)-241D

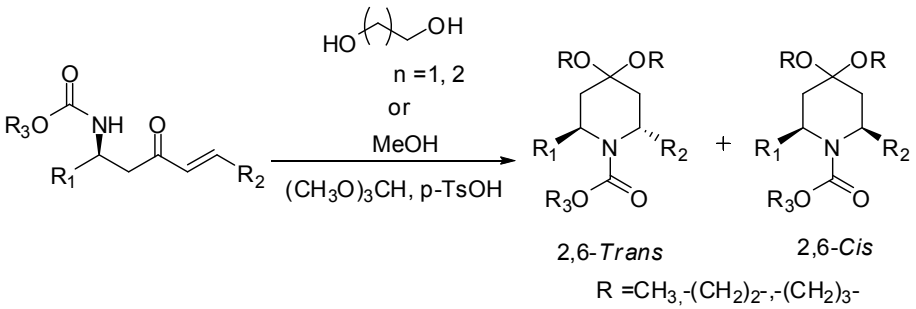
Isabelle Abrunhosa-Thomas[†,‡], Aurélie Plas[†,‡], Alexandre Vogrig[†,‡], Nishanth Kandepedu[†,‡], Pierre Chalard[†,‡], Yves Troin*[†,‡]

[†]Clermont Université, ENSCCF, Institut de Chimie de Clermont-Ferrand (ICCF), BP 10448,F-63000 CLERMONT-FERRAND, France.

[‡]CNRS, UMR 6296, Institut de Chimie de Clermont-Ferrand (ICCF), BP 80026, F-63171 AUBIERE, France.

Corresponding author : yves.troin@ensccf.fr

ABSTRACT :



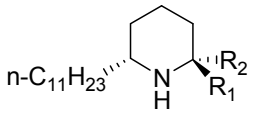
Scope and limitations in diastereoselective preparation of 2,6-*cis* or 2,6-*trans* disubstituted piperidines are described, through intramolecular reaction of chiral β'-carbamate-α,β-unsaturated ketone. This methodology has been applied to the total synthesis of a few well chosen examples, such as (-)-Solenopsine A and alkaloid (+)-241D.

Introduction

Substituted piperidines and their analogues are key structural units in numerous naturally occurring alkaloids and in a number of successful pharmaceutical compounds[1] This is the reason why a number of methodologies for the elaboration of these structures have been described[2-5] especially when stereogenic centers are involved. In particular, those possessing a chiral center at C-2 and/or C-6, stereoselectivity which is essential for the defined activity, have attracted much attention because they are one of the most common framework encountered in many interesting compounds which exhibit a broad range of biological activities. For example, (-)-solenopsin A and (-)-isosolenopsin A (active components of fire

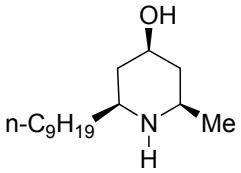
ants venom) are reported to possess a broad range of activities,[6] alkaloid (+)-241D (isolated from methanolic skin extracts of Panamanian poison frogs *Dendrobates speciosus*) is active on nicotinic acetylcholine receptors[7] and (-)-lasubine II (extracted from plants of the *Lythraceae* family) has showed cytotoxic, haemolytic, necrotic, insecticidal, antibacterial, antifungal, and anti-HIV properties[8] (Scheme 1). So, developing approaches to allow the stereoselective synthesis of 2,6-dialkylpiperidines is of great value.

Scheme 1

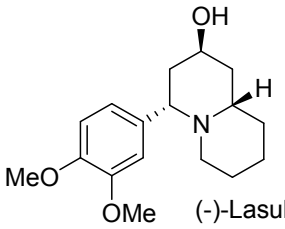


R_1= Me, R_2= H : (-)-Solenopsine A

R_1= H, R_2= Me : (-)-Isosolenopsine A



alkaloid(+)-241D

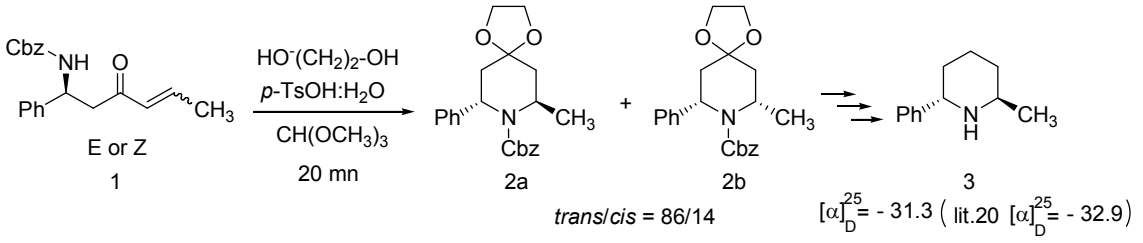


(-)-Lasubine II

For this purpose, many synthetic methods have been developed including Mannich-type reaction,[9] or Ring-Closing Metathesis.[10] In order to control the diastereoselectivity excess on the positions α and α' of the piperidine core, some of those routes have focused on the construction of the ring by C-N ring closure bond formation,[11-13] including reductive amination,[14] intramolecular substitution,[15] cyclization of sulfinimides on propargylic ether,[16] intramolecular allylic substitution with 1,3-chirality transfer,[17] iminium ion cyclization,[18] cycloaddition [4+2] of aldimines,[19] intramolecular aza-[2,3]-Wittig rearrangement,[20] catalyzed hydroamination[21] or Michael addition.[13,22] Therefore, all these methods show that there is always a considerable interest in developing stereoselective access to 2,6-dialkylpiperidines. However, even though *cis*-2,6-disubstituted piperidines are readily accessible, only a few methods have been devoted to the synthesis of *trans*-2,6-disubstituted isomers.[23-30]

During the course of our recent studies on the asymmetric synthesis of 2,6-disubstituted piperidines by C-N bond formation, we have demonstrated that the Michael "type" cyclisation,[31] using β'-carbamate-α,β-unsatured ketone **1** as key precursor, induced systematically and predominantly the formation of piperidine ring with the 2,6-*trans* configuration (Scheme 2). The relative stereochemistry was confirmed by further transformation of *trans* derivative in known chiral compound **3**[30] with an 95% ee.

Scheme 2



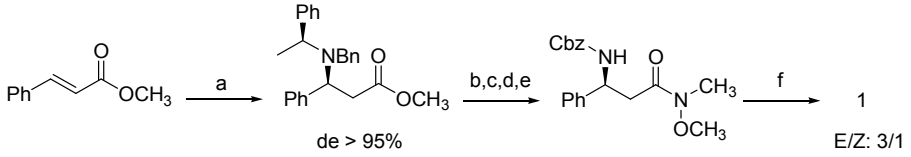
In order to establish this new approach as a general method for the preparation of chiral 2,6-disubstituted piperidines and to understand the requirements for the best selectivity, we have synthesized various β'-carbamate-α,β-unsatured ketones and tested their cyclization reaction using different conditions.

Results and discussion

I- General synthesis of a wide range of β'-carbamate-α,β-insatured ketones

We have previously shown that the necessary β'-carbamate-α,β-unsatured ketone **1** could be easily obtained from the corresponding α,β-unsatured methylester in 6 steps with an overall yield of about 30 %[31](Scheme 3).

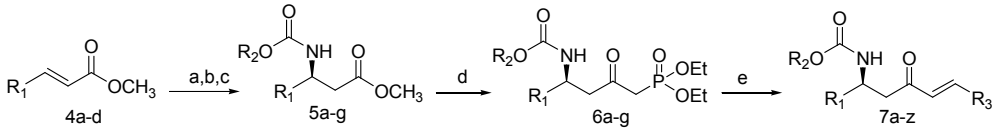
Scheme 3



a) Davies amine, BuLi, THF, -78°C; (b) H_2, $Pd(OH)_2/C$, MeOH; (c) Na_2CO_3, CbzCl, CH_2Cl_2/H_2O; (d) NaOH 1N, MeOH; (e) CDI, (MeO)MeNH.HCl; (f) Mg, 1-bromo-2-propene, THF, 0°C.

As Grignard's reagents don't allow the use of a wide range of functionalities, we have devised a general and simple method to access a variety of compounds of type **1** easily by using a more convenient way through a Wittig-Horner-Emmons[32] reaction as the key step (Scheme 4). By this method, the needed compounds were prepared in four steps from the corresponding α,β-unsatured methylester according to described procedure.[33]

Scheme 4



4a R_1 = Me; 4b R_1 = Pr; 4c R_1 = Oct; 4d R_1 = Ph

5a	R_1 = Me	R_2 = Et	**57 %**	6a	R_1 = Me	R_2 = Et	**68 %**	7a	R_1 = Me R_2 = Et R_3 = ph **95 %**
5b		R_2 = Bn	**62 %**	6b		R_2 = Bn	**57 %**	7b	R_2 = Et R_3 = ph(*o*-NO_2) **89 %**
5c	R_1 = Pr	R_2 = Et	**77 %**	6c	R_1 = Pr	R_2 = Et	**65 %**	7c	R_2 = Et R_3 = ph(*m*-NO_2) **86 %**
5d	R_1 = Oct	R_2 = Et	**73 %**	6d	R_1 = Oct	R_2 = Et	**66 %**	7d	R_2 = Et R_3 = ph(*p*-NO_2) **91 %**
5e	R_1 = Ph	R_2 = Et	**72 %**	6e	R_1 = Ph	R_2 = Et	**58 %**	7e	R_2 = Et R_3 = ph(*p*-OMe) **79 %**
5f		R_2 = t-Bu	**76 %**	6f		R_2 = t-Bu	**62 %**	7f	R_2 = Et R_3 = ph(*o*-Br) **91 %**
5g		R_2 = Bn	**66 %**	6g		R_2 = Bn	**66 %**	7g	R_2 = Et R_3 = ph(*p*-Br) **89 %**
								7h	R_2 = Et R_3 = ph(2-Cl)(5-NO_2) **95 %**
								7i	R_2 = Et R_3 = 3-pyridinyl **87 %**
								7j	R_2 = Et R_3 = ethyl acrylate **85 %**
								7k*	R_2 = Et R_3 = COOEt **53 %**
								7l	R_2 = Et R_3 = $(CH_2)_2CH_3$ **95 %**
								7m	R_2 = Et R_3 = $(CH_2)_7CH_3$ **95 %**
								7n	R_2 = Bn R_3 = ph **96 %**
								7o	R_2 = Bn R_3 = $(CH_2)_8CH_3$ **78 %**
								7p	R_2 = Bn R_3 = $(CH_2)_{10}CH_3$ **91 %**
								7q	R_1 = Pr R_2 = Et R_3 = ph **91 %**
								7r	R_2 = Et R_3 = ph(*p*-NO_2) **84 %**
								7s	R_1 = Oct R_2 = Et R_3 = ph **94 %**
								7t	R_2 = Et R_3 = CH_3 **78 %**
								7u	R_2 = Et R_3 = $(CH_2)_2CH_3$ **95 %**
								7v	R_1 = Ph R_2 = Et R_3 = ph **84 %**
								7w	R_2 = Et R_3 = CH_3 **80 %**
								7x	R_2 = Et R_3 = $(CH_2)_2CH_3$ **95 %**
								7y	R_2 = Et R_3 = $(CH_2)_7CH_3$ **89 %**
								7z	R_2 = *t*-Bu R_3 = CH_3 **81 %**
								1	R_2 = Bn R_3 = CH_3 **96 %**

a) Davies amine, BuLi, THF, -78°C; (b) H_2, $Pd(OH)_2/C$, MeOH; (c) Na_2CO_3, R^2CO_2Cl, CH_2Cl_2/H_2O; (d) BuLi, $(EtO)_2P(O)Me$, THF, -78°C; (e) $Ba(OH)_2$, THF/H_2O (40/1), R^3CHO.

* In the case of enone **7k**, we obtained a mixture of Z and E stereoisomers in a 60/40 ratio respectively.

Addition of enantiopure lithium *N*-benzyl-*N*-α-methylbenzylamide on α,β-unsaturated ester **4** following by hydrogenation to the corresponding primary amine and further protection as a carbamate gave the β-amino methylester **5a-g**. After purification, the ester function was transformed into the ketophosphonate **6a-g** by treatment with 2.5 equivalents of diethyl lithiomethylphosphonate[34] in THF at -78°C, in moderate yields. Over the years, many examples of base-promoted Wittig-Horner-Emmons reaction have been reported in scientific literature,[35-37] various combinations of bases and solvents (K_2CO_3/CH_3CN, DBU/THF, NaH/THF, $Et_3N/LiCl/CH_3CN$ or $Ba(OH)_2/(THF/H_2O)$...) have been used. In our case, we have found that the use of 1.3 equiv of $Ba(OH)_2$ in biphasic medium THF/H_2O (40/1) was the more general and convenient route to obtain compounds **7a-z** with good to excellent yield.

II- Scope and limitations of the Michael "type"cyclization

As mentioned previously,[31] we have shown that compound **1** could be easily transformed diastereoselectively by intramolecular Michael "type" reaction in 2,6-disubstituted-*N*-protected-4-ketal piperidine (**2a/2b**) as a mixture of *cis/trans* isomers in which the *trans*

conformation represents the major compound (Scheme 2). We have also shown, that the character *Z* or *E* of the geometry of the double bond in compound **1** didn't have any influence on the diastereoselectivity of the cyclization reaction, as similar results have been obtained starting either from stereoisomer (*E*) or (*Z*) of **1** treated in the same optimized conditions (0.2 equiv. of *p*-toluenesulphonic acid monohydrate, 5 equiv. of ethylene glycol, 5 equiv. of trimethyl orthoformate which has been used here as solvent and as a water scavenger).

So, we decided to use this protocol for the cyclization of a range of dissymmetric (aliphatic/aromatic for R^1 and R^3) ene-carbamates of type **7,** hoping to evaluate at first the influence of steric hindrance on the selectivity. For a better evaluation of the *cis/trans* ratio (^{1}H NMR) the mixture of ketals **8** and **9** were directly converted into the more stable thioketals **10** and **11** by known procedure, using 1,2-ethane dithiol in the presence of boron trifluoride diethyl etherate, as it has been shown that this transformation induced no variation of the diastereoisomeric ratio (Scheme 5 and Table 1).

Scheme 5

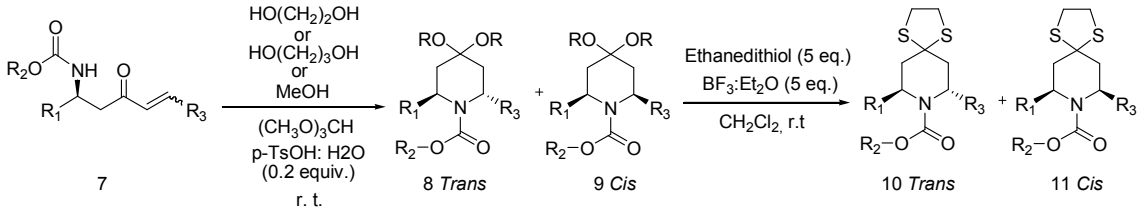
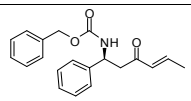
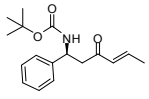
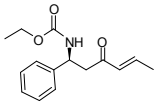
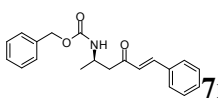
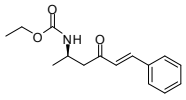
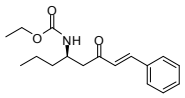
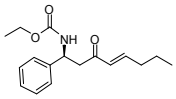
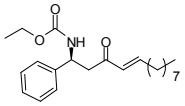
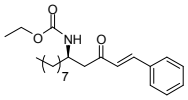
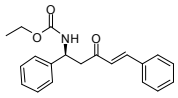
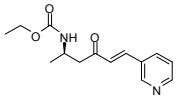


Table 1 : first scope of intramolecular Michael reaction

Entry	Ketone **7**	cyclization react. time (min)	**alcohol**	(*Trans*/*Cis*) **8/9 (%[a])**	(*Trans*/*Cis*) **10/11 %[a] [yield %[b]]**
1	 **1**	20 min	$HO(CH_2)_2OH$	86/14 (**8a/9a**)	86/14 **[68]**[c] (**10a/11a**)
2	 **7z**	30 min	$HO(CH_2)_2OH$	83/17 (**8b/9b**)	83/17 **[71]** (**10b/11b**)
3	 **7w**	20 min	$HO(CH_2)_2OH$	44/56 (**8c/9c**)	44/56 **[75]** (**10c/11c**)
4	 **7n**	20 min	$HO(CH_2)_2OH$	51/49 (**8d/9d**)	51/49 **[65]*** (**10d/10d**)

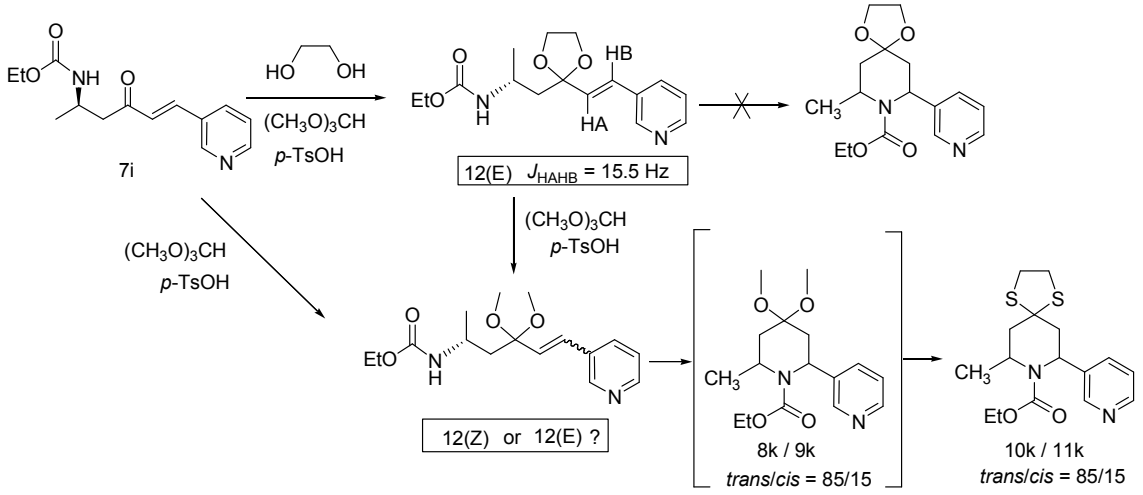
5		**7a**	20 min	$HO(CH_2)_2OH$	39/61 (**8e/9e**)	39/61 **[73]** (**10e/11e**)
6		**7q**	40 min	$HO(CH_2)_2OH$	≥ 95/5 (**8f/9f**)	≥ 95/5 **[60]** (**10f/11f**)
7		**7x**	40 min	$HO(CH_2)_2OH$	62/38 (**8g/9g**)	62/38 **[67]** (**10g/11g**)
8		7**y**	2 h	$HO(CH_2)_2OH$	62/38 (**8h/9h**)	62/38 **[65]** (**10h/11h**)
9		**7y**	2 h	$HO(CH_2)_3OH$	95/5 (**8h/9h**)	95/5 **[67]** (**10h/11h**)
10		**7s**	1 h	$HO(CH_2)_2OH$	95/5 (**8i/9i**)	95/5 **[67]** (**10i/11i**)
11		**7v**	2h	$HO(CH_2)_2OH$	≥ 96/4 (**8j/9j**)	≥ 96/4 **[65]** (**10j/11j**)
12		**7i**	2 h	$HO(CH_2)_2OH$	see text	
13		**7i**	6 h	MeOH	85/15 (**8k/9k**)	85/15 **[48]** (**10k/11k**)

[a] Diastereoisomeric ratio are determined by integration of characteristic protons of the piperidine ring in the crude H^1 NMR spectra (*Trans* and *Cis* isomers where determined according to their respective coupling constants); [b] Isolated yield of pure diastereoisomeric mixture after chromatography on silica gel. [c] **10a/11a** and **10d/11d** are enantiomers; for **10a/11a (10d/11d)** the benzyl carbamate was cleaved during the thioketalation process, leading to the free amine on the piperidine ring, see experimental part).

