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PAPER

One-pot reductive coupling of *N*-acylcarbamates with activated alkenes: application to the asymmetric synthesis of pyrrolo[1,2-*a*]azepin-5-one ring system and (−)-xenovenine†

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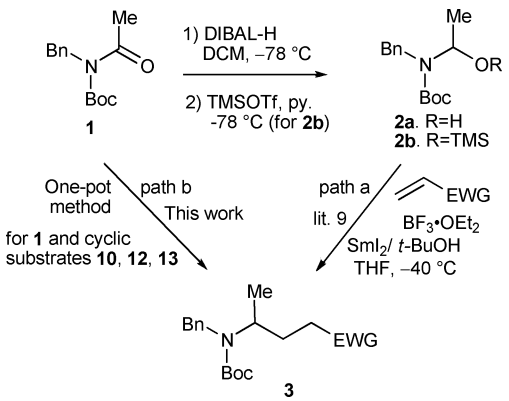
The one-pot reductive coupling of *N*-acylcarbamates with activated alkenes is described. The method is based on partial reduction of *N*-acylcarbamates with DIBAL-H, followed by *N*-acyliminium ion formation and SmI_2-mediated radical coupling with activated alkenes. Both acyclic and cyclic *N*-acylcarbamates can be used as stable substrates, and a range of activated alkenes serve as effective radical receptors. The reductive coupling of L-*N*-acylcarbamates **12**/**13** gave 2,5-disubstituted pyrrolidine derivatives in high *trans*-diastereoselectivities. The reductive coupling with penta-2,4-dienoate proceeded exclusively in a 1,6-addition fashion, producing a single non-conjugated *E*-isomer. On the basis of this method, a three-step construction of pyrrolo[1,2-*a*]azepin-5-one **16**, the skeleton of many stemona alkaloids and lehmizidine alkaloids, and a seven-step synthesis of (−)-xenovenine (pyrrolizidine *cis*-223H, *ent*-**6**), the unnatural enantiomer of the frog/ant venom alkaloid possessing potent inhibitory activity towards nAChR channel, were achieved starting from L-**12**.

Introduction

Efficiency is an important goal in organic synthesis.[1] Step-economic organic transformations,[2] such as one-pot and tandem reactions that combine at least two reactions in one pot,[3] constitute a valuable approach to that aim. In this context, methods based on the DIBAL-H reduction in tandem with other reactions in one pot have attracted much attention.[4–7] Among the reported one-pot DIBAL-H reduction/C–C bond formation methods, carboxylic acid esters[4] and nitriles[5] are mostly involved as substrates. To the best of our knowledge, no one-pot DIBAL-H reduction/radical-based C–C bond formation method has been reported so far.

In connection with our interest in the development of efficient α-amino C–C bond formation methods for the synthesis of alkaloids,[8] we recently reported a SmI_2-mediated cross-coupling of *N,O*- and *N,S*-acetals and cyclic hemiaminals with activated alkenes (Scheme 1, path a).[9] A drawback in that method is associated with the lability of the tertiary acyclic hemiaminals substrates (*e.g.* **2a**),[6c] which are prepared by partial reduction of the corresponding acyclic *N*-acylcarbamates and can only be used after protection of the hydroxyl group (*e.g.* as *O*-TMS *N,O*-acetal **2b**).[6,7] In addition, the coupling reaction of less reactive α,β-unsaturated compounds, such as acrylamides, gave low yields (*vide infra*). To develop a more efficient coupling method allowing the use of diverse and readily available substrates, a one-pot method consisting of partial reduction of *N*-acylcarbamates[10] and *in situ* SmI_2-mediated radical coupling with activated alkenes was envisioned (Scheme 1, path b). The establishment of such a method would pave the way for the synthesis of stemona[11] alkaloids, such as stemonine (**4**),[12] and ant venom/frog alkaloids, such as **5**–**8**[13–17] (Figure 1). We now report the results of this investigation, which include direct reductive coupling of *N*-acylcarbamates with



Scheme 1 Stepwise (path a) *versus* one-pot (path b) reductive coupling of *N*-acylcarbamate **1** with activated alkenes.