According to Table 1, for the defined conditions, the selectivity observed for the cyclization reaction is predominantly in favour of the *trans* isomer, which is the less stable conformation for a 2,6-disustituted piperidine. This *d.e.* is markedly dependent of a lot of factors, namely the nature of the nitrogen protective group and also the nature of steric hindrance (R^1, R^2 and R^3) on compounds **7**. On the one hand, when R^1 and R^3 are fixed (R^1= Ph, R^3 = Me, entry 1, 2 and 3), a strong steric hindrance around the nitrogen atom is necessary to induce a good diastereoselectivity. On the other hand, when R^1=Ph and R^3 was a much longer alkyl chain (propyl or nonyl, entry 7, 8, 9), the ethyl carbamate function is sufficient to ensure predominantly the formation of the *trans* isomer, however with a small diastereoselectivity excess (*de* = 24%). Furthermore, changing ethylene glycol to 1,3-propane diol now increases

the *de* up to 90% showing by this way the importance of the resulting keto protecting group. Permutation of R^1 and R^3 (entry 3 *versus* entry 5) doesn't show a significant influence on the diastereoselectivity unless the alkyl chain is much longer than a methyl group (entries 5, 6, 10), or if R^1 is a phenyl group (entry 11), in which the observed *d.e* is again around 90%. Another observation is the dependency of the cyclization on the nature of the alcohol used. So, when R^1= Me and R^3= pyridine (**7i**) the formation of the piperidine ring is not observed if ethylene glycol is used to form the ketal (entry 12). The only product which can be identified (by H NMR spectroscopy), is the ketal **12**, in which the double bond is exclusively in a (*E)* conformation (*J*=15,5 Hz). Assuming that the relative hindrance between the dioxolane group and the pyridine was too high, we decided to realize the reaction with a less crowded acetal. To our delight, when compound **7i** was engaged (entry 13) in presence of trimethyl orthoformate and *p*-toluenesulphonic acid, leading to the *in situ*, formation of methanol, we could now isolate the corresponding piperidines (**10k**/**11k**) with a *d.e.* of 70% in favour of the *trans* conformation (Scheme 6).

Scheme 6

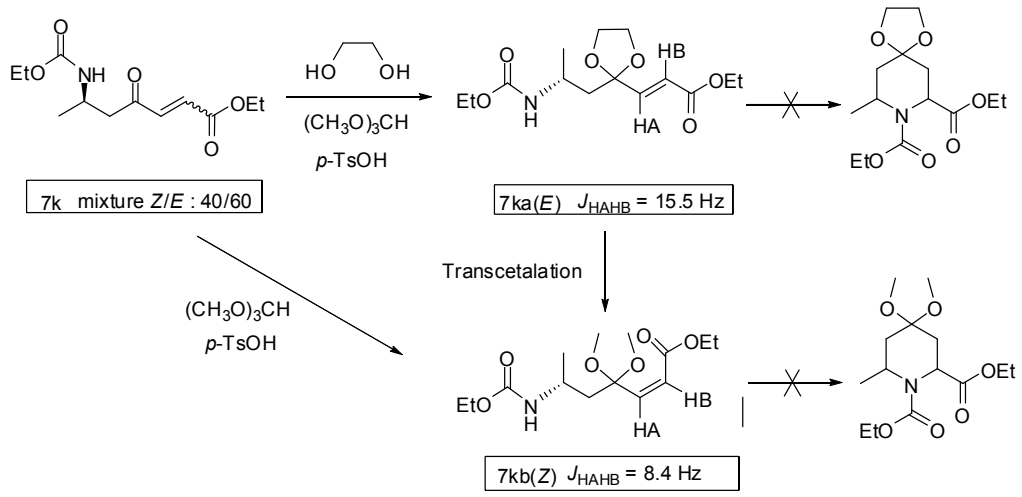


This last result confirmed the fact that the first step, for the elaboration of the piperidine ring, is the formation of the ketal on compounds **7**, and thus, can constitute the critical step for the diastereoselectivity of the reaction. Moreover, the formation of the ketal induces the *E* or Z configuration of the double bond which is dependent of the nature of the ketal. This hypothesis based on the role of the geometry of the double bond of a Michael acceptor in the control of the diastereoselectivity, during the formation of 2,6-disubstituted piperidines, has already been put forward by Banwell and co-workers[38], although in the case of an exo-

cyclization process. They had demonstrated, that the geometry of the double bond conducted to two different transition states, resulting in the formation of 2,6-*cis* or 2,6-*trans* piperidine. Thus, reducing this fact to our model, we suppose that the formation of the 2,6 *trans* piperidine or either 2,6 *cis* piperidine can be correlated with the geometry of the double bond of the crucial intermediate acetal.

In order to confirm this hypothesis we engaged the compound **7j** (*Z*/*E* conformers = 40/60) in reaction with trimethyl orthoformate, with and without ethylene glycol and in presence of acid (Scheme 7). Compound **7j** was specially chosen for the strong steric hindrance which could be generated in the transition state. At this stage, no formation of piperidine ring was expected, but rather the formation of the intermediate ketal form and the possibility to measure the corresponding coupling constant of both intermediates, to validate our hypothesis.

Scheme 7

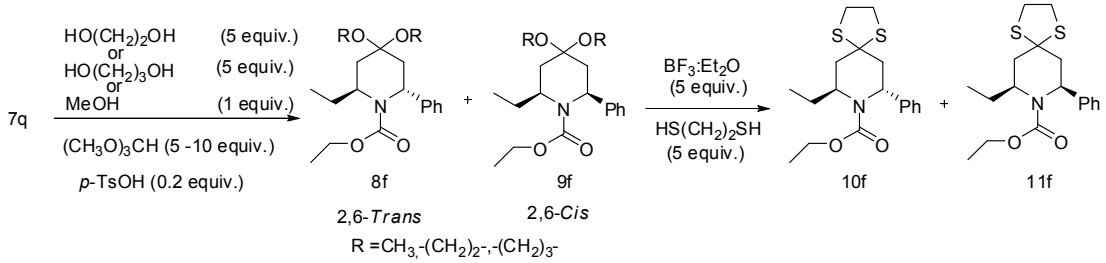


Then, it was possible to identify two α,β-insatured ketals **7ka(*E*)** and **7kb(*Z*)**, a dioxolane and a dimethylketal respectively. The coupling constant values for the double bond in ^{1}H NMR spectroscopy, then, demonstrated the existence of two different stereoisomers depending on the ketal formed. The *E* configuration (J_{HAHB}= 15.5 Hz) was observed for the cyclic ketal **7ka(*E*)** whereas the *Z* (J_{HAHB}= 8.4 Hz) was observed for the dimethyl ketal **7kb(*Z*)**. As for compound **7ka(*E*)**, if trimethyl orthoformate is added to the mixture, a transacetalation reaction is observed, leading to the formation of **7kb(*Z*)**. Thus, this result first of all confirmed the formation of the ketal as the first step of the transformation; and second, it strongly suggested that the diastereoselectivity of the piperidine formed can be dependent on the configuration of the double bond of the intermediate ketal in the transition state. *However at this stage we can't connect the configuration of the double bond with the configuration of*

the piperidine formed. We can only assume the existence of two different transition states corresponding to the formation of two different acetals.

Therefore, to confirm the real role of this geometry on the resulting diastereoisomeric excess for the piperidine generated, we selected the compound **7q,** which gave a *d.e.* ≥ 90% in favour of the *trans* isomer (Table 1, entry 6) and compared the importance of the nature of the alcohol on the result when methanol, ethylene glycol or propan-1,3-diol is used in the cyclization process (Table 2), both enantiomers of **7q** were tested. The quantity of acid was fixed at 0.2 equiv. and all the crude mixtures **8f, 9f** were respectively directly converted into the corresponding 4-thioketal piperidine **10f** and **11f** (Table 2). The diastereomeric excess was as before, calculated according to the ^{1}H NMR values.

Table 2 : influence of the ketal formation on the stereoselectivity



Entry	Alcohol used	Cyclisation react. time **8f/9f** (min)	**10f/11f (**ratio %[a]) [yield[b] %]
1	HO-$(CH_2)_2$-OH (**7q*R*)**	20	> 95/5 [67]
2	HO-$(CH_2)_2$-OH (**7q*S*)**	20	> 95/5 [68]
3	HO-$(CH_2)_3$-OH	15	87/13 [68]
4	MeOH	15	64/36 [68]

[a] Diastereoisomeric ratio are determined by integration of characteristic protons of the piperidine ring in the crude H[1] NMR spectra (*Trans* and *Cis* isomers where determined according to their respective coupling constants); [b] Isolated yield of pure diastereoisomeric mixture after chromatography on silica gel.

Cyclization was observed in all cases with a good overall yield, but a significant difference on the *d.e.* was observed. The higher diastereoselectivity was obtained (Table 2, entry 1 and 2) when ethylene glycol is used to form the ketal, corresponding to the more overcrowded intermediate. On the contrary, the lower diastereoselectivity is observed when methanol is used (Table 2, entry 4), as the dimethyl acetal gave a higher flexibility to the intermediate. Both enantiomers of **7q** gave the same result (Table 2, entry 1 and 2). If steric hindrance appeared here as the predominant factor for the stereoselectivity of the reaction, however, *in all cases the trans isomer was obtained.* So, in order to reinforce the existence of two

different transition state according to the geometry of the double bond of the ketal, we envisaged that this critical step could be under a kinetic control. Compound **7q** was now engaged under two different experimental protocols: on the one hand with ethylene glycol, on the other hand with methanol. And for each case increasing quantities of acid, from catalytic to stoechiometric, were used (Table 3).

Table 3 : kinetic effect on the stereoselectivity in the cyclization process

Entry	Alcohol (x equiv.)	*p*-TsOH/H_2O (x equiv.)	Cyclization react. time **8f/9f** (min)	**10f/11f** (%[a])
1	HO-$(CH_2)_2$-OH (5)	0.1	25	85/15
2	HO-$(CH_2)_2$-OH (5)	0.2	20	85/15
3	HO-$(CH_2)_2$-OH (5)	0.5	15	86/14
4	HO-$(CH_2)_2$-OH (5)	1	10	87/13
5	HO-$(CH_2)_2$-OH (5)	0.2	24 h	40/60
6	MeOH (1)	0.02	45	50/50
7	MeOH (1)	0.05	40	55/45
8	MeOH (1)	0.1	20	64/36
9	MeOH (0 or 1)	0.2	15	69/31
10	MeOH (0)[b]	1	10	72/28

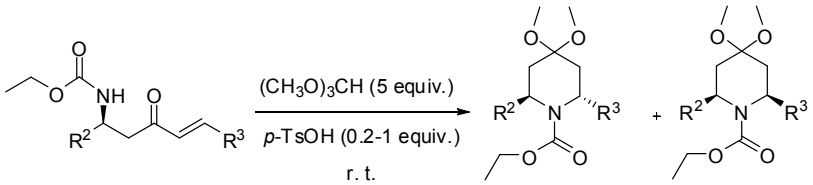
[a] Diastereoisomeric ratio are determined by integration of characteristic protons of the piperidine ring in the crude H^1 NMR spectra (*Trans* and *Cis* isomers where determined according to their respective coupling constants); [b] When the concentration of acid is upper 0.2 equiv. the degradation of trimethyl orthoformate is sufficient to generate methanol *in situ*.

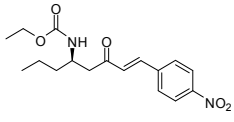
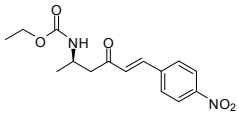
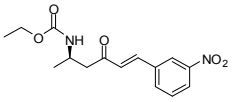
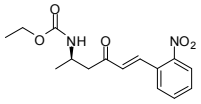
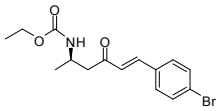
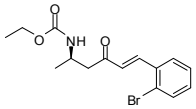
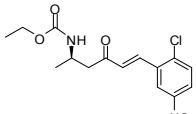
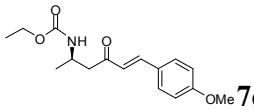
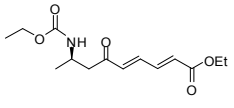
When ethylene glycol is used for the formation of the ketal, the quantity of acid doesn't affect the diastereoisomeric excess obtained for **10f/11f** (Entry 1 to 4), only the reaction time is reduced. After 24 h (entry 5), an epimerisation through retro-Mannich or retro-Michael reaction is observed, the more stable *cis* isomer **11f** becoming now the major compound. On the contrary, when methanol was used (Entry 6 to 10) to generate the ketal, there is a significant difference in the diastereoisomeric excess depending on the quantity of catalyst used, and this evolution is in agreement with a kinetic effect.

To evaluate the importance of this kinetic effect, in the transition state, compared to the steric effect, we substituted the aromatic ring of **7a** and **7q** (respectively table 3, entry 5, 39 % of *trans* isomer and entry 6, ≥ 95 % of *trans* isomer, with the use of ethylene glycol and 0.2 % of acid) with various ERG or EWG groups in *ortho*, *meta* or *para* position of the aromatic ring,

and we used the methanol generated by the trimethyl orthoformate for the formation of the ketal. Results on the selectivity such obtained are reported in Table 4.

Table 4: electronic effects



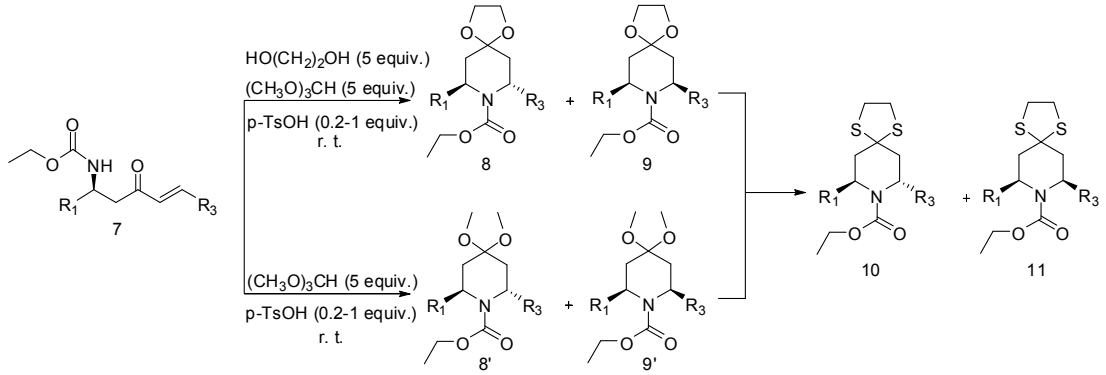
Entry	Ketone **7**	Reaction time (min) *p*-TsOH/H_2O (x equiv.)		(*Trans*/*Cis*) **8/9** (%)[a] [yield %][b]
1	 **7r**	(90min) (0.2 equiv.)	(20min) (1 equiv.)	83/17 [71] (**8l/9l**)
2	 **7d**	(120min) (0.2 equiv.)	(30 min) (1 equiv.)	89/11 [80] (**8m/9m**)
3	 **7c**	(60min) (1 equiv.)		40/60 [71] (**8n/9n**)
4	 **7b**	(60min) (1 equiv.)		60/40 [67] (**8o/9o**)
5	 **7g**	(45 min) (1 equiv.)		33/67 [73] (**8p/9p**)
6	 **7f**	(60min) (1 equiv.)		29/71 [75] (**8q/9q**)
7	 **7h**	(180min) (1 equiv.)		56/43 [76] (**8r/9r**)
8	 **7e**			decomposition
9	 **7j**	(240min) (0.2 equiv.)		90/10 [93] (**8s/9s**)

[a] Diastereoisomeric ratio are determined by integration of characteristic protons of the piperidine ring in the crude H^1 NMR spectra (*Trans* and *Cis* isomers where determined according to their respective coupling constants); [b] Isolated yield of pure diastereoisomeric mixture after chromatography on silica gel..

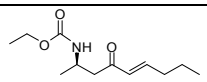
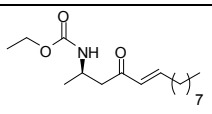
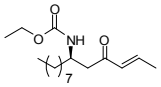
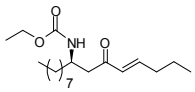
Strong EWG located in *para* position on the aromatic ring for **7r** and **7d** (Table 4, entries 1 and 2) or placed on a conjugated system **7j** (Table 4, entry 9), led predominantly and respectively to 83, 89 or 90 % in favour to the *trans* isomer, but, no significant influence on the selectivity can be related with the quantity of acid used. When the EWG is in *meta* position, (compound **7c,** Table 4**,** entry 3), a deactivating position, the opposite diastereoselectivity (40/60) is observed and a longer reaction time is required. Concerning the *ortho* position (compound **7b,** Table 4**,** entry 4), the EWG effect is counterbalanced by steric hindrance in the transition state and therefore a small diastereoisomeric excess (60/40) is obtained. As expected, the presence of an ERG group in *ortho* or *para* position (Table 4**,** entries 5 and 6) led predominantly to the *cis* derivative (30/70). However, if this effect is too strong, decomposition of the starting material is observed (Table 4, entry 8). Thus, when compounds **7** have an aromatic or a conjugated system as a substituent on the double bond, a lot of parameters (steric hindrance, angle pressure, kinetic effect and electronic effect) has to be considered to access a high selectivity and this selectivity is in favour of the *trans* isomer of the piperidine.

So, in order to validate the existence of two transition states, according to the alcohol used in the cyclization step, we carried out the reaction with four representative ketones **7k,l,t,u** in which only a steric hindrance was induced by the size of an alkyl chain. As usual, we measured the outcomes observed for the diastereoselectivity when a cyclic ketal or a dimethyl ketal formation was involved. Here too, we converted all the crude mixture **8** and **9** or **8'** and **9'directly** into the corresponding 4-thioketal piperidines **10** and **11** (Table 5).

Table 5 : Michael cyclization of enones **7** bearing aliphatic substituents



Entry	Ketone 7	Cyclisation	Alcohol	(*Trans*/*Cis*)

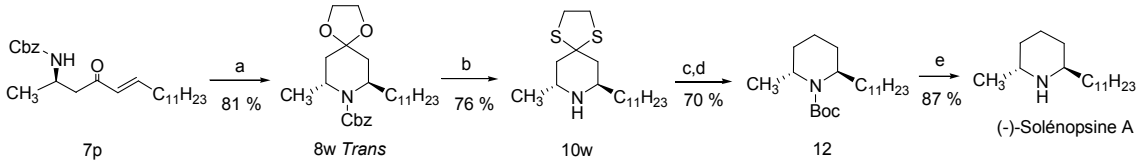
		(React. time) *p*-TsOH [x equiv.]		10/11 (%[a]) [yield %]
1	 **7l**	40 min [0.2]	$HO(CH_2)_2OH$	80/20 **[73]** (**10v/11v**)
2	 **7m**	1 h [0.2]	$HO(CH_2)_2OH$	80/20 **[62]** (**10t/11t**)
3		1 h [0.2]	MeOH[c]	20/80 **[66]** (**10t/11t**)
4	 **7t**	2 h [0.2]	$HO(CH_2)_2OH$	82/18 **[68]** (**10s/11s**)
5		0.5 h [1]	$HO(CH_2)_2OH$	65/35 **[70]** (**10s/11s**)
6		0.5 h [0.2]	MeOH[c]	20/80 **[71]** (**10s/11s**)
7		0.5 h [1]	MeOH[c]	20/80 **[69]** (**10s/11s**)
8	 **7u**	2 h [0.2]	$HO(CH_2)_2OH$	83/17 **[70]** (**10u/11u**)

[a] Diastereoisomeric ratio are determined by integration of characteristic protons of the piperidine ring in the crude H^1 NMR spectra (*Trans* and *Cis* isomers where determined according to their respective coupling constants); [b] Isolated yield of pure compounds after chromatography on silica gel; [c] MeOH was generated *in situ* by decomposition of trimethyl orthoformate

According to the results obtained (Table 5) and the stereoselectivity observed, it becomes evident now to affirm the formation of two different transition states in the formation of the piperidine ring. Both transition states are strongly dependent on the alcohol used to generate the ketal on the α,β-insatured ketone. As we have mentioned in Table 3, there are two behave according the nature of the ketal group. When dioxolane is used, *trans* isomer is the major product formed, ~ 80 %, with a catalytic amount of acid (Table 5, entries 1, 4, 5, 7), however when stoechiometric quantity of acid is used, a fast epimerisation process occurs (retro Mannich or Michael reaction) and consequently a higher formation of the thermodynamic specie, namely the 2,6-*cis* piperidine is observed, even if the *trans* isomere was the fisrt formed. In contrary, as observed in table 3, there is no kinetic effect on the cyclisation when methanol is used. In this case, *cis* isomer was the major product, ~ 80 % of the reaction, whatever the quantity of acid engaged (Table 5, entries 3, 6, 8), the thermodynamic product was formed predominantly. And then, as for Banwell's studies, our results are in agreement with the formation of two possible conformations depending of the conformation of the double bond *before* nucleophilic attack of the carbamate, leading to the formation of the piperidine. At this stage, after examination of all potential parameters which can interfere with

diastereoselectivity, it becomes easy to prepare either the *trans* or the *cis* isomer by a wise choice of experimental conditions. In order to demonstrate this, we applied these protocols to the synthesis of (-)-solenopsin-A[39,40] and (+)-alkaloid 241D[41-43] (Scheme 8 and 9). (-)-Solenopsin A can be rapidly prepared from compound **7p** by using for the cyclization step, ethylene glycol which led, as a major product, the *trans* isomer **8w** (82 %, Scheme 8). Then, after subsequent transformations we already described in previous paper[44] (thioketalation **10w**, *Boc* protection, desulfuration **12**), (-)-solenopsin A was obtained in 10 steps, after regeneration of the free amine, from the α,β-ethylenic ester **4**, with an overall yield of 9 % with $[\alpha]_D$ = -1.21 (c 0.94 MeOH, litt.[34] $[\alpha]_D$ = -1.30 (c 1.30 MeOH).

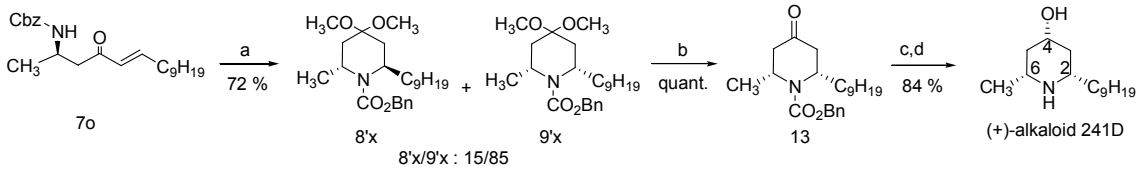
Scheme 8



a) $OH(CH_2)_2OH$, $(CH_3O)_3CH$, *p*-TsOH ; (b) $SH(CH_2)_2SH$, BF_3:Et_2O, CH_2Cl_2; (c) $(Boc)_2O$, DMAP, CH_2Cl_2; (d) W-2 Raney Nickel, EtOH, reflux ; (e) TFA, CH_2Cl_2.

To reach (+)-alkaloid 241D, methanol is now used for the cyclization, starting from compound **7o**. The intermediates **8'x/9'x** were obtained in a *ratio* of 15/85 in a favour of the *cis* isomer. After separation on deactivated silica**, 9'x** was keto-deprotected using a 40% aqueous trifluoroacetic acid solution at room temperature to give the corresponding piperidones **13** in very good yield. *N*-deprotection of the piperidone **13,** followed by reduction with $NaBH_4$ gave selectively (+)-alkaloid 241D in 9 steps from the α,β-ethylenic ester **4** with an overall yield of 16 % with a *de* ≥ 95 % and an *ee* of 92 % (Scheme 9).

Scheme 9



a) $(CH_3O)_3CH$, pTsOH ; (b) TFA/H_2O, CH_2Cl_2 (c) Pd/C (5 %), MeOH, H_2, 1 atm. ; (d) $NaBH_4$, MeOH.

Conclusion

In conclusion, we have described herein a methodology to prepare stereoselectively either 2,6-*cis* or 2,6-*trans* disubstituted piperidines. The efficient of this methodology has been demonstrated through the asymmetric synthesis of (-)-solenopsine A and (+)-alkaloid 241D together with their respective isomer in C-6, demonstrating by this way that this strategy will

be applied efficiently to the total synthesis of other piperidinic alkaloids exhibiting important biological interest.

Experimental Section

Generalities

Organic solutions were dried over Na_2SO_4 and filtered. When anhydrous solvents were used, they were prepared as follows: tetrahydrofuran (THF) was distilled under N_2 from sodium benzophenone ketyl, and used immediately; anhydrous acetonitrile was freshly distilled from CaH_2. All ^1H NMR and ^{13}C spectra were measured in $CDCl_3$ or C_6D_6 and recorded on a Brüker 400 MHz (101 MHz for ^{13}C) spectrometer using TMS as the internal standard. Chemical shifts are expressed in ppm and *J* values are given in Hertz. The following abbreviations are used: singlet (s), broad singlet (brs), doublet (d), doubled doublet (dd), triplet (t), multiplet (m). High resolution mass spectroscopy (HRMS, TOF) were carried out in electrospray mode. Monitoring of the reactions was performed using silica gel TLC plates. Spots were visualized by UV light at 254 nm. Flash chromatography columns were performed using silica gel 60 (70–230 mesh).

General procedure for the synthesis of β-aminoesters 5

(*R*)-methyl 3-(ethoxycarbonylamino)butanoate **5a**

To a cold solution (0°C) of (+)-(R)-*N*-benzyl-*N*-α-methyl benzylamine (23.0 mL, 110 mmol, 1.1 equiv.) in dry THF (280 mL) was added slowly under argon, *n*-butyl lithium (75.0 mL, 1.6 M in hexane, 120 mmol, 1.2 equiv). The resultant pink solution of lithium amide was stirred for 30 min at 0°C then cooled to -78°C before drop wise addition of a solution of methyl crotonate (10.0 mL, 100 mmol, 1 equiv.) in dry THF (100 mL). The mixture was stirred at –78°C for 3h30. Then, a saturated aqueous solution of NH_4Cl (100 mL) was added slowly and the resulting solution was allowed to warm to room temperature. Then, the solution was extracted twice with ethyl acetate. Combined organic extracts were dried over Na_2SO_4, filtered and evaporated. The crude product was added to a suspension of 10 % Pd/C (5.00 g) in methanol (200 mL). The mixture was placed on a Parr apparatus and stirred under a hydrogen atmosphere (60 Psi) for 4 days. The catalyst was then removed by filtration on Celite®. The residue was concentrated in *vacuum* and dissolved in dichloromethane (200 mL) and water (200 mL). Then, sodium carbonate (42.4 g, 400 mmol, 4.0 equiv.) and ethyl chloroformate (28.5 mL, 200 mmol, 2 equiv.) were added drop wise. The resulting solution was stirred at room temperature for 3 h. The aqueous material was extracted with

dichloromethane and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by chromatography on silica gel (cyclohexane/EtOAc : 9/1 to 5/5) afforded **5a** as a yellow oil (10.8 g, 57 % over 3 steps): $[\alpha]_D$ = - 35.60 (c = 0.99, $CHCl_3$), litt.[27] $[\alpha]_D$ = - 37.07 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (brs, 1H, NH), 4.03 (m, 3H), 3.62 (s, 3H), 2.46 (d, *J* = 6.9 Hz, 2H), 1.16 (t, *J* = 6.9Hz, 3H), 1.15 (d, *J* = 6.6Hz, 3H). Spectral data are identical with those reported.[27]

(*R*)-methyl-3-(ethoxycarbonylamino)butanoate **5a.** (starting from 0.100 mol of **4a**, yellow oil, 10.8 g, yield = 57 %)

Spectral data are identical with those reported[45] : $[\alpha]_D$ = - 37.07 (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (brs, 1H), 4.03 (m, 3H), 3.62 (s, 3H), 2.46 (d, *J* = 6.9 Hz, 2H), 1.16 (t, *J* = 6.9 Hz, 3H), 1.15 (d, *J* = 6.6 Hz, 3H)

(*R*)-methyl-3-(benzyloxycarbonylamino)butanoate **5b.** (starting from 0.100 mol of **4a**, yellow oil, 15.6 g, yield = 62 %)

Spectral data are identical with those reported[46] : $[\alpha]_D$ = + 16.9 (c 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (brs, 1H), 4.03 (m, 3H), 3.62 (s, 3H), 2.46 (d, *J* = 6.9 Hz, 2H), 1.16 (t, *J* = 6.9 Hz, 3H), 1.15 (d, *J* = 6.6, 3H).

(*R*)-methyl-3-(benzyloxycarbonylamino)butanoate **5c** and (*S*)-methyl-3-(benzyloxycarbonylamino)butanoate **5c'**. (starting from 0.100 mol of **4b**, yellow oil, 16.7 g, yield = 77 %)

R enantiomer: $[\alpha]_D$ = + 41.5 (c 1.03, $CHCl_3$), *S* enantiomer: $[\alpha]_D$ = - 40.9 (c 1.035, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (brs, 1H), 4.02 (m, *2*H), 3.90 (m, 1H), 3.61 (s, 3H), 2.49 (dd, *J* = 15.8, 4.8 Hz, 1H), 2.43 (dd, *J* = 15.8, 5.3 Hz, 1H), 1.48 – 1.22 (m, 2H), 1.16 (t, *J* = 7.0 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172,0, 156.0, 60.7, 51.6, 47.7, 38.9, 36.6, 19.3, 14.6, 13.8. HRMS-ESI (M + Na), *m/z*: calcd. for $C_{10}H_{19}NO_4Na$ 240.1212, found 240.1216.

(*R*)-methyl-3-(ethoxycarbonylamino)undecanoate **5d.** (starting from 0.100 mol of **4c**, yellow oil, 20.9 g, yield = 73 %)

$[\alpha]_D$ = + 29.2 (c 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (brs, 1H), 4.22 – 4.03 (m, 2H), 3.98 (m, 1H), 3.69 (s, 3H), 2.57 (dd, *J* = 15.1, 4.6 Hz, 1H), 2.51 (dd, *J* = 15.1, 5.1, Hz 1H), 1.55 – 1.45 (m, 2H), 1.41 – 1.10 (m, 15H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 156.1, 60.7, 51.5, 48.0, 38.9, 34.4, 31.8, 29.4, 29.3, 29.2, 26.1, 22.6, 14.6, 14.1; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{15}H_{29}NO_4Na$ 310.1994, found 310.1996.

(*S*)-methyl-3-(ethoxycarbonylamino)-3-phenylpropanoate **5e.** (starting from 0.100 mol of **4d**, yellow oil, 18.0 g, yield = 72 %)

$[\alpha]_D$ = - 9.7 (c 0.99, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 5H), 5.75 (brs, 1H), 5.17 (m, 1H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.62 (s, 3H), 2.91 (dd, *J* = 15.5, 6,0 Hz, 1H), 2.84 (dd, *J* = 15.5, 5.9 Hz, 1H), 1.23 (t, *J* = 7.0, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 155.8, 140.9, 128.6, 127.6, 126.2, 61.0, 51.8, 51.7, 40.5, 14.6; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{13}H_{17}NO_4Na$ 274.1055, found 274.1069.

(*S*)-methyl-3-(*tert*-butoxycarbonylamino)-3-phenylpropanoate **5f** (starting from 0.100 mol of **4d**, yellow oil, 21.2 g, yield = 76 %)

Spectral data are identical with those reported.[47] (*S*)-methyl-3-(benzyloxycarbonylamino)-3-phenylpropanoate **5g .** (starting from 0.100 mol of **4d**, yellow oil, 20.7 g, yield = 66 %)

Spectral data are identical with those reported[52] : $[\alpha]_D$ = - 16.1 (c 0.97, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 10 H), 5.73 (brs, 1H), 5.09 (m, 1H), 5.01 (d, *J* = 12.3 Hz, 1H), 4.97 (d, *J* = 12.3 Hz, 1H), 3.50 (s, 3H), 2.81 (dd, *J* = 15.3, 5.0 Hz, 1H), 2.74 (dd, *J* = 15.3, 5.7 Hz, 1H).

General procedure for the synthesis of ketophosphonates 6

(*R*)-ethyl 5-(diethoxyphosphoryl)-4-oxopentan-2-ylcarbamate **6a**

To a solution of diethyl methylphosphonate (5.8 mL, 39.7 mmol, 2.5 equiv.) in anhydrous THF (15 mL) placed at -78°C, was added drop wise *n*-butyl lithium (24.8 mL, 1.6 M in hexane, 39.7 mmol, 2,5 equiv.). After 20 min at -78°, a solution of **5a** (3 g, 15.9 mmol, 1 equiv.) in anhydrous THF (15 mL) was added dropwise. After addition, the temperature of the reaction was kept at -78°C for 30 min and then allowed to reach 0°C in 1 hour, and quenched with a solution of ammonium chloride and extracted twice with ethyl acetate. After drying over Na_2SO_4 and concentrated under vacuum, the crude oil was first distillated at low pressure to remove excess of diethyl methylphosphonate and the residue purified by flash chromatography (eluent: cyclohexane/EtOAc 2/1 to EtOAc) afforded compound **6a** as a yellow oil (3.3 g, 68% yield): $[\alpha]_D$ = + 33.60 (c = 1.17, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (brs, 1H,), 4.16 – 3.94 (m, 7H), 3.08 (dd, *J* = 23.0, 14.0 Hz, 1H), 2.99 (dd, *J* = 22.6, 14.0 Hz, 1H), 2.84 (dd, *J* = 17.1, 6.0 Hz, 1H), 2.71 (dd, *J* = 17.1, 5.7 Hz, 1H), 1.33 – 1.21 (m, 6H), 1.15-1.20 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.6, 155.8, 62.6 (d, *J* = 6.6 Hz), 62.5 (d, *J* = 6.5 Hz), 60.5, 49.6, 43.5, 42.9 (d, *J* = 127.4 Hz), 20.7, 16.2, 16.1, 14.6; HRMS-ESI (M + Na), *m/z* calcd. for $C_{12}H_{24}NO_6PNa$ 332.1239, found 332.1239.