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† Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectra of all new compounds; NOESY and 1D GOESY spectra of compound **16**. See DOI: 10.1039/c1ob06697h

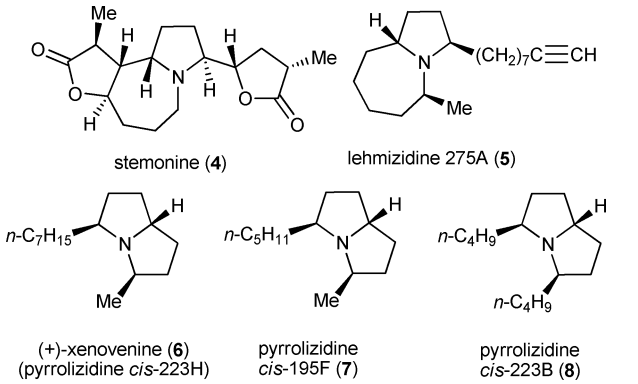


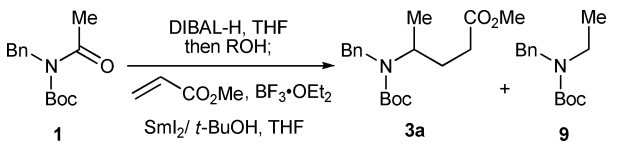
Fig. 1 Structures of stemonine and some ant venom/poison frog alkaloids.

activated alkenes and the application of this method to the construction of the pyrrolo[1,2-*a*]azepin-5-one core, skeleton of stemona and lehmizidine alkaloids [*e.g.* frog alkaloid 275A (**5**)], as well as to the asymmetric synthesis of the 3,5-disubstituted pyrrolizidine alkaloid (–)-xenovenine (pyrrolizidine *cis*-223H, *ent*-**6**).

Results and discussion

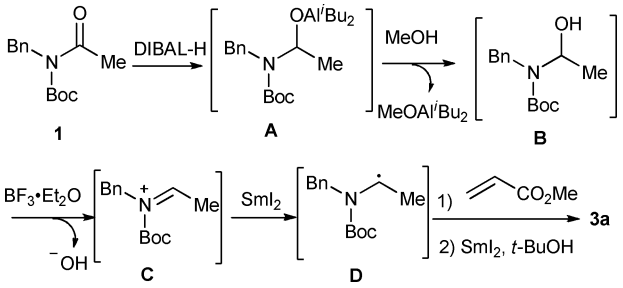
To test the feasibility of the envisioned idea, the reductive coupling of *N*-acylcarbamate **1**[6c] with methyl acrylate was first investigated. *N*-Acylcarbamate **1** was treated with DIBAL-H (1.5 equiv.) in THF at –78 °C for 30 minutes. The resulting mixture was warmed to –40 °C and then treated successively with methyl acrylate (2.0 equiv.), $BF_3{\cdot}OEt_2$ (2.0 equiv.) and a freshly prepared *t*-BuOH-containing (4.0 equiv.) SmI_2 solution in THF.[18–20] To our disappointment, neither the desired product **3a**, nor the reduction product **9** was obtained (Table 1, entry 1). The result was attributed to the failure in formation of the *N*-acyliminium ion intermediate[21] from the stable aluminum alkoxide of the hemiaminal intermediate (cf. Scheme 2). To tackle this problem, the use of alcohols as useful additives for the SmI_2-mediated coupling reactions[22] to decompose the complexes formed in the DIBAL-H reduction was envisaged. Because *t*-BuOH is a beneficial additive in SmI_2-mediated coupling reactions,[22c] it was chosen to quench the DIBAL-H reduction. Thus, after the reduction of *N*-acylcarbamate **1** with DIBAL-H in THF at –78 °C, 4 equiv. of *t*-BuOH was added. The mixture was then treated successively with methyl acrylate (2.0 equiv.), $BF_3{\cdot}OEt_2$ (2.0 equiv.) and a freshly prepared *t*-BuOH-containing SmI_2 solution (4.0 equiv.) in THF at –40 °C. The desired reductive coupling product **3a** was obtained in 60% yield, along with the reduced product **9** in 12% yield (Table 1, entry 2). A similar yield was obtained when running the reaction along at –40 °C (Table 1, entry 3). To further improve the yield, EtOH and MeOH were also investigated as additives (Table 1, entries 4–6). To our delight, when 1.6 equiv. of MeOH and 1.5 equiv. of DIBAL-H were used, the yield was improved to 86% and only a trace of the reduced product **9** was observed (Table 1, entry 6). Although theoretically only 2 equiv. of SmI_2 are needed for the reaction, as in the stepwise protocol,[9] if less than 4.0 equiv. of SmI_2 was used, the reaction was incomplete and the yield dropped. This may due to the high dilution of the reaction mediate (in our case, initial concentration: 0.047 M, final concentration: 0.016 M). In addition, activated alkenes may consume some SmI_2 as well.[23] As such, 2.0 equiv. of activated alkenes and 4.0 equiv. of SmI_2 were used.