(*R*)-benzyl-5-(diethoxyphosphoryl)-4-oxopentan-2-ylcarbamate **6b.** (starting from 16 mmol of **5b**, yellow oil, 3.4 g, yield = 57 %); $[\alpha]_D$ = - 26.4 (c 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.22 (m, 5H), 5.26 (brs, 1H), 5.00 (s, 2H), 4.03 (m, 5H), 3.05 (dd, *J* = 23.2, 13.6 Hz, 1H), 2.96 (dd, *J* = 22.7, 13.6 Hz, 1H), 2.85 (dd, *J* = 17.3, 5.8 Hz, 1H), 2.70 (dd, *J* =

17.3, 5.6 Hz, 1H), 1.26 (t, *J* = 6.2 Hz, 6H), 1.16 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.7, 155.6, 136.6, 128.5, 128.0, 66.5, 62.7 (d, *J* = 6.6 Hz), 62.6 (d, *J* = 6.8 Hz), 49.5, 43.6, 43.3 (d, *J* = 129.5 Hz), 20.4, 16.3, 16.2; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{17}H_{26}NO_6PNa$ 394.1395, found 394.1395.

(*R and S*)-ethyl-1-(diethoxyphosphoryl)-2-oxoheptan-4-ylcarbamate **6c and 6c'.** (starting from 16 mmol of **5c**, yellow oil, 3.4 g, yield = 65 %); *R* enantiomer: $[\alpha]_D$ = + 43.09 (c 1.03, $CHCl_3$), *S* enantiomer: $[\alpha]_D$ = - 42.55 (c 1.075, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (d, *J* = 9.0 Hz, 1H), 4.15 – 3.97 (m, 6H), 3.90 (m, 1H), 3.09 (dd, *J* = 22.9, 13.5 Hz, 1H), 2.96 (dd, *J* = 22.5, 13.5 Hz, 1H), 2.80 (dd, *J* = 17.2, 5.9 Hz, 1H), 2.74 (dd, *J* = 17.2, 5.3 Hz, 1H), 1.48 – 1.39 (m, 2H), 1.37 – 1.29 (m, 2H), 1.27 (dt, *J* = 7.2, 2.0 Hz, 6H), 1.15 (t, *J* = 7.1 Hz, 3H), 0.84 (t, *J* = 7.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9, 156.2, 62.7 (d, *J* = 6.5 Hz), 62.6 (d, *J* = 6.6 Hz), 60.6, 48.2, 47.5, 42.9 (d, *J* = 126.6 Hz), 36.7, 19.3, 16.3, 16.2, 14.6, 13.8; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{14}H_{28}NO_6PNa$ 360.1552, found 360.1562.

(*R*)-ethyl-1-(diethoxyphosphoryl)-2-oxododecan-4-ylcarbamate **6d.** (starting from 16 mmol of **5d**, yellow oil, 4.2 g, yield = 66 %); $[\alpha]_D$ = + 30.06 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (brs, 1H), 4.17 – 3.99 (m, 6H), 3.95 (m, 1H), 3.07 (dd, *J* = 23.1, 13.5 Hz, 1H), 2.98 (dd, *J* = 22.7, 13.5 Hz, 1H), 2.83 (dd, *J* = 17.4, 5.8 Hz, 1H), 2.75 (dd, *J* = 17.4, 5.2 Hz, 1H), 1.51 – 1.41 (m, 2H), 1.39 – 1.23 (m, 12H), 1.21 (t, *J* = 7.2 Hz, 6H), 1.16 (t, *J* = 7.1 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.8, 156.1, 62.9 (d, *J* = 6.6 Hz), 62.8 (d, *J* = 6.7 Hz), 60.7, 48.2, 48.1, 42.7 (d, *J* = 127.1 Hz), 34.4, 31.8, 29.4, 29.3, 29.2, 26.1, 22.6, 16.4, 16.3, 14.6, 14.0; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{19}H_{38}NO_6PNa$ 430.2334 found 430.2349.

(*S*)-ethyl 4-(diethoxyphosphoryl)-3-oxo-1-phenylbutylcarbamate **6e.** (starting from 16 mmol of **5e**, yellow oil, 3.4 g, yield = 58 %); $[\alpha]_D$ = + 1.65 (c 1.09, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 4H), 7.16 (m, 1H), 5.72 (s, 1H), 5.09 (dd, *J* = 12.7, 6.7 Hz, 1H), 4.11 – 3.94 (m, 6H), 3.26 (dd, *J* = 16.9, 7.3 Hz, 1H), 3.04 (dd, *J* = 23.3, 13.1 Hz, 1H), 2.97 (dd, *J* = 16.9, 12.7 Hz, 1H), 2.93 (dd, *J* = 22.9, 13.1 Hz, 1H), 1.22 (td, *J* = 7.1, 1.9 Hz, 6H), 1.13 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 155.9, 141.4, 128.6, 127.4, 126.3, 62.8 (d, *J* = 6.2 Hz), 62.6 (d, *J* = 6.5 Hz), 60.8, 51.1, 49.4, 43.3 (d, *J* = 125.5 Hz), 16.2 (d, *J* = 6.1 Hz), 14.6; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{17}H_{26}NO_6PNa$ 394.1395, found 394.1414.

(*S*)-*tert*-butyl 4-(diethoxyphosphoryl)-3-oxo-1-phenylbutylcarbamate **6f.** (starting from 16 mmol of **5f**, yellow oil, 3.9 g, yield = 62 %); $[\alpha]_D$ = + 3.12 (c 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.12 (m, 4H), 7.16 (m, 1H), 5.44 (brs, 1H), 5.03 (brs, 1H), 4.04 – 3.95

(m, 4H), 3.20 (dd, *J* = 16.8, 7.4 Hz, 1H), 3.01 (dd, *J* = 23.1, 12.9 Hz, 1H), 2.99 (m, 1H), 2.92 (dd, *J* = 22.7, 12.9 Hz, 1H), 1.32 (s, 9H), 1.21 (td, *J* = 7.1, 1.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.2, 155.1, 133.6, 130.9, 128.5, 126.3, 66.7, 62.8 (d, *J* = 6.3 Hz), 62.6 (d, *J* = 6.2 Hz), 50.9, 49.6, 41.0 (d, *J* = 127.6 Hz), 16.3 (d, *J* = 5.8 Hz), 16.2 (d, *J* = 5.6 Hz); HRMS-ESI (M + Na), *m/z*: calcd. for $C_{19}H_{30}NO_6PNa$ 422.1708, found 422.1722.

(*S*)-benzyl-4-(diethoxyphosphoryl)-3-oxo-1-phenylbutylcarbamate **6g.** (starting from 16 mmol of **5g**, yellow oil, 4.5 g, yield = 66 %) ; $[\alpha]_D$ = + 8.66 (c 1.55, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.20 (m, 8H), 7.16 (m, 2H), 5.88 (brs, 1H), 5.11 (dd, *J* = 13.1, 7.4 Hz, 1H), 5.04 (d, *J* = 12.3 Hz, 1H), 4.96 (d, *J* = 12.3 Hz, 1H), 4.02 – 3.89 (m, 4H), 3.27 (dd, *J* = 16.6, 7.4 Hz, 1H), 3.02 (dd, *J* = 23.3, 13.1 Hz, 1H), 2.97 (m, 1H), 2.90 (dd, *J* = 22.6, 13.1 Hz, 1H), 1.21 (t, *J* = 7.0 Hz, 3H), 1.15 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0, 155.6, 141.3, 136.5, 128.6, 128.4, 128.0, 127.5, 126.3, 66.7, 62.9 (d, *J* = 5.3 Hz), 62.6 (d, *J* = 6.4 Hz), 51.3, 49.3, 43.5 (d, *J* = 123.8 Hz), 16.3 (d, *J* = 4.1 Hz), 16.2 (d, *J* = 3.7 Hz); HRMS-ESI (M + Na), *m/z*: calcd. for $C_{22}H_{28}NO_6PNa$ 456.1552, found 456.1559.

General procedure for the synthesis of enones 7

(*R*,*E*)-ethyl 4-oxo-6-phenyl-hex-5-en-2-ylcarbamate **7a**

To a solution of **6a** (0.5 g, 1.6 mmol, 1equiv.) in THF (7 mL), was poured in one time $Ba(OH)_2$ (0.346 g, 2.0 mmol, 1.25 equiv.) at room temperature. After 30 min, a solution of benzaldehyde (0.172 ml, 1.7 mmol, 1.05 equiv.) in THF/H_2O: 40/1 (7 mL) was slowly added at room temperature. After 1 hour, the reaction mixture was quenched with an aqueous solution of ammonium chloride and extracted three times with ethyl acetate. Then the organic layer was dried over Na_2SO_4, concentrated under vacuum and purified by flash chromatography (eluent: cyclohexane to cyclohexane/EtOAc 8/2) and gave compound **7a** as a white solid (0.40 g, 95%): mp 74 °C; $[\alpha]_D$ = + 9.50 (c = 1.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 16.7 Hz, 1H), 7.47 (dd, *J* = 7.8, 3.0 Hz, 1H), 7.33 – 7.30 (m, 3H), 6.65 (d, *J* = 16.7 Hz, 1H), 5.14 (s, 1H), 4.14 – 4.06 (m, 1H), 4.02 (q, *J* = 6.9 Hz, 2H), 2.95 (dd, *J* = 15.9, 4.2 Hz, 1H), 2.71 (dd, *J* = 15.9, 6.5 Hz, 1H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.14 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.8, 155.9, 143.4, 134.3, 130.6, 128.9, 128.4, 126.3, 60.6, 46.3, 44.1, 20.5, 14.6; HRMS-ESI (M + Na): calcd. for $C_{15}H_{19}NO_3Na$ 284.1263, found 284.1275.

(*R*,*E*)-ethyl-6-(2-nitrophenyl)-4-oxohex-5-en-2-ylcarbamate **7b.**

$[\alpha]_D$ = + 21.94 (c 1.015, $CHCl_3$) ; Yellow solid ; starting from 1.6 mmol of **6a**, 0.43g, yield = 89 % ; mp 90°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 16.1 Hz, 1H), 7.71 – 7.59 (m, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 6.58 (d, *J* = 16.1 Hz, 1H), 5.08 (brs, 1H),

4.22 – 4.08 (m, 3H), 3.04 (dd, *J* = 16.3, 4.7 Hz, 1H), 2.85 (dd, *J* = 16.3, 6.3 Hz, 1H), 1.28 (d, *J* = 6.7 Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3, 155.8, 148.3, 138.7, 133.7, 131.1, 130.8, 130.5, 129.1, 125.1, 60.7, 46.0, 43.9, 20.6, 14.6 ; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{15}H_{18}N_2O_5Na$ 329.1113, found 329.1117.

(*R*,*E*)-ethyl-6-(3-nitrophenyl)-4-oxohex-5-en-2-ylcarbamate **7c.**

$[\alpha]_D$ = + 5.92 (c 0.995, $CHCl_3$) ; Yellow solid ; starting from 1.6 mmol of **6a**, 0.41g, yield = 86 % ; mp 97°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.27 (d, *J* = 8.1 Hz, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.65 (d, *J* = 16.2 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 16.2 Hz, 1H), 5.08 (brs, 1H), 4.27 – 4.04 (m, 3H), 3.07 (dd, *J* = 16.1, 3.3 Hz, 1H), 2.84 (dd, *J* = 16.1, 6.6 Hz, 1H), 1.31 (d, *J* = 6.7 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3, 155.6, 148.5, 140.2, 136.0, 133.9, 130.0, 128.6, 124.8, 122.6, 60.8, 47.0, 44.0, 20.5, 14.6 ; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{15}H_{18}N_2O_5Na$ 329.1113, found 329.1125.

(*R*,*E*)-ethyl-6-(4-nitrophenyl)-4-oxohex-5-en-2-ylcarbamate **7d.**

$[\alpha]_D$ = + 16.42 (c 0.52, $CHCl_3$) ; Yellow solid ; starting from 1.6 mmol of **6a**, 0.44g, yield = 91 % ; mp 98°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 16.2 Hz, 1H), 6.75 (d, *J* = 16.2 Hz, 1H), 4.97 (s, 1H), 4.10 (m, 1H), 4.03 (q, *J* = 7.0 Hz, 2H), 2.99 (dd, *J* = 15.6, 3.5 Hz, 1H), 2.74 (dd, *J* = 15.6, 6.5 Hz, 1H), 1.21 (d, *J* = 6.8 Hz, 1H), 1.15 (t, *J* = 7.0 Hz, 1H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0, 155.9, 140.5, 140.1, 128.5, 128.9, 124.8, 124.2, 60.8, 47.1, 44.0, 20.5, 14.6 ; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{15}H_{18}N_2O_5Na$ 329.1113, found 329.1119.

(*R*,*E*)-ethyl-6-(4-methoxyphenyl)-4-oxohex-5-en-2-ylcarbamate **7e.**

$[\alpha]_D$ = + 6.1 (c 1.055, $CHCl_3$) ; Yellow solid ; starting from 1.6 mmol of **6a**, 0.37g, yield = 79 % ; mp 108°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 16.1 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 2H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.60 (d, *J* = 16.1 Hz, 1H), 5.21 (brs, 1H), 4.22 – 4.07 (m, 3H), 3.83 (s, 3H), 2.99 (dd, *J* = 15.8, 4.4 Hz, 1H), 2.76 (dd, *J* = 15.8, 5.8 Hz, 1H), 1.25 (d, *J* = 6.8 Hz, 1H), 1.21 (t, *J* = 7.0 Hz, 1H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.8, 161.9, 155.9, 143.2, 130.3, 127.1, 124.3, 114.6, 60.8, 55.5, 46.2, 44.4, 20.6, 14.7 ; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{16}H_{21}NO_4Na$ 314.1368, found 314.1371.

(*R*,*E*)-ethyl 6-(2-bromophenyl)-4-oxohex-5-en-2-ylcarbamate **7f.**

$[\alpha]_D$ = + 18.2 (c 1.175, $CHCl_3$) ; Yellow solid ; starting from 1.6 mmol of **6a**, 0.53g, yield = 91 % ; mp 65°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 16.2 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.17 (td, *J* = 7.8, 1.5 Hz, 1H), 6.57 (d, *J* = 16.2 Hz, 1H), 5.08 (brs, 1H), 4.15 – 3.88 (m, 3H), 2.96 (dd, *J* = 16.4, 4.8 Hz, 1H), 2.79 (dd, *J* = 16.3, 6.2 Hz, 1H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H) ; ^{13}C NMR (101 MHz,

$CDCl_3$) δ 198.8, 158.1, 145.0, 141.6, 133.5, 131.5, 129.0, 127.8, 60.7, 46.5, 44.0, 20.6, 14.6 ; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{15}H_{18}BrNO_3Na$ 362.0368, found 362.0371.

(*R*,*E*)-ethyl-6-(4-bromophenyl)-4-oxo-hex-5-en-2-ylcarbamate **7g.**

$[\alpha]_D$ = + 4.0 (c 1.03, $CHCl_3$) ; Yellow solid ; starting from 1.6 mmol of **6a**, 0.48g, yield = 89 % ; mp 90°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 16.2 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 6.70 (d, *J* = 16.2 Hz, 1H), 5.10 (s, 1H, NH), 4.14 (m, 1H), 4.09 (q, *J* = 7.1 Hz, 1H), 3.01 (dd, *J* = 15.5, 3.4 Hz, 1H), 2.77 (dd, *J* = 15.5, 6.6 Hz, 1H), 1.27 (d, *J* = 6.8 Hz, 1H), 1.23 (t, *J* = 7.1, 1H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4, 156.0, 141.9, 133.2, 132.2, 129.7, 126.7, 124.9, 60.7, 50.0, 46.5, 44.1, 20.5, 14.6 ; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{15}H_{18}BrNO_3Na$ 362.0368, found 362.0380.

(*R*,*E*)-ethyl-6-(2-chloro-5-nitrophenyl)-4-oxo-hex-5-en-2-ylcarbamate **7h.**

$[\alpha]_D$ = + 15.06 (c 1.06, $CHCl_3$) ; Yellow solid ; starting from 1.6 mmol of **6a**, 0.52g, yield = 95 % ; mp 149°C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.6 Hz, 1H), 7.97 (d, *J* = 16.0 Hz, 1H), 7.62 (s, 1H), 7.51 (d, *J* = 8.6, 1H), 6.57 (d, *J* = 16.0 Hz, 1H), 5.09 (brs, 1H), 4.23 – 4.03 (m, 3H), 3.05 (dd, *J* = 16.5, 5.2 Hz, 1H), 2.84 (dd, *J* = 16.5, 6.5 Hz, 1H), 1.28 (d, *J* = 6.9 Hz, 3H), 1.21 (t, *J* = 7.5 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0, 158.9, 146.5, 140.4, 137.7, 132.9, 131.9, 130.5, 129.3, 126.7, 60.9, 46.5, 44.1, 20.7, 14.7 ; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{15}H_{17}ClN_2O_5Na$ 363.0724, found 363.0717.

(*R*,*E*)-ethyl-4-oxo-6-(pyridin-3-yl)hex-5-en-2-ylcarbamate **7i.**

$[\alpha]_D$ = + 10.25 (c 0.865, $CHCl_3$) ; White solid ; starting from 1.6 mmol of **6a**, 0.36g, yield = 87 % ; mp 90°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 1.6 Hz, 1H), 8.56 (d, *J* = 4.7 Hz, 1H), 7.82 (dt, *J* = 7.9,1.6, 1H), 7.51 (d, *J* = 16.3 Hz, 1H), 7.30 (dd, *J* = 7.9, 4.9 Hz, 1H), 6.72 (d, *J* = 16.3 Hz, 1H), 5.03 (brs, 1H), 4.20 – 3.70 (m, 3H), 2.98 (dd, *J* = 16.1, 4.0 Hz, 1H), 2.74 (dd, *J* = 16.1, 6.7 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.16 (t, *J* = 7.5 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.1, 155.9, 151.1, 149.9, 139.4, 134.5, 130.2, 128.0, 123.8, 60.7, 46.7, 44.1, 20.5, 14.6 ; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{14}H_{18}N_2O_3Na$ 285.1215, found 285.1210.

(*R*,2*E*,4*E*)-ethyl-8-(ethoxycarbonylamino)-6-oxo-nona-2,4-dienoate **7j.**

$[\alpha]_D$ = + 17.6 (c 0.695, $CHCl_3$) ; Viscous yellow oil ; starting from 1.6 mmol of **6a**, 0.38g, yield = 85 % . ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 14.9, 11.4 Hz, 1H), 7.14 (dd, *J* = 15.1, 11.4 Hz, 1H), 6.35 (d, *J* = 15.0 Hz, 1H), 6.19 (d, *J* = 15.0 Hz, 1H), 4.97 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.05 – 4.00 (m, 3H), 2.89 (d, *J* = 12.5 Hz, 1H), 2.67 (dd, *J* = 16.3, 6.5 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4, 165.7, 155.8, 141.1, 139.1, 135.3, 129.5, 60.9, 60.7, 46.7, 43.9,

20.4, 14.6, 14.2 ; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{14}H_{21}NO_5Na$ 306.1317, found 306.1331.