Table 1 Optimization of the conditions for the one-pot reductive coupling of *N*-acylcarbamate **1** with methyl acrylate



Entry	ROH (equiv.)	*T* (°C)	% yield[a] of **3a**	% yield[a] of **9**
1	—	–78 to – 40	—[b]	—[b]
2	*t*-BuOH (4.0)	–78 to – 40	60	12
3	*t*-BuOH (4.0)	– 40	62	10
4	EtOH (4.0)	– 40	65	16
5	MeOH (4.0)	– 40	70	25
6	MeOH (1.6)	– 40	86	trace

[a] Isolated yield. [b] No product isolated.

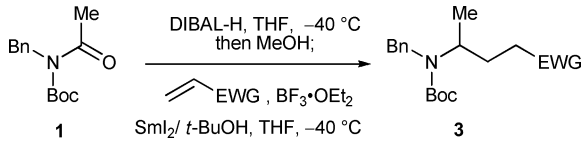


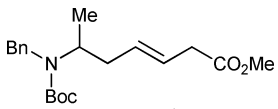
Scheme 2 A plausible mechanism for the one-pot reductive coupling reaction.

A plausible mechanism for the one-pot reductive cross-coupling of *N*-acylcarbamates with activated alkenes is depicted in Scheme 2. Partial reduction of *N*-acylcarbamate **1** with DIBAL-H formed the aluminum alkoxide of hemiaminal intermediate **A**, which was quenched with MeOH to give the hemiaminal **B**. In the presence of a Lewis acid, such as $BF_3{\cdot}OEt_2$, the *N*-acyliminium ion[21] **C** was generated, which was reduced by SmI_2 to give the α-acylaminoalkyl radical intermediate **D**. The radical intermediate **D** was trapped by an activated alkene to give another radical species that received an electron from a second SmI_2. Finally, quenching the samarium(III) salt with *t*-BuOH yielded the cross-coupling product **3a**.

With the optimal conditions for the direct reductive coupling of *N*-acylcarbamate **1** with methyl acrylate defined, the reactions with other activated alkenes were investigated. As can be seen from Table 2, the one-pot reductive coupling reactions of acyclic *N*-acylcarbamate **1** with a variety of activated alkenes underwent smoothly to afford the desired coupling products **3b**–**3f**. Compared with the stepwise method (path a in Scheme 1),[9b] the yield of the coupling reaction with *t*-butyl acrylate increased from 62% to 83% (Table 2, entry 2). Notably, the reductive coupling reactions of *N*-acylcarbamate **1** with less reactive acrylamides gave the desired coupling products **3c** and **3d** in excellent yields (Table 2, entries 3 and 4, both in 95% yield), while only 23% and 26% yields, respectively, were obtained from the coupling of *N*,*O*-acetal **2b** with acrylamides (cf. Scheme 1, path a).

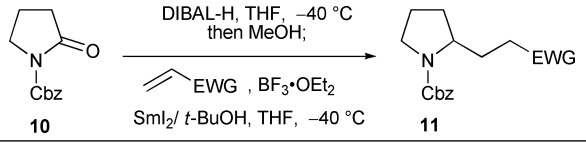
Table 2 One-pot reductive coupling of acyclic *N*-acylcarbamate **1** with activated alkenes

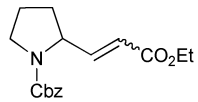
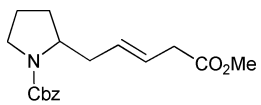


Entry	Activated alkenes	Coupling product (% yield)[a]
1	CO_2Me	**3a** (85)
2	CO_2Bu-*t*	**3b** (83) (62)[b]
3	CONHBn	**3c** (95) (23)[c]
4	$CONMe_2$	**3d** (95) (26)[c]
5	CO_2Me	 **3e** (73)[d]

[a] Isolated yield; [b] Yield obtained by the stepwise method from **1** (cf. ref. 9*b*); [c] Yield obtained by coupling with **2b**. [d] *E*-geometry determined by variable temperature NMR.

Table 3 One-pot reductive coupling reactions of cyclic *N*-acylcarbamate **10** with activated alkenes



Entry	Activated alkenes	Coupling product (% yield)[a]
1	CO_2Me	**11a** (78)
2	CO_2Bu-*t*	**11b** (64) (40)[b]
3	CONHBn	**11c** (69)
4	$CONMe_2$	**11d** (91)
5	CO_2Et	 **11e** (74) (*Z*: *E* = 42: 58)[c] (53) (*Z*: *E* = 42: 58)[b]
6	CO_2Me	 **11f** (73)[d]

[a] Isolated yield; [b] Yield obtained by the stepwise method from *N*-benzyloxycarbonyl-L-proline (cf. ref. 9*b*); [c] Determined by chromatographic separation; [d] *E*-geometry assumed by analogy with compound **3e**.