(*R*)-ethyl-6-(ethoxycarbonylamino)-4-oxohept-2-enoate **7k.**

Mixture of Z and E isomers (Z/E : 60/40): Colorless oil ; starting from 1.6 mmol of **6a**, 0.22g, yield = 53 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, *J* = 16.0 Hz, 1H), 6.62 (d, *J* = 16.0 Hz, 1H), 6.43 (d, *J* = 12.0 Hz, 1H), 5.97 (d, *J* = 12.0 Hz, 1H), 5.18 (s, 1H), 5.12 (s, 1H), 4.25 – 4.11 (m, 6H), 2.91 (d, *J* = 15.0 Hz, 1H), 2.81 (dd, *J* = 16.9, 5.7 Hz, 1H), 2.78 – 2.67 (m, 1H), 1.27 – 1.13 (m, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) (mixture of Z and E) δ 201.1, 197.3, 164.4, 164.2, 155.7, 155.0, 140.6, 138.3, 130.4, 124.0, 60.5, 60.3, 59.8, 59.7, 47.3, 46.0, 42.7, 42.4, 19.6, 19.4, 13.6, 13.1, 13.0 ; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{12}H_{19}NO_5Na$ 280.1161, found 280.1163.

(*R*,*E*)-ethyl-4-oxo-non-5-en-2-ylcarbamate **7l.**

$[\alpha]_D$ = + 12.13 (c 1.025, $CHCl_3$) ; Colorless oil ; starting from 1.6 mmol of **6a**, 0.34g, yield = 95 % .^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (dt, *J* = 15.9, 7.2 Hz, 1H), 6.07 (dd, *J* = 15.9, 1.5 Hz, 1H), 5.13 (brs, 1H), 4.11 – 4.02 (m, 3H), 2.87 (dd, *J* = 16.1, 4.4 Hz, 1H), 2.65 (dd, *J* = 16.1, 6.4 Hz, 1H), 2.19 (td, *J* = 7.2, 1.5 Hz, 2H), 1.49 (qd, *J* = 7.2 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.21 (d, *J* = 6.8 Hz, 3H), 0.92 (t, *J* = 7.1 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.1, 156.0, 148.5, 130.9, 60.7, 45.5, 44.2, 34.6, 21.4, 20.6, 14.7, 13.8 ; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{12}H_{21}NO_3Na$ 250.1419, found 250.1421.

(*R*,*E*)-ethyl 4-oxo-tetradec-5-en-2-ylcarbamate **7m.**

$[\alpha]_D$ = + 10.71 (c 1.025, $CHCl_3$) ; Yellow oil ; starting from 1.6 mmol of **6a**, 0.42g, yield = 88 % .^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (dt, *J* = 15.8, 6.9 Hz, 1H), 6.01 (d, *J* = 15.8 Hz, 1H), 5.16 (s, 1H), 4.07 – 4.03 (m, 1H, 3H), 2.86 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.63 (dd, *J* = 16.0, 6.4 Hz, 1H), 2.14 (q, *J* = 6.9 Hz, 2H), 1.45 – 1.32 (m, 2H), 1.30 – 1.18 (m, 15H), 1.15 (d, *J* = 7.1 Hz, 3H), 0.81 (t, *J* = 6.9 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.1, 155.9, 148.7, 130.7, 60.7, 45.5, 44.1, 32.6, 31.9, 29.5, 29.4, 29.3, 29.2, 28.1, 22.7, 20.5, 14.7, 14.2 ; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{17}H_{31}NO_3Na$ 320.2202, found 320.2209.

(*R*,*E*)-benzyl-4-oxo-6-phenyl-hex-5-en-2-ylcarbamate **7n**.

$[\alpha]_D$ = + 2.56 (c 1.95, $CHCl_3$) ; White solid ; starting from 1.3 mmol of **6b**, 0.40g, yield = 96 % ; mp 96°C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 16.1 Hz, 1H), 7.48 – 7.46 (m, 2H), 7.33 – 7.19 (m, 8H), 6.64 (d, *J* = 16.1 Hz, 1H), 5.23 (s, 1H), 5.10 – 4.96 (m, 2H), 4.18 – 4.06 (m, 1H), 2.97 (d, *J* = 15.7 Hz, 1H), 2.73 (dd, *J* = 15.7, 5.6 Hz, 1H), 1.21 (d, *J* = 6.2 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.5, 155.6, 143.1, 134.0, 130.7, 129.0, 128.5, 128.4, 128.1,

126.3, 66.6, 46.1, 44.3, 20.5 ; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{20}H_{21}NO_3Na$ 346.1419, found 346.1424.

(*R*,*E*)-benzyl-4-oxo-pentadec-5-en-2-ylcarbamate **7o.**

$[\alpha]_D$ = -9.86 (c 0.975, $CHCl_3$) ; Yellow oil ; starting from 1.3 mmol of **6b**, 0.38g, yield = 78 % . ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 5H), 6.87 (dt, *J* = 16.0, 6.7 Hz, 1H), 6.09 (d, *J* = 16.0 Hz, 1H), 5.29 (brs, 1H), 5.10 (brs, 2H), 4.13 (m, 1H), 2.91 (dd, *J* = 16.1, 3.1 Hz, 1H), 2.69 (dd, *J* = 16.1, 6.1 Hz, 1H), 2.22 (dt, *J* = 6.7, 7.1 Hz, 2H), 1.52 – 1.41 (m, 2H), 1.36 – 1.27 (m, 12H), 1.25 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.4, 155.6, 148.7, 139.5, 130.5, 128.5, 128.1, 128.0, 66.5, 45.2, 44.2, 32.5, 31.8, 29.5, 29.4, 29.3, 29.2, 28.04, 22.6, 20.4, 14.1 ; HRMS-ESI $(M + H)^+$, *m/z*: calcd. for $C_{23}H_{36}NO_3$ 374.2695, foun- 374.2706.

(*R*,*E*)-benzyl-4-oxo-heptadec-5-en-2-ylcarbamate **7p.**

$[\alpha]_D$ = -9.80 (c 1.015, $CHCl_3$) ; Yellow oil ; starting from 1.3 mmol of **6b**, 0.45g, yield = 91 % . ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 5H), 6.87 (dt, *J* = 15.9, 7.2 Hz, 1H), 6.06 (d, *J* = 15.9 Hz, 1H), 5.31 (brs, 1H), 5.08 (brs, 2H), 4.10 (m, 1H), 2.89 (d, *J* = 15.6 Hz, 1H), 2.66 (dd, *J* = 15.6, 5.3 Hz, 1H), 2.19 (q, *J* = 7.2 Hz, 2H), 1.47 – 1.40 (m, 6H), 1.33 – 1.21 (m, 15H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.1, 155.7, 148.9, 136.7, 130.6, 128.6, 128.1, 66.6, 45.3, 44.3, 32.6, 32.0, 29.7, 29.6, 29.5, 29.4, 29.3, 28.1, 27.0, 22.8, 20.5, 14.2; HRMS-ESI $(M + H)^+$, *m/z*: calcd. for $C_{25}H_{40}NO_3$ 402.3008, found 402.3015.

(*E*)-ethyl-6-oxo-8-phenyl-oct-7-en-4-ylcarbamate **7q and 7q'.**

R enantiomer: $[\alpha]_D$ = + 21.87 (c 0.97, $CHCl_3$) ; *S* enantiomer: $[\alpha]_D$ = - 21.32 (c 0.76 $CHCl_3$) ; White solid ; starting from 1.5 mmol of **6c**, 0.39g, yield = 91 % ; mp 96°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 16.8 Hz, 1H), 7.45 – 7.3 (m, 2H), 7.33 – 7.30 (m, 3H), 6.64 (d, *J* = 16.8 Hz, 1H), 5.06 (brs, 1H), 4.09 – 3.91 (m, 3H), 2.90 (dd, *J* = 17.2, 6.0 Hz, 1H), 2.78 (dd, *J* = 17.2, 5.5 Hz, 1H), 1.62 – 1.29 (m, 4H), 1.17 (t, *J* = 6.9 Hz, 3H), 0.85 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.0, 156.2, 143.2, 134.3, 130.6, 128.9, 128.4, 126.3, 60.6, 48.1, 44.8, 36.5, 19.5, 14.6, 13.8; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{17}H_{23}NO_3Na$ 312.1576, found 312.1585.

(*R*,*E*)-ethyl-8-(4-nitrophenyl)-6-oxo-oct-7-en-4-ylcarbamate **7r.**

$[\alpha]_D$ = + 13.8 (c 0.985, $CHCl_3$) ; Yellow solid; starting from 1.5 mmol of **6c**, 0.42g, yield = 84 %; mp 102°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.1 Hz, 2H), 7.60 (d, *J* = 16.2 Hz, 1H), 6.83 (d, *J* = 16.2 Hz, 1H), 5.01 (s, 1H), 4.14 – 4.01 (m, 3H), 3.01 (d, *J* = 16.2 Hz, 1H), 2.85 (dd, *J* = 16.2, 5.7 Hz, 1H), 1.64 – 1.49 (m, 2H), 1.47 – 1.30 (m, 2H), 1.22 (t, *J* = 6.8 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5,

156.2, 140.6, 140.0, 129.5, 128.9, 124.2, 124.2, 60.8, 48.1, 45.8, 36.6, 19.5, 14.6, 13.8; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{17}H_{22}N_2O_5Na$ 357.1426, found 357.1420.

(*R*,*E*)-ethyl 3-oxo-1-phenyl-tridec-1-en-5-ylcarbamate **7s.**

$[\alpha]_D$ = + 17.26 (c 1.015, $CHCl_3$) ; White solid ; starting from 1.2 mmol of **6d**, 0.40g, yield = 94 % ; mp 76°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 16.1 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.44 – 7.36 (m, 3H), 6.74 (d, *J* = 16.1 Hz, 1H), 5.23 (d, *J* = 7.4 Hz, 1H), 4.21 – 3.94 (m, 3H), 3.01 (d, *J* = 15.2 Hz, 1H), 2.84 (dd, *J* = 15.2, 3.8 Hz, 1H), 1.69 – 1.49 (m, 2H), 1.48 – 1.11 (m, 15H), 0.85 (t, *J* = 6.8 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.0, 156.2, 143.2, 134.3, 130.6, 129.6, 128.9, 128.4, 126.3, 60.6, 48.4, 44.9, 34.4, 31.8, 29.5, 29.2, 26.3, 22.6, 14.6, 14.1 ; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{22}H_{33}NO_3Na$ 382.2358, found 382.2364.

(*R*,*E*)-ethyl-4-oxo-tetradec-2-en-6-ylcarbamate **7t.**

$[\alpha]_D$ = + 17.44 (c 1.12, $CHCl_3$) ; White solid ; starting from 1.2 mmol of **6d**, 0.27g, yield = 78 % ; mp 59°C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (dt, *J* = 15.8, 6.8, 1H), 6.10 (d, *J* = 15.8, 1.6 Hz, 1H), 5.1 (brs, 1H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.91 (m, 1H), 2.84 (dd, *J* = 15.8, 4.2 Hz, 1H), 2.67 (dd, *J* = 15.8, 5.5 Hz, 1H), 1.90 (d, 3H, *J* = 6.8 Hz), 1.55 – 1.46 (m, 2H), 1.33 – 1.20 (m, 15H), 0.86 (t, *J* = 6.9 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2, 156.3, 143.6, 132.4, 60.7, 48.5, 44.0, 34.5, 31.9, 29.6, 29.5, 29.4, 26.4, 22.8, 18.5, 14.7, 14.2 ; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{17}H_{31}NO_3Na$ 320.2202, found 320.2207.

(*R*,*E*)-ethyl-6-oxo-hexadec-4-en-8-ylcarbamate **7u.**

$[\alpha]_D$ = + 12.1 (c 1.05, $CHCl_3$) ; Colorless oil ; starting from 1.2 mmol of **6d**, 0.37g, yield = 95 % . ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (dt, *J* = 15.9, 7.2 Hz, 1H), 6.07 (dd, *J* = 15.9, 1.4 Hz, 1H), 5.11 (brs, 1H), 4.07 (qd, *J* = 6.9, 2H), 3.91 (m, 1H), 2.85 (dd, *J* = 16.3, 4.5 Hz, 1H), 2.69 (dd, *J* = 16.3, 5.7 Hz, 1H), 2.18 (dd, *J* = 7.2, 1.4 Hz, 1H), 1.53 – 1.44 (m, 2H), 1.49 (qd, *J* = 7.2 Hz, 2H), 1. 29 – 1.19 (m, 15H), 0.92 (t, *J* = 7.2 Hz, 3H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.4, 156.3, 148.3, 130.9, 60.7, 46.5, 44.1, 34.6, 34.5, 31.9, 29.6, 29.5, 29.4, 26.4, 22.8, 21.4, 14.7, 14.2, 13.8; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{19}H_{35}NO_3Na$ 348.2515, found 348.2525.

(*S*,*E*)-ethyl-3-oxo-1,5-diphenyl-pent-4-enylcarbamate **7v.**

$[\alpha]_D$ = + 6.6 (c 0.94, $CHCl_3$) ; Yellow oil ; starting from 1.3 mmol of **6e**, 0.35g, yield = 84 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 16.2 Hz, 1H), 7.41 – 7.11 (m, 10H), 6.59 (d, *J* = 16.2 Hz, 1H), 5.74 (brs, 1H), 5.16 (m, 1H), 4.01 (q, *J* = 6.3 Hz, 1H), 3.26 (dd, *J* = 15.9 Hz, 1H), 3.06 (dd, *J* = 15.9, 5.0 Hz, 1H), 1.13 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 155.9, 143.6, 134.2, 130.7, 128.9, 128.6, 128.4, 127.5, 126.3, 126.0, 61.0, 51.7, 46.1, 14.6; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{20}H_{21}NO_3Na$ 346.1419, found 346.1414.

(*S*,*E*)-ethyl-3-oxo-1-phenyl-hex-4-enylcarbamate **7w.**

$[\alpha]_D$ = - 13.3 (c 0.715, $CHCl_3$) ; Yellow oil ; starting from 1.3 mmol of **6e**, 0.27g, yield = 80 % . ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.12 (m, 5H), 6.75 (dq, *J* = 15.9, 6.8 Hz, 1H), 5.96 (dd, *J* = 15.9,1.5 Hz, 1H), 5.68 (brs, 1H), 5.09 (m, 1H), 4.01 (q, *J* = 6.9 Hz, 2H), 3.12 (dd, *J* = 16.6, 5.8 Hz, 1H), 2.93 (dd, *J* = 16.6, 6.8 Hz, 1H), 1.79 (dd, *J* = 6.8, 1.5 Hz, 3H), 1.10 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.2, 158.2, 146.2, 143.7, 134.2, 130.8, 129.6, 128.5, 63.2, 53.9, 45.5, 20.6, 16.8; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{15}H_{19}NO_3Na$ 284.1263, found 284.1275.

(*S*,*E*)-ethyl-3-oxo-1-phenyl-oct-4-enylcarbamate **7x.**

$[\alpha]_D$ = - 9.11 (c 1.14, $CHCl_3$) ; Colorless oil ; starting from 1.3 mmol of **6e**, 0.36g, yield = 95 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.21 (m, 5H), 6.80 (dt, *J* = 15.9, 6.9 Hz, 1H), 6.05 (td, *J* = 15.9, 1.5, 1H), 5.75 (s, 1H), 5.15 (dd, *J* = 5.8,3.1 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.23 (dd, *J* = 16.1, 3.1 Hz, 1H), 3.04 (dd, *J* = 16.1, 5.8 Hz, 1H), 2.16 (qd, *J* = 6.9, 1.5 Hz, 2H), 1.47 (sex, *J* = 6.8 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3, 156.1, 148.8, 141.6, 130.6, 128.6, 127.4, 126.4, 61.0, 51.8, 45.3, 34.6, 21.3, 14.6, 13.7; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{17}H_{23}NO_3Na$ 312.1576, found 312.1576.

(*S*,*E*)-ethyl-3-oxo-1-phenyl-tridec-4-enylcarbamate **7y.**

$[\alpha]_D$ = - 1.22 (c 0.995, $CHCl_3$) ; White solid ; starting from 1.3 mmol of **6e**, 0.41g, yield = 89 % ; mp 60°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.17 (m, 4H), 7.13 (m, 1H), 6.70 (dt, *J* = 15.9, 6.9 Hz, 1H), 5.93 (d, *J* = 15.9 Hz, 1H), 5.88 (brs, 1H), 5.07 (m, 1H), 3.98 (q, *J* = 7.1 Hz, 2H), 3.09 (d, *J* = 16.1 Hz, 1H), 2.89 (dd, *J* = 16.1, 5.7 Hz, 1H), 2.06 (q, *J* = 6.9 Hz, 2H), 1.39 – 1.29 (m, 2H), 1.27 – 1.13 (m, 10H), 1.10 (t, *J* = 7.1 Hz, 3H), 0.79 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.2, 156.0, 148.9, 141.7, 130.3, 128.5, 127.3, 126.3, 60.8, 51.6, 45.3, 32.5, 31.8, 29.4, 29.3, 29.2, 29.1, 27.9, 22.6, 14.5, 14.1; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{22}H_{33}NO_3Na$ 382.2358, found 382.2362.

(*S*,*E*)-*tert*-butyl-3-oxo-1-phenyl-hex-4-enylcarbamate **7z.**

$[\alpha]_D$ = - 10.68 (c 1.015, $CHCl_3$) ; White solid ; starting from 1.2 mmol of **6f**, 0.28g, yield = 81 %; mp 94°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.18 (m, 5H), 6.84 (dq, *J* = 15.9, 6.8 Hz, 1H), 6.06 (dd, *J* = 15.9, 1.6 Hz, 1H), 5.55 (brs, 1H), 5.09 (m, 1H), 3.12 (d, *J* = 16.6 Hz, 1H), 2.98 (dd, *J* = 16.6, 5.6 Hz, 1H), 1.85 (dd, *J* = 6.8, 1.6 Hz, 3H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.2, 155.3, 144.0, 132.1, 128.7, 127.4, 126.4, 51.5, 45.6, 28.5, 18.5; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{17}H_{23}NO_3Na$ 312.1576, found 312.1591.

(*S*,*E*)-benzyl-3-oxo-1-phenyl-hex-4-enylcarbamate **1.**

$[\alpha]_D$ = - 5.34 (c 1.05, $CHCl_3$) ; White solid ; starting from 1.1 mmol of **6g**, 0.34g, yield = 96 %; mp 60°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.17 (m, 5H), 6.80 (dq, *J* = 15.8, 6.8 Hz, 1H), 6.05 (d, *J* = 15.8 Hz, 1H), 5.88 (brs, 1H), 5.18 (dd, *J* = 6.2, 5.6 Hz, 1H), 5.10 (d, *J* = 12.3 Hz, 1H), 5.05 (d, *J* = 12.3 Hz, 1H), 3.19 (dd, *J* = 16.2, 5.6 Hz, 1H), 3.00 (dd, *J* = 16.2, 6.2 Hz, 1H), 1.85 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.8, 155.7, 144.0, 136.4, 136.2, 131.9, 128.7, 128.6, 128.5, 128.0, 126.4, 126.3, 66.8, 51.8, 45.1, 18.3; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{21}H_{21}NO_3Na$ 346.1419, found 346.1426.

General procedure for the synthesis of piperidines 8l-s/9l-s

(2*S*,6*R*)-ethyl 4,4-dimethoxy-6-methyl-2-[(4-nitrophenyl)]piperidine-1-carboxylate **8m** (*trans* isomer) and (2*R*,6*R*)-ethyl 4,4-dimethoxy-6-methyl-2-[(4-nitrophenyl)]piperidine-1-carboxylate **9m** (*cis* isomer).

In a one neck flash, to compound **7d** (0.1 g, 0.32 mmol 1 equiv.) were added successively, trimethyl orthoformate (1.75 ml, 1.60 mmol, 5 equiv.) and *p*-toluenesulphonic acid (5.5 mg, 0.32 mmol, 1 equiv.). The reaction is followed by TLC and after 0.5h ethyl acetate was added to the crude mixture, then a saturated solution of $NaHCO_3$ and extracted twice with ethyl acetate. The organic layer was dried and concentrated under vacuum before purified by flash chromatography (eluent: cyclohexane to cyclohexane/EtOAc 8/2) to yield a mixture of both isomer **8m** and **9m** (86 mg, 81 % yield) in a ratio of **8m/9m**: 89/11 in favor of the *trans* isomer. **8m** : ^{1}H NMR (400 MHz, C_6D_6) δ 7.87 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.98 (t, *J* = 5.3 Hz, 1H), 4.26 (m, 1H), 4.09 – 3.92 (m, 2H), 2.87 (s, 3H), 2.58 (s, 3H), 2.03 (d, *J* = 5.3 Hz, 2H), 1.67 (dd, *J* = 3.5, 14.4 Hz, 1H),1.61 (dd, *J* = 5.5, 14.4 Hz, 1H), 1.37 (d, *J* = 6.7 Hz, 3H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 155.7 , 150.8, 146.8, 123.3, 126.6, 98.2, 61.2, 53.7, 47.6, 47.2, 47.0, 37.6, 36.7, 20.6, 14.4;. HRMS $(M+H)^+$ ion by direct probe): calcd. for $C_{17}H_{25}N_2O_6$ 353.1713, found 353.1699. **9m:** ^{1}H NMR (400 MHz, C_6D_6) δ 7.84 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 5.19 (dd, *J* = 6.6, 6.9 Hz, 1H), 4.43 (m, 1H), 4.09 – 3.92 (m, 2H), 2.98 (s, 3H), 2.79 (s, 3H), 2.01 (dd, *J* = 6.9, 14.1 Hz, 1H), 1.94 (dd, *J* = 6.6, 14.1 Hz, 1H), 1.79 (dd, *J* = 6.7, 14.2 Hz, 1H), 1.43 (dd, *J* = 5.9, 14.2 Hz, 1H), 1.16 (d, *J* = 6.7 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 155.7, 151.9, 146.8, 123.8, 126.9, 98.6, 61.5, 54.0, 48.2, 47.2, 47.0, 36.9, 34.0, 23.0, 14.4.

(6*R*,2*S*)-ethyl-4,4-dimethoxy-6-methyl-2-(pyridin-3-yl)piperidine-1-carboxylate **8k** and (6*R*,2*R*)-ethyl-4,4-dimethoxy-6-methyl-2-(pyridin-3-yl)piperidine-1-carboxylate **9k.** (yellow oil, starting from 0.8 mmol of **7i**, 0.20g, yield = 81 % in a ratio of **8k/9k**: 85/15 in favor of the *trans* isomer. **8k**):

8k : ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (m, 1H), 8.38 (d, *J* = 4.5 Hz, 1H), 7.44 (d, *J* = 7.3 Hz, 1H), 7.16 (dd, *J* = 7.3, 4.5 Hz, 1H), 5.09 (t, *J* = 5.3 Hz, 1H), 4.26 (m, 1H), 4.06 – 3.94 (m, 2H), 3.11 (s, 3H), 2.85 (s, 3H), 2.35 (dd, *J* = 14.4, 5.3 Hz, 1H), 2.29 (dd, *J* = 14.4, 5.3 Hz, 1H), 1.88 (dd, *J* = 14.4, 5.3 Hz, 1H), 1.82 (dd, *J* = 14.4, 5.5 Hz, 1H), 1.32 (d, *J* = 6.8 Hz, 3H), 1.04 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 147.7, 147.5, 137.9, 133.5, 122.9, 98.2, 61.3, 51.7, 47.8, 47.6, 46.8, 37.3, 36.6, 20.6, 14.4.

9k :^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (m, 1H), 8.37 (d, *J* = 4.5 Hz, 1H), 7.55 (d, *J* = 7.3 Hz, 1H), 7.18 (dd, *J* = 7.3, 4.5 Hz, 1H), 5.16 (dd, *J* = 7.1, 6.4 Hz, 1H), 4.35 (m, 1H), 4.06 – 3.94 (m, 2H), 3.16 (s, 3H), 3.05 (s, 3H), 2.27 (m, 1H), 2.15 (dd, *J* = 14.6, 6.4 Hz, 1H), 2.00 (dd, *J* = 14.4, 6.9 Hz,1H), 1.66 (dd, *J* = 14.4, 5.5 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.04 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 147.4, 147.9, 138.1, 133.8, 123.1, 98.4, 61.5, 52.3, 47.9, 47.6, 47.3, 37.4, 36.7, 22.9, 14.4; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{16}H_{24}N_2O_4Na$ 331.1634, found 331.1634.

(2*S*,6*R*)-ethyl-4,4-dimethoxy-6-propyl-2-[(4-nitrophenyl)]piperidine-1-carboxylate **8l** and **9l.** (yellow oil, starting from 0.6 mmol of **7r**, 0.16g, yield = 71 % in a ratio of **8l/9l**: 83/17 in favor of the *trans* isomer. **8l**).

8l : ^{1}H NMR (400 MHz, C_6D_6) δ 7.83 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.87 (t, *J* = 5.4 Hz, 1H), 3.99 (m, 1H), 4.09 – 3.92 (q, *J* = 7.1 Hz, 2H), 2.82 (s, 3H), 2.56 (s, 3H), 1.95 (d, *J* = 5.4 Hz, 2H), 1.78 (dd, *J* = 14.6, 4.0 Hz, 1H), 1.58 (m, 1H), 1.51 (dd, *J* = 14.6, 5.3 Hz, 1H), 1.37 – 1.25 (m, 3H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.81 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 155.9, 150.5, 146.8, 126.7, 123.2, 98.7, 61.2, 53.6, 52.0, 47.4, 47.0, 37.0, 36.4, 34.1, 20.6, 14.5, 14.1; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{19}H_{28}N_2O_6Na$ 403.1845, found 403.1831

(2*S*,6*R*)-ethyl-4,4-dimethoxy-6-methyl-2-[(4-nitrophenyl)]piperidine-1-carboxylate **8m** and (2*R*,6*R*)-ethyl-4,4-dimethoxy-6-methyl-2-[(4-nitrophenyl)]piperidine-1-carboxylate **9m.** (yellow oil, starting from 1.0 mmol of **7d**, 0.28g, yield = 80 % in a ratio of **8m/9m**: 89/11 in favor of the *trans* isomer. **8m**)

8m : ^{1}H NMR (400 MHz, C_6D_6) δ 7.87 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.98 (t, *J* = 5.3 Hz, 1H), 4.26 (m, 1H), 4.09 – 3.92 (m, 2H), 2.87 (s, 3H), 2.58 (s, 3H), 2.03 (d, *J* = 5.3 Hz, 2H), 1.67 (dd, *J* = 14.4, 3.5 Hz, 1H),1.61 (dd, *J* = 14.4, 5.5 Hz, 1H), 1.37 (d, *J* = 6.7 Hz, 3H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 155.7, 150.8, 146.8, 123.3, 126.6, 98.2, 61.2, 53.7, 47.6, 47.2, 47.0, 37.6, 36.7, 20.6, 14.4.

9m : ^{1}H NMR (400 MHz, C_6D_6) δ 7.84 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 5.19 (dd, *J* = 6.9, 6.6 Hz, 1H), 4.43 (m, 1H), 4.09 – 3.92 (m, 2H), 2.98 (s, 3H), 2.79 (s, 3H), 2.01 (dd, *J*

= 14.1, 6.9 Hz, 1H), 1.94 (dd, *J* = 14.1, 6.6 Hz, 1H), 1.79 (dd, *J* = 14.2, 6.7 Hz, 1H), 1.43 (dd, *J* = 14.2, 5.9 Hz, 1H), 1.16 (d, *J* = 6.7 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 155.7, 151.9, 146.8, 123.8, 126.9, 98.6, 61.5, 54.0, 48.2, 47.2, 47.0, 36.9, 34.0, 23.0, 14.4; HRMS $(M+H)^+$ ion by direct probe: calcd. for $C_{17}H_{25}N_2O_6$ 353.1713, found 353.1699.

(2*S*,6*R*)-ethyl-4,4-dimethoxy-6-methyl-2-[(3-nitrophenyl)]piperidine-1-carboxylate **8n** and (2*R*,6*R*)-ethyl-4,4-dimethoxy-6-methyl-2-[(3-nitrophenyl)]piperidine-1-carboxylate **9n.** (yellow oil, starting from 1.0 mmol of **7c**, 0.25g, yield = 71 % in a ratio of **8n**/**9n**: 40/60 in favor of the *cis* isomer. **9n**)

8n : ^{1}H NMR (400 MHz, C_6D_6) δ 8.21 (m, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 6.91 (dd, *J* = 8.0, 7.8 Hz, 1H), 4.98 (dd, *J* = 5.3, 4.5 Hz, 1H), 4.26 (m, 1H), 4.18 – 4.10 (m, 2H), 2.96 (s, 3H), 2.71 (s, 3H), 2.18 (dd, *J* = 14.4, 4.5 Hz, 1H), 2.13 (dd, *J* = 14.4, 5.3 Hz, 1H), 1.67 (dd, *J* = 14.4, 4.0 Hz, 1H), 1.73 (dd, *J* = 14.4, 4.8 Hz, 1H), 1.47 (d, *J* = 6.8 Hz, 3H), 1.02 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 155.8, 148.7, 145.6, 131.6, 128.8, 121.3, 121.1, 98.2, 61.2, 53.5, 47.5, 47.2, 47.0, 37.4, 36.8, 20.6, 14.5.

9n : ^{1}H NMR (400 MHz, C_6D_6) δ 8.40 (m, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 6.91 (dd, *J* = 8.0, 7.8 Hz, 1H), 5.40 (dd, *J* = 6.8, 6.6 Hz, 1H), 4.55 (qd, *J* = 6.8, 5.8 Hz, 1H), 4.13 – 4.04 (m, 2H), 3.02 (s, 3H), 2.90 (s, 3H), 2.19 (dd, *J* = 14.6, 6.8 Hz, 1H), 2.06 (ddd, *J* = 14.6, 6.6, 0.7 Hz, 1H), 1.90 (ddd, *J* = 14.1, 6.8, 0.7 Hz, 1H), 1.55 (dd, *J* = 14.4, 5.8 Hz, 1H), 1.29 (d, *J* = 6.8 Hz, 3H), 0.99 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 156.3, 148.7, 146.8, 132.2, 129.0, 121.5, 121.4, 98.6, 61.5, 54.0, 47.6, 47.6, 47.2, 37.4, 36.7, 23.0, 14.5; HRMS $(M+H)^+$ ion by direct probe): calcd. for $C_{17}H_{25}N_2O_6$ 353.1713, found 353.1710.

(2*S*,6*R*)-ethyl-4,4-dimethoxy-6-methyl-2-[(2-nitrophenyl)]piperidine-1-carboxylate **8o** and (2*R*,6*R*)-ethyl-4,4-dimethoxy-6-methyl-2-[(2-nitrophenyl)]piperidine-1-carboxylate **9o**. (yellow oil, starting from 1.0 mmol of **7b**, 0.23g, yield = 67 % in a ratio of **8o**/**9o**: 60/40 in favor of the *trans* isomer. **8o**)

8o : ^{1}H NMR (400 MHz, C_6D_6) δ 7.51 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.07 (td, *J* = 8.0, 1.0 Hz, 1H), 6.77 (ddd, *J* = 8.0, 7.8, 1.2 Hz, 1H), 5.59 (dd, *J* = 12.4, 5.3 Hz, 1H), 4.72 (qtd, *J* = 6.8, 4.5 Hz, 1H), 3.91 – 3.71 (m, 2H), 3.2 (s, 3H), 3.01 (s, 3H), 2.18 (ddd, *J* = 14.4, 5.3, 1.2 Hz, 1H), 2.80 (ddd, *J* = 14.4, 6.8, 1.2 Hz, 1H), 1.95 (dd, *J* = 14.4, 12.4 Hz, 1H),1.71 (dd, *J* = 14.4, 4.5 Hz, 1H), 1.52 (d, *J* = 6.8 Hz, 3H), 0.74 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 156.1, 149.6, 141.5, 132.6, 127.6, 126.9, 124.5, 98.4 , 61.2, 52.2, 47.9, 47.7, 47.0, 37.9, 36.9, 24.0, 13.9.

9o : ^{1}H NMR (400 MHz, C_6D_6) δ 7.55 (dd, *J*= 8.0, 1.2 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.03 (td, *J* = 8.0, 1.0 Hz, 1H), 6.76 (ddd, *J* = 8.0, 7.8, 1.2 Hz, 1H), 5.94 (dd, *J* = 6.6, 5.3 Hz, 1H), 4.55 (m, 1H), 4.02 – 3.84 (m, 2H), 3.00 (s, 3H), 2.79 (s, 3H), 2.40 (dd, *J* = 14.4, 5.3 Hz, 1H), 2.21 (dd, *J* = 14.4, 6.6 Hz, 1H), 1.86 (dd, *J* = 14.4, 5.5 Hz, 1H), 1.80 (dd, *J* = 14.4, 3.3 Hz, 1H), 1.47 (d, *J* = 6.8 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 156.0, 149.2, 139.3, 132.0, 127.8, 127.0, 123.8, 98.1, 61.1, 50.6, 48.5, 47.7, 47.4, 38.8, 37.4, 20.2, 14.3; HRMS $(M+H)^+$ ion by direct probe): calcd. for $C_{17}H_{25}N_2O_6$ 353.1713, found 353.1711.

(2*S*,6*R*)-ethyl-2-(4-bromophenyl)-4,4-dimethoxy-6-methylpiperidine-1-carboxylate **8p** and (2*R*,6*R*)-ethyl-2-(4-bromophenyl)-4,4-dimethoxy-6-methylpiperidine-1-carboxylate **9p**. (yellow oil, starting from 0.9 mmol of **7g**, 0.25g, yield = 73 % in a ratio of **8p**/**9p**: 33/67 in favor of the *cis* isomer. **9p**)

8p : ^{1}H NMR (400 MHz, C_6D_6) δ 7.13 (d, *J* = 8.3 Hz, 2H), 6.68 (d, *J* = 8.3 Hz, 2H), 4.91 (dd, *J* = 5.3, 4.5 Hz, 1H), 4.15 (m, 1H), 3.91 (qd, *J* = 7.1 Hz, 2H), 2.75 (s, 3H), 2.49 (s, 3H), 2.10 (dd, *J* = 14.4, 4.5 Hz, 1H), 2.03 (dd, *J* = 14.4, 5.3 Hz, 1H), 1.82 (dd, *J* = 14.4, 5.3 Hz, 1H), 1.78 (dd, *J* = 14.4, 3.8 Hz, 1H), 1.40 (d, *J* = 6.8 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 155.9, 142.5, 131.3, 128.0, 120.1, 98.5, 61.0, 53.5, 47.7, 47.5, 47.4, 37.5, 36.7, 20.6, 14.6.

9p : ^{1}H NMR (400 MHz, C_6D_6) δ 7.12 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 5.13 (t, *J* = 6.8 Hz, 1H), 4.32 (sex, *J* = 6.6 Hz, 1H), 3.88 (qd, *J* = 7.1 Hz, 2H), 2.79 (s, 3H), 2.69 (s, 3H), 2.09 (dd, *J* = 14.6, 6.8 Hz, 1H), 2.01 (ddd, *J* = 14.6, 6.8, 0.7 Hz, 1H), 1.82 (ddd, *J* = 14.1, 6.6, 0.7 Hz, 1H), 1.49 (dd, *J* = 14.1, 6.6 Hz, 1H), 1.18 (d, *J* = 6.6 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 156.5, 143.8, 131.5, 128.3, 120.5, 98.8, 61.3, 53.8, 47.2, 47.0, 37.6, 36.9, 23.0, 14.5; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{17}H_{24}NO_4BrNa$ 408.0786, found 408.0794

(2*S*,6*R*)-ethyl-2-(4-bromophenyl)-4,4-dimethoxy-6-methylpiperidine-1-carboxylate **8q** and (2*R*,6*R*)-ethyl-2-(4-bromophenyl)-4,4-dimethoxy-6-methylpiperidine-1-carboxylate **9q**. (yellow oil, starting from 0.9 mmol of **7f**, 0.26g, yield = 75 % in a ratio of **8q**/**9q**: 29/71 in favor of the *cis* isomer. **9q**)

8q : ^{1}H NMR (400 MHz, C_6D_6) δ 7.51 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.47 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.79 (t, *J* = 7.7 Hz, 1H), 5.58 (dd, *J* = 12.4, 5.1 Hz, 1H), 4.85 (qtd, *J* = 7.0, 3.7 Hz, 1H), 3.91-4.08 (m, 2H), 3.15 (s, 3H), 2.97 (s, 3H), 2.57 (dd, *J* = 14.3, 5.1 Hz, 1H), 2.11 (dd, *J* = 14.1, 7.5 Hz, 1H), 1.93 (dd, *J* = 14.3, 12.4 Hz, 1H), 1.72 (dd, *J* = 14.1, 3.7 Hz, 1H), 1.40 (d, *J* = 7,0 Hz, 3H), 0.83 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, C_6D_6) δ

156.8, 133.0, 129.7, 128.3, 127.9, 126.8, 98.6, 61.1, 56.0, 47.5, 47.4, 47.3, 39.0, 37.4, 24.1, 14.1.