For the coupling with methyl penta-2,4-dienoate, the regioselectivity was a major concern. Although the 1,4-addition (Michael addition) of nucleophiles to electron-deficient olefins is popular in organic chemistry, the corresponding 1,6-addition to electron-deficient dienes has been less explored[24] and has recently attracted much attention.[25] In our case, it was found that when an *E*- and *Z*- stereoisomeric mixture of methyl penta-2,4-dienoate was subjected to the one-pot coupling conditions, the desired 1,6-addition product **3e** was obtained in 73% yield as a single non-conjugated *E*-isomer (Table 2, entry 5). The geometry of the olefin was established on the basis of the observed *J* value (15.4 Hz) in the ^{1}H NMR spectrum recorded at 70 °C. This kind of β,γ-unsaturated compounds can be exploited in further synthetic transformations, such as Michael addition,[26] Diels–Alder[27] reaction and so on.[28]

We next investigated the one-pot reductive coupling reaction of cyclic *N*-acylcarbamate **10**,[10a] and the results are compiled in Table 3. As can be seen from Table 3, the one-pot coupling of cyclic *N*-acylcarbamate **10** with activated alkenes gave similar results to those for the acyclic *N*-acylcarbamate **1** (Table 2). When ethyl propiolate was used,[29] the desired coupling product **11e** was obtained as a separable geometric mixture with a *Z*/*E* ratio of 42 : 58 (entry 5).

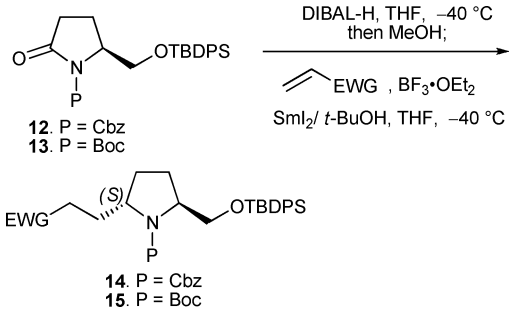
It is worth noting that compared with the stepwise method,[9b] which requires using the hemiaminal of *N*-acylcarbamate **10** as the substrate, the present method is not only more efficient, but also broader in scope. A reliable method for the preparation of the hemiaminal of *N*-acylcarbamate **10** was by oxidation of *N*-benzyloxycarbonyl-L-proline,[30] and that by partial reduction of the corresponding cyclic *N*-acylcarbamate may suffer from dehydration.[31] The direct use of *N*-acylcarbamates as the substrates overcome those limitations.

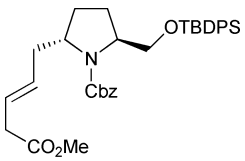
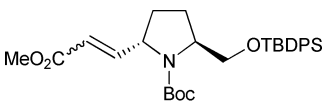
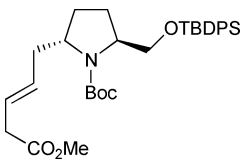
To further extend the scope of the method, the reductive coupling reactions of the known L-pyroglutamic acid-derived cyclic *N*-acylcarbamates **12**[32] and **13**[33] (Table 4) were investigated. As can be seen from Table 4, compared with the stepwise method,[9b] the one-pot method afforded higher yields (entry 3, **15a**: 81% *vs* 68% and entry 4, **15b**: 92% *vs* 49%), while maintaining the same level of *trans*-diastereoselectivity.[9b]

Synthesis of pyrrolo[1,2-*a*]azepin-5-one 16

To demonstrate the synthetic value of the method, we undertook the synthesis of pyrrolo[1,2-*a*]azepin-5-one **16**,[34] the basic skeleton of many stemona alkaloids,[11] such as stemonine[12] (**4**) and lehmizidine 275A (**5**). The latter is an alkaloid isolated from skin extracts of the Colombian poison frog *Dendrobates lehmanni*.[14] Thus, compound **14b** was subjected to catalytic hydrogenation conditions to give the saturated and concomitantly *N*-deprotected product, which, without further purification, was heated with triethylamine in toluene at reflux to produce the desired lactam **16** in 70% yield over two steps (Scheme 3). The stereochemistry of **16** was confirmed by combined ^{1}H-^{1}H COSY, 2D NOESY and 1D GOESY experiments. From the NOESY spectrum, it was difficult to determine the stereochemistry of the lactam **16**. But from the 1D GOESY spectrum, it is easy to observe the NOE correlations of H_{9a} with H_{10} and $H_{10'}$. No correlation between H_{9a} and H_3 was observed. Thus the stereochemistry of **16** was established as *trans* (3*S*,9*aR*).

Table 4 One-pot reductive coupling of cyclic *N*-acylcarbamates **12**/**13** with activated alkenes

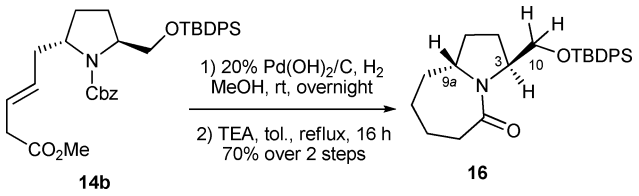


Entry	*N*-Acylcarbamate/ activated alkenes	Coupling product[a] (% yield)[b] (*trans*:*cis*)
1	**12**/ CO_2Me	**14a** (86) (85 : 15)[c]
2	**12**/ CO_2Me	 **14b** (77) (>99: 1)[c,g]
3	**13**/ CO_2Me	**15a** (81) (90 : 10)[c] (68) (91 : 9)[d]
4	**13**/ CO_2Bu-*t*	**15b** (92) (93 : 7)[c] (49) (92 : 8)[d]
5	**13**/ CONHBn	**15c** (74) (>99 : 1)[c]
6	**13**/ $CONMe_2$	**15d** (84) (90 : 10)[c]
7	**13**/ CO_2Et	 **15e** (91) (92: 8)[e] (*Z* : *E* = 35 : 65 for 2,5-*trans*-**15e**)[f]
8	**13**/ CO_2Me	 **15f** (86) (91: 9)[c,g]

[a] Only the major diastereomer is shown; [b] Isolated yield; [c] Determined by HPLC analysis; [d] Results of the stepwise method from **12**/**13** (cf. ref. 9*b*); [e] Determined by HPLC analysis after hydrogenation of the diastereomeric mixture. [f] Determined by ^{1}H NMR analysis; [g] *E*-geometry assumed by analogy with compound **3e**.

Asymmetric synthesis of (–)-xenovenine (pyrrolizidine *cis*-223H, *ent*-6)

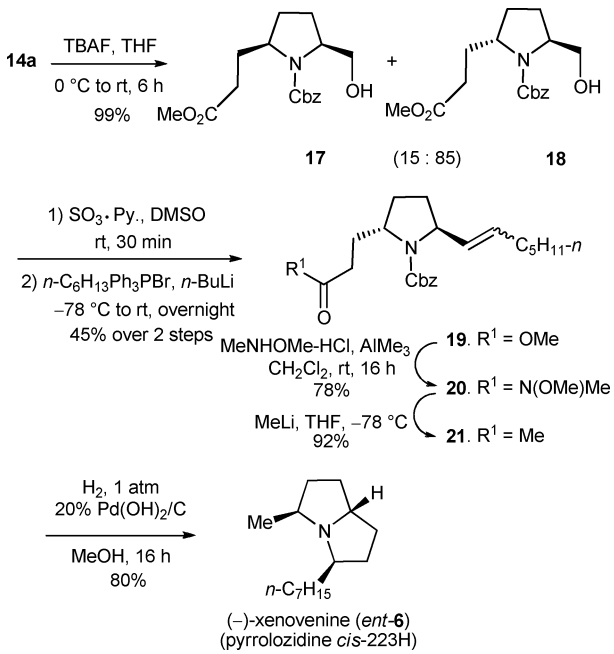
(5*Z*,8*E*)-3-Heptyl-5-methylpyrrolizidine (xenovenine, **6**) is the first 3,5-disubstituted pyrrolizidine alkaloid isolated from the cryptic thief ant *Solenopsis sp.* near *tenneseensis*.[35] This compound was later identified in anuran skin of a bufonid (*Melanophryniscus*) toad by J. W. Daly and named as *cis*-223H.[17] The alkaloids



Scheme 3 The synthesis of pyrrolo[1,2-*a*]azepin-5-one **16**.

from ants and frog skins are believed to have the same absolute configuration as 3*R*,5*S*,8*S*.[15b,c,36] To date, both enantiomers of xenovenine have been synthesized for several times.[37,38] Using the stepwise reduction-coupling method, we have previously developed a total synthesis of (+)-xenovenine (**6**) starting from L-pyroglutamic acid.[9b] In view of the high inhibitory activity towards nicotinic acetylcholine receptor (nAChR) channel of *torpedo californica* (IC_{50} 0.05 μM) exhibited by the unnatural enantiomer (–)-xenovenine (*ent*-**6**),[38a] we sought to develop a divergent enantioselective synthesis of (–)-xenovenine (*ent*-**6**) starting from *N*-L-acylcarbamate **12**, which was also readily available from L-pyroglutamic acid.