9q : ^{1}H NMR (400 MHz, C_6D_6) δ 7.77 (d, *J* = 8.2 Hz, 1H), 7.46 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 6.76 (m, 1H), 5.56 (dd, *J* = 5.8, 5.4 Hz, 1H), 4.69 (m, 1H), 3.90 (m, 2H), 3.03 (s, 3H), 2.80 (s, 3H), 2.62 (dd, *J* = 14.5, 5.4 Hz, 1H), 2.33 (dd, *J* = 14.5, 5.8 Hz, 1H), 2.05 (dd, *J* = 14.6, 6.2 Hz, 1H), 1.89 (m, 1H), 1.57 (d, *J* = 6.9 Hz, 3H), 0.91 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 156.3, 133.1, 128.6, 128.3, 127.9, 127.2, 98.5, 60.9, 54.6, 48.2, 48.0, 47.0, 37.2, 36.2, 20.7, 14.4; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{17}H_{24}NO_4BrNa$ 408.0786, found 408.0790

(2*S*,6*R*)-ethyl-4,4-dimethoxy-6-methyl-2-[(3-nitro-5-chlorophenyl)]piperidine-1-carboxylate **8r** and (2*S*,6*R*)-ethyl-4,4-dimethoxy-6-methyl-2-[(3-nitro-5-chlorophenyl)]piperidine-1-carboxylate **9r**. (yellow oil, starting from 1.2 mmol of **7h**, 0.35g, yield = 76 % in a ratio of **8r/9r**: 56/43 in favor of the *trans* isomer. **8r**)

8r : ^{1}H NMR (400 MHz, C_6D_6) δ 7.60 (d, *J* = 8.6 Hz, 1H), 7.56 (d, *J* = 2.3 Hz, 1H), 6.60 (dd, *J* = 8.6, 2.3 Hz, 1H), 5.47 (dd, *J* = 12.1, 5.3 Hz, 1H), 4.49 (qtd, *J* = 6.8, 4.8 Hz, 1H), 3.77 – 3.58 (m, 2H), 3.03 (s, 3H), 2.87 (s, 3H), 2.59 (ddd, *J* = 14.4, 5.3, 1.5 Hz, 1H), 1.89 (ddd, *J* = 14.4, 6.8, 1.5 Hz, 1H), 1.75 (dd, *J* = 14.4, 12.1 Hz, 1H), 1.48 (dd, *J* = 14.4, 4.8 Hz, 1H), 1.32 (d, *J* = 6.8 Hz, 3H), 0.63 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 156.0, 147.7, 143.8, 139.0, 127.9, 127.2, 125.6, 98.2, 61.4, 52.5, 47.9, 48.5, 47.5, 38.6, 37.5, 19.2, 13.9.

9r : ^{1}H NMR (400 MHz, C_6D_6) δ 7.44 (d, *J* = 2.3 Hz, 1H), 6.6 (d, *J* = 8.6 Hz, 1H), 6.59 (dd, *J* = 8.6, 2.3 Hz, 1H), 5.70 (dd, *J* = 6.8, 5.3 Hz, 1H), 4.30 (m, 1H), 3.90 – 3.75 (m, 2H), 2.86 (s, 3H), 2.68 (s, 3H), 2.29 (dd, *J* = 14.4, 5.3 Hz, 1H), 1.96 (dd, *J* = 14.4, 6.8 Hz, 1H), 1.68 (dd, *J* = 14.4, 5.5 Hz, 1H), 1.64 (dd, *J* = 14.4, 3.3 Hz, 1H), 1.28 (d, *J* = 6.8 Hz, 3H), 0.78 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 156.0, 147.7, 141.7, 138.6, 129.7, 127.2, 126.2, 98.0, 61.3, 50.5, 47.7, 47.5, 47.1, 37.3, 36.9, 24.0, 14.3; HRMS $(M+H)^+$ ion by direct probe): calcd. for $C_{17}H_{24}ClN_2O_6$ 387.1323, found 387.1325.

(*2S,*6*R*)-ethyl-2-((*E*)-3'-ethoxy-3'-oxoprop-1'-enyl)-4,4-dimethoxy-6-methylpiperidine-1-carboxylate **8s**. (yellow oil, starting from 0.7 mmol of **7j**, 0.21g, yield = 93 % in a ratio of **8s/9s**: 90/10 in favor of the *trans* isomer. **8s**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (dd, *J* = 15.7, 5.3 Hz, 1H), 5.71 (dd, *J* = 15.7, 2.0 Hz, 1H), 4.60 (tdd, *J* = 5.3, 4.2, 2.0 Hz, 1H), 4.14 – 4.02 (m, 5H), 3.12 (s, 3H), 3.06 (s, 3H), 2.13 (dd, *J* = 14.2, 5.3 Hz, 1H), 2.06 (dd, *J* = 14.2, 4.2 Hz, 1H), 1.92 (dd, *J* = 14.4, 4.5 Hz, 1H), 1.83 (dd, *J* = 14.4, 3.3 Hz, 1H), 1.24-1.17 (m, 9H); ^{13}C NMR (101 MHz, C_6D_6) δ 166.1, 155.4, 149.4,

141.2, 98.2, 61.2, 60.1, 51.7, 47.3, 47.2, 47.0, 37.1, 36.8, 20.7, 14.7, 14.2; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{16}H_{27}NO_6Na$ 352.1736, found 352.1729

General procedure for the synthesis of piperidines 10/11

(7*R*,9*S*)-ethyl 7-methyl-9-phenyl-1,4-dithia-8-azaspiro[4.5]decane-8-carboxylate **10c** and (7*S*,9*S*)-ethyl 7-methyl-9-phenyl-1,4-dithia-8-azaspiro[4.5]decane-8-carboxylate **11c.**

To a solution of compound **7w** (100 mg, 0.38 mmol, 1 equiv.) were added successively, trimethyl orthoformate (0.21 ml, 1.90 mmol, 5 equiv.) and *p*-toluenesulphonic acid PTSA/H_2O (1.5 mg, 0.08 mmol, 0.2 equiv.). The reaction is followed by TLC and after 0.5 h; ethyl acetate was added to the crude mixture, quenched with a saturated solution of $NaHCO_3$ and extracted twice with ethyl acetate. Then the organic layer was dried and concentrated under vacuum. After ^{1}H NMR spectroscopy for identifying the product and measure the *d.e*, the crude mixture **8c/9c** (0.117 g, 0.38 mmol, ratio **8c/9c**: 44/56) was engaged in reaction without any purification. To a solution of **8c/9c** in dry CH_2Cl_2 (5 mL), were added successively, 1,2-ethandithiol (161 ml, 1.9 mmol, 5 equiv.) and BF_3:Et_2O (243 ml, 1.9 mmol, 5 equiv.) dropwise at 0 °C. After 2 hours at room temperature, the solution was quenched dropwise with a solution of NaOH at 0 °C and extracted three times with ethyl acetate. Then the organic layer was dried over Na_2SO_4 and concentrated under vacuum before beeing purified by flash chromatography (eluent: cyclohexane to cyclohexane/EtOAc 9/1) to give a mixture of both isomer **10c** and **11c** (0.088 g, 68%) was obtained (ratio **10c/11c** 44/56). HRMS-ESI (M + Na), *m/z* calcd. for $C_{17}H_{23}NO_2S_2Na$ 360.1068, found 360.1069. **10c :** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.12 (m, 5H), 5.26 (dd, *J* = 4.8, 5.0 Hz, 1H), 4.41 (m, 1H), 3.97 (q, *J* = 7.1 Hz, 2H), 3.14 – 3.01 (m, 4H), 2.80 (dd, *J* = 5.0, 14.9 Hz, 1H), 2.74 (dd, *J* = 4.8, 14.9 Hz, 1H), 2.51 (dd, *J* = 5.0, 14.9 Hz, 1H), 2.22 (dd, *J* = 4.3, 14.9 Hz, 1H), 1.43 (d, *J* = 7.1 Hz, 3H), 1.03 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2, 141.2, 128.2, 126.7, 125.9, 61.1, 61.0, 55.2, 48.6, 46.3, 46.0, 39.3, 39.2, 20.5, 14.5; **11c :** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.12 (m, 5H), 5.26 (dd, *J* = 7.8, 8.3, Hz, 1H), 4.41 (tdd, *J* = 7.0, 7.5, 6.8 Hz, 1H), 4.03 (q, *J* =7.1 Hz, 2H), 3.26 – 3.21 (m, 4H), 2.63 (ddd, *J* = 7.8, 14.6, 1.8 Hz, 1H), 2.57 (dd, *J* = 8.3, 14.6 Hz, 1H), 2.44 (ddd, *J* = 7.0, 14.4, 1.8 Hz, 1H), 2.03 (dd, *J* = 7.5, 14.4 Hz, 1H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.06 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 143.7, 128.3, 126.6, 125.9, 62.4, 61.4, 55.7, 48.2, 46.2, 45.5, 39.2, 39.1, 23.5, 14.5.

(7*R*,9*S*)-7-methyl-9-phenyl-1,4-dithia-8-azaspiro[4.5]decane **10a** (yellow oil, starting from 0.8 mmol of **7a**, 0.15g, yield = 68 % in a ratio of **10a/11a**: 86/14 in favor of the *trans* isomer. **10a**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.25 (m, 5H), 4.18 (dd, *J* = 8.8, 3.4 Hz, 1H), 3.47 (m, 1H), 3.35-3.10 (m, 4H), 2.38 (ddd, *J* = 13.7, 5.2 Hz, 1H), 2.28 (ddd, *J* = 13.4, 3.4, 1.6 Hz, 1H), 2.18 (dd, *J* = 13.3, 8.8 Hz, 1H), 1.96 (ddd, *J* = 13.7, 4.0, 1.6 Hz, 1H), 1.52 (s, 1H), 1.30 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 128.4, 127.0, 126.7, 65.2, 53.8, 49.9, 48.1, 45.8, 39.6, 37.7, 20.8; HRMS $(M+H)^+$ ion by direct probe): calcd. for $C_{14}H_{19}NS_2$ 266.1037, found 266.1042

(7*R*,9*R*)-7-methyl-9-phenyl-1,4-dithia-8-azaspiro[4.5]decane **11a**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.25 (m, 5H), 3.85 (dd, *J* = 11.2, 2.3 Hz, 1H), 3.30-3.20 (m, 4H), 2.95 (m, 1H), 2.15 (dt, *J* = 13.1, 2.3 Hz, 1H), 2.05 (dt, *J* = 12.9, 2.3 Hz, 1H), 1.95 (dd, *J* = 13.3,11.2 Hz, 1H), 1.75 (dd, *J* = 12.9, 11.0 Hz, 1H), 1.08 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 127.4, 126.3, 125.8, 65.9, 59.9, 51.0, 49.4, 48.7, 38.2, 36.7, 21.3; HRMS $(M+H)^+$ ion by direct probe): calcd. for $C_{14}H_{19}NS_2$ 266.1037, found 266.1040.

(7*S*,9*R*)-ethyl-7-phenyl-9-propyl-1,4-dithia-8-azaspiro[4.5]decane-8-carboxylate **10f** and (7*R*,9*R*)-ethyl-7-phenyl-9-propyl-1,4-dithia-8-azaspiro[4.5]decane-8-carboxylate **11f.** (yellow oil, starting from 1.0 mmol of **7q**, 0.22g, yield = 60% (entry 6, Table 1) in a ratio of **10f/11f**: ≥ 95/5 in favor of the *trans* isomer. **10f**)

10f : ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.12 (m, 5H), 5.20 (dd, *J* = 9.3, 7.3 Hz, 1H), 4.29 (m, 1H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.28-3.20 (m, 4H), 2.56 (ddd, *J* = 14.4, 7.31, 1.8 Hz, 1H), 2.53 (dd, *J* = 14.4, 9.3 Hz, 1H), 2.50 (ddd, *J* = 14.1, 8.4, 1.8 Hz, 1H), 2.11 (dd, *J* = 14.1, 5.8 Hz, 1H), 1.67 (m, 1H), 1.42-1.21 (m, 3 H), 1.04 (t, *J* = 6.9 Hz, 3H), 0.82 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 143.8, 128.2, 126.6, 125.9, 62.4, 61.4, 55.8, 52.1, 45.9, 44.2, 39.2, 39.1, 19.7, 14.4, 13.8.

11f : ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.12 (m, 5H), 5.09 (dd, *J* = 5.5, 5.2 Hz, 1H), 4.04-3.95 (m, 3H), 3.17-3.03 (m, 4H), 2.75 (dd, *J* = 14.6, 5.2 Hz, 1H), 2.68 (dd, *J* = 14.6, 5.5 Hz, 1H), 2.36 (dd, *J* = 14.8, 4.6 Hz, 1H), 2.32 (dd, *J* = 14.8, 4.8 Hz, 1H), 1.85 (m, 1H), 1.42-1.21 (m, 3 H), 1.00 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 156.1, 141.9, 128.4, 126.8, 126.2, 62.3, 61.0, 55.8, 53.5, 45.9, 43.6, 40.7, 36.1, 20.3, 14.2, 13.9; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{19}H_{27}NO_2S_2Na$ 388.1381, found 388.1377.

(7*R*,9*S*)-ethyl 7-octyl-9-phenyl-1,4-dithia-8-azaspiro[4.5]decane-8-carboxylate **10h** and (7*R*,9*R*)-ethyl 7-octyl-9-phenyl-1,4-dithia-8-azaspiro[4.5]decane-8-carboxylate **11h.** (yellow oil, starting from 0.8 mmol of **7s**, 0.23g, yield = 65 % (entry 8, Table 1) in a ratio of **10h/11h**: 62/38 in favor of the *trans* isomer. **10h**)

10h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.12 (m, 5H), 5.20 (dd, *J* = 9.1, 7.3 Hz, 1H), 4.27 (m, 1H), 4.00 (q, *J* = 7.1 Hz, 2H), 3.28-3.20 (m, 4H), 2.56 (ddd, *J* = 14.4, 7.3, 1.5 Hz, 1H), 2.50

(dd, *J* = 14.4, 9.3 Hz, 1H), 2.49 (ddd, *J* = 14.1, 8.8, 1.5 Hz, 1H), 2.09 (dd, *J* = 14.1, 5.5 Hz, 1H), 1.67 (m, 1H), 1.38-1.11 (m, 15 H), 1.04 (t, *J* = 7.1 Hz, 3H), 0.80 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 143.8, 128.2, 126.6, 126.0, 62.5, 61.4, 55.8, 52.4, 45.9, 44.3, 39.2, 39.1, 38.0, 31.8, 29.5, 29.4, 26.5, 22.7, 14.5, 14.1.

11h : ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.12 (m, 5H), 5.09 (t, *J* = 5.1 Hz, 1H), 4.15 (m, 1H), 3.96 (q, *J* = 7.1 Hz, 2H), 3.17-3.02 (m, 4H), 2.76 (dd, *J* = 14.6, 5.1 Hz, 1H), 2.69 (dd, *J* = 14.6, 5.1 Hz, 1H), 2.36 (dd, *J* = 14.8, 5.1 Hz, 1H), 2.32 (dd, *J* = 14.8, 4.2 Hz, 1H), 1.85 (m, 1H), 1.76-1.01 (m, 15 H), 1.08 (t, *J* = 7.1 Hz, 3H), 0.82 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 128.4, 126.8, 126.2, 62.3, 61.0, 55.8, 53.5, 45.9, 43.6, 40.7, 37.9, 36.1, 32.0, 29.4, 29.6, 26.3, 22.6, 14.6, 14.0; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{24}H_{37}NO_2S_2Na$ 458.2163, found 458.2165.

(7*S*,9*S*)-ethyl-7,9-diphenyl-1,4-dithia-8-azaspiro[4.5]decane-8-carboxylate **10j.** (yellow oil, starting from 0.6 mmol of **7v**, 0.16g, yield = 65 % in a ratio of **10j/11j**: ≥ 96/4 in favor of the *trans* isomer. **10j**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.11 (m, 10H), 5.22 (dd, *J* = 8.6, 6.3 Hz, 2H), 3.91 (q, *J* = 7.1 Hz, 2H), 3.31-3.23 (m, 4H), 2.64 (dd, *J* = 14.4, 8.6 Hz, 2H), 2.52 (dd, *J* = 14.4, 6.3 Hz, 2H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6, 143.6, 128.2, 126.8, 126.7, 62.4, 61.5, 57.5, 46.0, 39.5, 39.0, 14.1; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{22}H_{25}NO_2S_2Na$ 422.1224, found 422.1225.

(9*R*,7*S*)-ethyl-9-methyl-7-(pyridin-3-yl)-1,4-dithia-8-azaspiro[4.5]decane-8-carboxylate **10k.** (yellow oil, yield = 48 % in a ratio of **10k/11k**: 85/15 in favor of the *trans* isomer. **10k**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (m, 1H), 8.42 (d, *J* = 4.5 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.21(m, 1H), 5.13 (t, *J* = 4.9 Hz, 1H), 4.26 (m, 1H), 4.07 – 3.93 (m, 2H), 3.30 – 3.01 (m, 4H), 2.78 (dd, *J* = 15.0, 4.9 Hz, 1H), 2.69 (dd, *J* = 15.0, 4.9 Hz, 1H), 2.44 (dd, *J* = 15.0, 5.1 Hz, 1H), 2.24 (dd, *J* = 15.1, 3.8 Hz, 1H), 1.42 (d, *J* = 6.9 Hz, 3H), 1.05 (t, *J* = 6.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 146.7, 146.6, 136.6, 122.1, 60.4, 59.8, 52.4, 47.7, 45.3, 44.9, 38.6, 38.0, 19.4, 13.4; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{16}H_{22}N_2O_2S_2Na$ 361.1020, found 361.1022.

(7*R*,9*R*)-ethyl-7-methyl-9-propyl-1,4-dithia-8-azaspiro[4.5]decane-8-carboxylate **10v** (yellow oil, starting from 0.9 mmol of **7l**, 0.20g, yield = 73 % in a ratio of **10v/11v**: 80/20 in favor of the *trans* isomer. **10v**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 - 3.96 (m, 2H), 3.93 (qdd, *J* = 7.0, 5.1, 4.8 Hz, 1H), 3.85 (m, 1H), 3.32-3.13 (m, 4H), 2.39 (dd, *J* = 14.7, 4.8 Hz, 1H), 2.35 (dd, *J* = 14.9, 4.8 Hz, 1H), 2.31 (dd, *J* = 14.9, 4.3 Hz, 1H), 2.17 (dd, *J* = 14.7, 5.1 Hz, 1H), 1.69 (m, 1H), 1.55 (m, 1H),

1.37 (m, 1H), 1.29 (d, *J* = 7.0 Hz, 3H), 1.25 (m, 1H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 61.7, 60.8, 52.4, 47.9, 46.7, 42.9, 39.4, 39.1, 35.5, 20.4, 19.8, 14.6, 13.8; HRMS $(M+H)^+$ ion by direct probe): calcd. for $C_{14}H_{26}NO_2S_2$ 304.1405, found 304.1394.

(7*R*,9*S*)-ethyl-7-methyl-9-propyl-1,4-dithia-8-azaspiro[4.5]decane-8-carboxylate **11v**

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (m, 1H), 4.26 (m, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.25-3.13 (m, 4H), 2.45 (ddd, *J* = 13.9, 9.1, 1.8 Hz, 1H), 2.35 (ddd, *J* = 13.6, 8.1, 1.8 Hz, 1H), 1.98 (dd, *J* = 13.9, 7.5 Hz, 1H), 1.95 (dd, *J* = 13.6, 7.3 Hz, 1H), 2.18-1.45 (m, 2H), 1.55 (m, 2H), 1.37-1.23 (m, 2H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.98 (t, *J* = 7.1 Hz, 3H), 0.84 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 61.9, 61.2, 52.4, 50.5, 47.6, 45.5, 39.4, 39.0, 35.5, 22.5, 19.6, 14.7, 13.9; HRMS $(M+H)^+$ ion by direct probe): calcd. for $C_{14}H_{26}NO_2S_2$ 304.1405, found 304.1401.

(7*R*,9*R*)-ethyl-7-methyl-9-octyl-1,4-dithia-8-azaspiro[4.5]decane-8-carboxylate **10t**. (yellow oil, starting from 1.0 mmol of **7m**, 0.23g, yield = 62 % ; entry 5 table 5, in a ratio of **10t/11t**: 80/20 in favor of the *trans* isomer. **10t**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (qd, *J* = 7.1, 3.5 Hz, 2H), 3.92 (qdd, *J* = 6.8, 5.3, 4.8 Hz, 1H), 3.83 (m, 1H), 3.32-3.15 (m, 4H), 2.40 (dd, *J* = 14.6, 4.8 Hz, 1H), 2.36 (dd, *J* = 15.1, 5.0 Hz, 1H), 2.30 (dd, *J* = 15.1, 4.3 Hz, 1H), 2.17 (dd, *J* = 14.6, 5.3 Hz, 1H), 1.70 (m, 1H), 1.59 (m, 1H), 1.37 (m, 1H), 1.31 (d, *J* = 6.8 Hz, 3H), 1.16-1.29 (m, 14H), 0.81 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 61.6, 60.7, 52.6, 47.9, 46.6, 42.7, 39.3, 39.1, 33.2, 31.8, 29.4, 29.3, 29.2, 26.4, 22.6, 20.3, 14.6, 14.0; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{19}H_{35}NO_2S_2Na$ 396.2007, found 396.2005

(7*R*,*9S)*-ethyl-7-methyl-9-octyl-1,4-dithia-8-azaspiro[4.5]decane-8-carboxylate **11t**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (sex, *J* = 7.1 Hz, 1H), 4.24 (m, 1H), 4.10 (qd, *J* = 7.1, 4.5 Hz, 2H), 3.24-3.19 (m, 4H), 2.44 (ddd, *J* = 13.9, 4.5, 2.0 Hz, 1H), 2.35 (ddd, *J* = 7.1, 13.9, 2.0 Hz, 1H), 1.99 (dd, *J* = 13.9, 7.1 Hz, 1H), 1.96 (dd, *J* = 13.9, 7.1 Hz, 1H), 1.99-1.47 (m, 2H), 1.24-1.17 (m, 18H), 0.84 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 62.9, 61.2, 51.0, 47.5, 43.9, 38.9, 38.7, 38.3, 31.8, 29.5, 29.4, 29.2, 26.4, 22.6, 22.5, 14.7, 14.1; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{19}H_{35}NO_2S_2Na$ 396.2007, found 396.2003

(7*R*,9*R*)-ethyl-7-octyl-9-propyl-1,4-dithia-8-azaspiro[4.5]decane-8-carboxylate **10u**. (yellow oil, starting from 0.6 mmol of **7u**, 0.16g, yield = 68 % entry 1 table 5; in a ratio of **10u/11u**: 80/20 in favor of the *trans* isomer. **10u**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (qd, *J* = 7.1, 2.7 Hz, 2H), 3.74 (m, 2H), 3.30-3.15 (m, 4H), 2.62 (ddd, *J* = 14.6, 4.8 , 1.5 Hz, 2H), 2.19 (dd, *J* = 14.6, 5.6 Hz, 2H), 1.87-1.73 & 1.58-

1.45 (2*m, 4H), 1.37-1.13 (m, 17H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 62.9, 60.8, 53.0, 52.7, 44.0, 43.9, 39.1, 39.0, 35.2, 33.0, 31.8, 29.5, 29.4, 29.3, 26.6, 22.6, 19.8, 14.6, 14.1, 13.9; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{21}H_{39}NO_2S_2Na$ 424.2320, found 424.2327

(7*R*,9*S*)-ethyl-7-octyl-9-propyl-1,4-dithia-8-azaspiro[4.5]decane-8-carboxylate **11u**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29-4.19 (m, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.20 (s, 4H), 2.41 (dd, *J* = 13.9, 8.6 Hz, 2H), 1.94 (dd, *J* = 13.9, 6.1 Hz, 2H), 1.62-1.56 & 1.49-1.40 (2*m, 4H), 1.32-1.18 (m, 17H), 0.85 (t, *J* = 7.6 Hz, 3H), 0.81 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 63.1, 61.2, 51.4, 51.1, 44.1, 44.0, 40.1, 39.1, 38.6, 37.9, 31.8, 29.5, 29.4, 29.2, 26.4, 22.6, 19.6, 14.7, 14.1, 13.9; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{21}H_{39}NO_2S_2Na$ 424.2320, found 424.2323.

Synthesis of (-)-Solenopsine A from 7p

(7*R*,9*R*)-benzyl 7-methyl-9-undecyl-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate **8w**

To a solution of compound **7p** (400 mg, 1.07 mmol, 1 equiv.) were added successively, trimethyl orthoformate (0.587 ml, 5.36 mmol, 5 equiv.), ethylene glycol (0.300 ml, 5.36 mmol 5 equiv.) and *p*-toluenesulphonic acid (0.04 g, 0.21 mmol 0.2 equiv.). The reaction is followed by TLC and after 1 hour, ethyl acetate was added to the crude mixture which was quenched with a saturated solution of NaHCO3 and extracted twice with ethyl acetate. Then the organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude residue was purified by flash chromatography (eluent: cyclohexane/EtOAc 95/5 to cyclohexane/EtOAc 85 /15), to afford *trans* **8w** (0,32 g, 67 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 5.17 (d, *J* = 12.4 Hz, 1H), 5.09 (d, *J* = 12.4 Hz, 1H), 4.10 (m, 1H), 4.00–3.91 (m, 3H), 3.90–3.81 (m, 2H), 2.14 (dd, *J* = 14.8, 5.6 Hz, 1H), 2.05 (dd, *J* = 15.2, 5.6 Hz), 1.97 (dd, *J* = 14.8, 3.8 Hz, 1H), 1.81 (dd, *J* = 15.2, 4.1 Hz, 1H), 1.76–1.58 (m, 2H), 1.34 (d, *J* = 7.1 Hz, 3H), 1.37 – 1.22 (m, 16H), 0.88 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 137.1, 128.6, 128.0, 106.7, 66.9, 64.0, 63.9, 51.5, 46.6, 39.6, 35.9, 34.2, 32.1, 29.8, 29.7, 29.5, 26.8, 21.0, 14.3; HRMS-ESI (M + Na), *m/z* : calcd. for $C_{27}H_{44}NO_4$ 446.3270 found 446.3261.

(7*R*,9*R*)-7-methyl-9-undecyl-1,4-dithia-8-azaspiro[4.5]decane **10 w**

To a solution of **8w** (300 mg, 0.64 mmol, 1 equiv.) in dry CH_2Cl_2 (5 mL), were added successively, 1,2-ethanedithiol (0.268 ml, 3.2 mmol, 5 equiv.) and BF_3:Et_2O (0.406 ml, 3.2 mmol, 5 equiv.) dropwise at 0 °C. After 24 hours at room temperature, the solution was quenched with a solution of NaOH at 0 °C and extracted three times with CH_2Cl_2. Then the organic layer was dried and concentrated under vacuum before purification by flash

chromatography (eluent: cyclohexane to cyclohexane/EtOAc 70/30) to give *trans* **10w** (0,175 g, 76 %) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32–3.27 (m, 4H), 3.20 (m, 1H), 3.02 (m, 1H), 2.26 (dd, *J* = 13.4, 3.9 Hz, 1H), 2.22 (dd, *J* = 13.1, 2.6 Hz), 1.92 (dd, *J* = 13.4, 5.6 Hz, 1H), 1.82 (dd, *J* = 13.1, 6.7 Hz, 1H), 1.57–1.51 (m, 2H), 1.35 – 1.20 (m, 16H), 1.16 (d, *J* = 6.7 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 65.3, 51.6, 49.2, 46.2, 46.0, 39.1, 38.7, 34.6, 32.1, 29.8, 29.7, 29.5, 26.9, 22.8, 21.0, 14.3; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{19}H_{37}NNaS_2$ 366,2265 found 366,2257.

(2*R*,6*R*)-tert-butyl 2-methyl-6-undecylpiperidine-1-carboxylate **12**

To a stirred solution of dithioketal **10w** (0,140 g, 0.44 mmol, 1 equiv.) in THF (5 mL) was added successively, di-*tert*-butyl dicarbonate (0,191 g, 0.88 mmol, 2 equiv.) and DMAP (25 mg, 0.02 mmol, 0.05 equiv.) at 0°C. After 1 hour at room temperature the resulting solution mixture was washed with a solution of NH_4Cl and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The resulting oil was directly engaged in the following steps without further purification. Then to a solution of the crude oil in ethanol (5 mL) was added freshly prepared W_2 Raney nickel (ca ≈ 1 g). The resulting suspension was heated at reflux for 2 h then cooled to room temperature. The suspension was then filtered through Celite® and the filtrate concentrated under reduced pressure. The residue was dissolved in 1M aqueous NaOH and extracted with dichloromethane. The combined organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of the solvent followed by column chromatography (eluent: cyclohexane to cyclohexane/EtOAc 80/20 %) gave compound **12** (100 mg, 70%) as a colorless oil. Spectral data are identical with those reported.[48]

(-)-Solenopsine A

Trifluoroacetic acid (1 mL) was added to a solution of **12** (80 mg, 0.22 mmol) in CH_2Cl_2 (1 mL) and the reaction mixture was stirred at room temperature for 2 h. The mixture was evaporated and the residue was basified with 2N NaOH. The solution was extracted with CH_2Cl_2 three times. The extracts were dried with Na_2SO_4 and evaporated. The residue was purified with chromatography (eluent: $CHCl_3$/MeOH 5/1) to yield (-)-Solenopsine A (50 mg, 87 %) as an oil. $[\alpha]_D$ = –1.21 (c = 0.94, CH_3OH), litt.[49] $[\alpha]_D$ = –1.30 (c = 1.30, CH_3OH). Spectral data are identical with those reported.[48]

Synthesis of 241D from 7o

(2*R*,6*S*)-benzyl 4,4-dimethoxy-2-methyl-6-nonylpiperidine-1-carboxylate **9'x**

To compound **7o** (0.25 g, 0.67 mmol, 1 equiv.) were added successively trimethyl orthoformate (0.367 ml, 3.35 mmol, 5 equiv) and *p*-toluenesulphonic acid (127 mg, 0.67

mmol, 1 equiv.). After 1 hour, ethyl acetate was added to the crude mixture, quenched with a saturated solution of $NaHCO_3$ and extracted twice with ethyl acetate. Then the organic layer was dried and concentrated under *vacuum*. The crude oil mixture was separated by flash chromatography (eluent: cyclohexane/EtOAc 95/5 to cyclohexane/EtOAc 85/15) to afford pure *cis* isomer **9'x** as an oil (172 mg, 61 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.19 (m, 5H), 5.09 (d, *J* = 12.6 Hz, 1H), 5.05 (d, *J* = 12.6 Hz, 1H), 4.37 (quintd, *J* = 7.1, 3.7 Hz, 1H), 4.21 (qd, *J* = 7.1, 2.1 Hz, 1H), 3.11 (s, 6H), 1.87 (dt, *J* = 14.0, 2.1 Hz, 1H), 1.81 (ddd, *J* = 13.7, 3.7, 2.1 Hz, 1H), 1.73 (dd, *J* = 14.0, 7.2 Hz, 1H), 1.69 (dd, *J* = 13.7, 7.7 Hz, 1H), 1.61 (m, 2H), 1.23 (d, *J* = 7.1 Hz, 3H), 1.22 – 1.17 (m, 12H), 0.81 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 137.0, 128.7, 128.4, 127.9, 98.7, 67.0, 50.7, 47.9, 47.4, 46.3, 36.2, 35.7, 33.6, 31.9, 29.7, 29.6, 29.3, 27.2, 22.7, 21.5, 14.1; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{25}H_{41}NO_4Na$ 442.2933 found 442.2948.

(2*R*,6*S*)-benzyl 2-methyl-6-nonyl-4-oxopiperidine-1-carboxylate **13**

To a solution of **9'x** (0.150 g, 0.35 mmol, 1 equiv.) in CH_2Cl_2 (0.5 mL) was added slowly TFA/H_2O (1/1, 0.5 mL) at room temperature. After 1 hour the mixture was quenched with NaOH (1M) and extracted twice with CH_2Cl_2. Then the organic layer was dried and concentrated under vacuum. The yellow oil obtained, was filtered through a pad of silica and washed with ethyl acetate to furnish after evaporation of the solvent compound **13** as a yellow oil in a quantitative yield : ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.21 (m, 5H), 5.12 (d, *J* = 12.4 Hz, 1H), 5.08 (d, *J* = 12.4 Hz, 1H), 4.72 (m, 1H), 4.59 (m, 1H), 2.65 (dd, *J* = 14.9, 7.7 Hz, 1H), 2.60 (d, *J* = 14.6, 7.5 Hz, 1H), 2.27 (ddd, *J* = 14.9, 3.7, 1.6 Hz, 1H), 2.23 (ddd, *J* = 14.6, 4.2, 1.6 Hz, 1H), 1.59 – 1.35 (m, 2H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.26 – 1.10 (m, 12H), 0.81 (t, *J* = 6.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1, 155.6, 136.5, 128.5, 128.1, 128.0, 67.5, 53.1, 48.8, 45.5, 43.7, 36.9, 31.9, 29.5, 29.3, 29.3, 26.3, 22.7, 21.5, 14.1; HRMS-ESI (M + Na), *m/z*: calcd. for $C_{23}H_{35}NO_3Na$ 396.2515 found 396.2511

(2R,4S,6S)-2-methyl-6-nonylpiperidin-4-ol: (+)-alkaloid 241D

To a solution of **13** (0.135 g, 0.35 mmol 1 equiv.), in MeOH (5 mL) was added Pd/C (5 %, 15 mg) under H_2 atmosphere (1 atm.). After 24 h, the solution was filtered through a pad of Celite® and washed 3 times with MeOH. After concentration under vacuum, to the crude oil product $NaBH_4$ (13 mg, 0.35 mmol, 1 equiv.) was added slowly at 0 °C. After 15 min at room temperature, the solution was quenched with a solution of brine and concentrated under vacuum. The residue was then diluted with ethyl acetate and washed with H_2O. Then the organic layer was dried and concentrated under vacuum. The yellow oil obtained was purified by flash chromatography (eluent: EtOAc to EtOAc/MeOH 90/10) to give (+)-alkaloid 241D

71 mg, 84 % over two steps) as colorless needles of (+)-241D: mp 107-108°C; $[\alpha]_D$ = + 5.66 (c = 0.60 MeOH, 95 % *ee*), litt.[17] $[\alpha]_D$ = + 5.90 (c = 0.65 MeOH, ≥ 99 % *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (tt, *J* = 5.0, 11.2 Hz, 1H), 2.69 (m, 1H), 2.55 (m, 1H), 1.96 (dt, *J* = 11.2, 5.0, 2H), 1.65 – 1.31 (m, 3H), 1.30 – 1.13 (m, 1H), 0.97 (q, *J* = 11.2 Hz, 1H), 0.91 (q, *J* = 11.2 Hz, 1H), 0.87 (t, *J* = 7.0 Hz, 1H).

Associated content

Supporting Information

^{1}H NMR and ^{13}C NMR of **5** to **11** are described and copies of spectra are given. This materialis available free of charge via the Internet at http://pubs.acs.org.

Author information

Corresponding Author

*E-mail: yves.troin@ensccf.fr

Notes

The authors declare no competing financial interest.

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