As shown in Table 4, the one-pot reductive coupling of *N*-L-acylcarbamate **12** with methyl acrylate gave diastereomeric mixture **14a**, which was treated with TBAF to give two separable desilylated products, *cis*-**17** and *trans*-**18** in 15% and 85% yield, respectively (Scheme 4). The major diastereomer **18** was subjected successively to Parikh-Doering oxidation[39] and Wittig reaction[37c,40] to produce olefin **19** in an overall yield of 45%. Compound **19** was converted to methyl ketone derivative **21** *via* Weinreb amide **20**.[41] Finally, in the presence of 20% $Pd(OH)_2$/C and under an atmosphere of H_2, pyrrolidine **21** was converted to (–)-xenovenine (*ent*-**6**) as the only observable diastereomer in 80% yield. The physical {$[\alpha]_D^{20}$ –10.5 (*c* 1.4, $CHCl_3$);[38a] $[\alpha]_D^{26}$ –10.93 (*c* 1.45, $CHCl_3$)} and spectral data of the synthetic compound (*ent*-**6**) match those reported.[38]



Scheme 4 Asymmetric synthesis of (–)-xenovenine (pyrrolizidine *cis*-223H, *ent*-**6**).

Conclusions

In summary, we developed a one-pot method for the direct reductive coupling of *N*-acylcarbamates with activated alkenes, which was based on the partial reduction with DIBAL-H, followed by *N*-acyliminium ion formation and SmI_2-mediated radical cross-coupling with activated alkenes. Compared with the stepwise approach that we developed previously, the one-pot method shows several advantages: (1) the scope of the method is greatly extended due to the direct use of both acyclic and cyclic *N*-acylcarbamates, which are both stable and readily available; (2) the overall efficiency is significantly improved compared with the stepwise one; (3) the one-pot method allows reaction with less reactive α,β-unsaturated compounds, such as acrylamides; (4) the coupling of pyroglutamic acid derived *N*-acylcarbamates **12**/**13** afforded high 2,5-*trans*-diastereoselectivities and that with *E*/*Z* stereomeric mixture of methyl penta-2,4-dienoate produced exclusively the 1,6-addition product as a non-conjugated *E*-isomer. The application of this method to **12** led to a three-step synthesis of pyrrolo[1,2-*a*]azepin-5-one **16**, the skeleton of many stemona alkaloids and lehmizidine alkaloids, in an overall yield of 54%. In addition, (–)-xenovenine (pyrrolizidine *cis*-223H, *ent*-**6**) was synthesized in seven steps with an overall yield of 18.9% from **12**.

Experimental section

General procedure for the one-pot reductive coupling of *N*-acylcarbamates with activated alkenes

To a solution of a *N*-acylcarbamate (0.5 mmol) in anhydride THF (10 mL) was added dropwise a solution of DIBAL-H (1 M in hexane, 0.75 mL, 0.75 mmol) at –40 °C. The reaction was stirred for 30 min and MeOH (32.4 μL, 0.8 mmol) was added. The resulting mixture was stirred for another 30 min, then an alkene substrate (1.0 mmol), $BF_3{\cdot}Et_2O$ (123 μL, 1.0 mmol) and a freshly prepared *t*-BuOH-containing SmI_2 (0.1 M in THF, 20 mL, 2.0 mmol)[9] were added successively. After being stirred at –40 °C for 10 min, the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL). The mixture was extracted with diethyl ether (15 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel (eluent: EtOAc/petroleum ether) to afford the desired coupling product.

Methyl 4-[benzyl(*t*-butoxycarbonyl)amino]pentanoate (3a)

Following the general procedure, the one-pot reaction of *N*-acylcarbamate **1** with methyl acrylate afforded **3a**[42] (85%) as a colorless oil. υ_{max}/cm^{-1} (film): 3029, 2975, 2921, 1739, 1689, 1453, 1165; δ_H (500 MHz, $CDCl_3$) 1.09 (3H, d, *J* 6.9, Me), 1.36 and 1.49 (9H, 2 s br, *t*-Bu), 1.66–1.80 (1H, m), 1.82–1.94 (1H, m), 2.08–2.38 (2H, m), 3.63 and 3.65 (3H, 2 s br, OMe), 3.76–4.45 (3H, m, NCH and OCH_2Ph), 7.16–7.34 (5H, m, Ph). δ_C (125 MHz, $CDCl_3$) 18.9 and 19.3, 28.2, 29.8, 30.9, 46.6 and 47.7, 51.0 and 52.1, 51.3, 79.6, 126.6, 127.4, 128.1, 139.7, 156.0, 173.5. HRMS [M + Na^+] calculated for $C_{18}H_{27}NO_4Na$, 344.1832; found: 344.1837.

t-Butyl 4-[benzyl(*t*-butoxycarbonyl)amino]pentanoate (3b)

Following the general procedure, the one-pot reaction of *N*-acylcarbamate **1** with *t*-butyl acrylate afforded **3b**[9b] (83%) as a colorless oil. The physical and spectral data are in agreement with those reported in ref. 9*b*.

t-Butyl benzyl(5-(benzylamino)-5-oxopentan-2-yl)carbamate (3c)

Following the general procedure, the one-pot reaction of *N*-acylcarbamate **1** with *N*-benzylacrylamide afforded **3c** (95%) as a colorless oil. υ_{max}/cm^{-1} (film): 3304, 3063, 2973, 2919, 1687, 1650, 1453, 1365, 1164, 1029; δ_H (500 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.9, Me), 1.34 and 1.48 (9H, 2 s, br, *t*-Bu), 1.68–1.92 (2H, m), 1.98–2.22 (2H, m), 3.78–4.62 (5H, m, NCH NCH_2Ph and OCH_2Ph), 6.46–6.64 (1H, br, NH), 7.08–7.52 (10H, m, Ph). δ_C (125 MHz, $CDCl_3$) 19.1, 28.2, 31.0, 33.6, 43.4, 46.0 and 47.3, 50.7 and 53.5, 79.9, 126.6, 127.2, 127.7, 128.2, 128.5, 138.4, 139.9, 156.3, 172.6. HRMS [M + K^+] calculated for $C_{19}H_{30}N_2O_3K$, 373.1888; found: 373.1891.

t-Butyl benzyl(5-(dimethylamino)-5-oxopentan-2-yl)carbamate (3d)

Following the general procedure, the one-pot reaction of *N*-acylcarbamate **1** with *N*,*N*-dimethylacrylamide afforded **3d** (95%) as a colorless oil. υ_{max}/cm^{-1} (film): 3032, 2974, 2931, 1686, 1650, 1407, 1365, 1166; δ_H (500 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.8, Me), 1.36 and 1.49 (9H, 2 s br, *t*-Bu), 1.70–1.82 (1H, m), 1.82–1.98 (1H, m), 2.02–2.28 (2H, m), 2.78–2.98 (6H, m, NMe_2), 3.72–4.62 (3H, m, NCH and OCH_2Ph), 7.12–7.38 (5H, m, Ph). δ_C (125 MHz, $CDCl_3$) 19.1, 28.2, 29.9, 30.1, 35.2, 36.9, 46.5 and 47.9, 51.5 and 52.7, 79.5, 126.7, 127.6, 128.1, 140.0, 155.7, 172.3. HRMS [M + Na^+] calculated for $C_{24}H_{32}N_2O_3Na$, 419.2305; found: 419.2309.

Methyl (*E*)-6-[benzyl(*t*-butoxycarbonyl)amino]hept-3-enoate (3e)

Following the general procedure, the one-pot reaction of *N*-acylcarbamate **1** with methyl penta-2,4-dienoate afforded **3e** (73%) as a colorless oil. υ_{max}/cm^{-1} (film): 3063, 3030, 2973, 2921, 1738, 1688, 1593, 1407, 1365, 1164, 1029; δ_H (500 MHz, $CDCl_3$) 1.05–1.16 (3H, m, Me), 1.36 and 1.49 (9H, 2 s br, *t*-Bu), 2.05–2.46 (2H, m), 2.80–3.10 (2H, m), 3.61–3.86 (4H, m, NCH and OMe), 4.18–4.46 (2H, m, OCH_2Ph), 5.30–5.65 (2H, m, HC═CH), 7.12–7.38 (5H, m, Ph). δ_H (500 MHz, DMSO-d_6 at 343K) 1.06 (3H, d, *J* 6.8, Me), 1.38 (9H, s, *t*-Bu), 2.10–2.18 (1H, m), 2.24–2.34 (1H, m), 3.00 (2H, d, *J* 6.2, COC**H**C═CH), 3.61 (3H, s, Me), 3.88–4.02 (1H, m, NCH), 4.29 (1H, d, *J* 16.0, OCH_2Ph), 4.33 (1H, d, *J* 16.0, OCH_2Ph), 5.42 (1H, td, *J* 6.2, 15.4, HC═CH), 5.47 (1H, td, *J* 6.2, 15.4, HC═CH), 7.12–7.38 (5H, m, Ph). δ_C (125 MHz, $CDCl_3$) 18.4, 28.4, 37.8, 38.0, 44.5, 51.4, 51.6, 79.5, 121.5, 122.8, 123.9, 126.6, 127.0, 127.2, 127.4, 128.1, 128.5, 129.6, 131.4, 149.0, 166.8, 172.2 and 172.6. HRMS [M + Na^+] calculated for $C_{20}H_{29}NO_4Na$, 370.1989; found: 370.1988.

Benzyl 2-(3-methoxy-3-oxopropyl)pyrrolidine-1-carboxylate (11a)

Following the general procedure, the one-pot reaction of *N*-acylcarbamate **10** with methyl acrylate afforded **11a** (78%) as a colorless oil. υ_{max}/cm^{-1} (film): 3030, 2953, 1738, 1698, 1587, 1410, 1357, 1097, 1028; δ_H (500 MHz, $CDCl_3$) 1.62–1.78 (2H, m),

1.80–2.14 (4H, m), 2.24–2.46 (2H, m, $COCH_2$), 3.32–3.55 (2H, m, NCH_2), 3.60 and 3.68 (3H, 2 s, OMe), 3.86–3.98 (1H, m, NCH), 5.02–5.24 (2H, m, OCH_2Ph), 7.22–7.35 (5H, m, Ph). δ_C (125 MHz, $CDCl_3$) 23.0 and 23.7, 29.5 and 29.8, 30.0 and 30.7, 30.9 and 31.1, 46.3 and 46.6, 51.5, 56.5 and 57.2, 66.6 and 66.8, 127.8, 127.9, 128.4, 137.1, 155.2, 173.9. HRMS [M + Na^+] calculated for $C_{16}H_{21}NO_4Na$, 314.1363; found: 314.1361.

Benzyl 2-(3-*t*-butoxy-3-oxopropyl)pyrrolidine-1-carboxylate (11b)

Following the general procedure, the one-pot reaction of *N*-acylcarbamate **10** with *t*-butyl acrylate afforded **11b**[9b] (64%) as a colorless oil. The physical and spectral data are in agreement with those reported in ref. 9*b*.

Benzyl 2-(3-(benzylamino)-3-oxopropyl)pyrrolidine-1-carboxylate (11c)

Following the general procedure, the one-pot reaction of *N*-acylcarbamate **10** with *N*-benzylacrylamide afforded **11c** (69%) as a white solid. mp 99–101 °C. υ_{max}/cm^{-1} (film): 3291, 3030, 2968, 1650, 1588, 1413, 1095, 1029; δ_H (500 MHz, $CDCl_3$) 1.62–2.02 (6H, m), 2.08–2.48 (2H, m, $COCH_2$), 3.32–3.62 (2H, m, NCH_2), 3.82–4.02 (1H, m, NCH), 4.22–4.58 (2H, m, NCH_2Ph), 4.93–5.23 (2H, m, OCH_2Ph), 5.50 (1H, br, NH), 7.22–7.42 (10H, m, Ph). δ_C (125 MHz, $CDCl_3$) 23.6, 30.6, 31.0, 33.3 and 33.6, 43.5, 46.2, 57.1, 66.8, 127.2, 127.5, 127.8, 127.9, 128.2, 128.4, 128.5, 136.8, 138.6, 155.8, 172.7. HRMS [M + Na^+] calculated for $C_{22}H_{26}N_2O_3Na$, 389.1836; found: 389.1840.

Benzyl 2-(3-(dimethylamino)-3-oxopropyl)pyrrolidine-1-carboxylate (11d)

Following the general procedure, the one-pot reaction of *N*-acylcarbamate **10** with *N,N*-dimethylacrylamide afforded **11d** (91%) as a colorless oil. υ_{max}/cm^{-1} (film): 3030, 2962, 2916, 1695, 1644, 1410, 1261, 1095, 1019; δ_H (500 MHz, $CDCl_3$) 1.64–2.02 (6H, m), 2.16–2.46 (2H, m, $COCH_2$), 2.64–3.02 (6H, m, NMe_2), 3.32–3.58 (2H, m, NCH_2), 3.86–4.02 (1H, m, NCH), 5.02–5.20 (2H, m, OCH_2Ph), 7.24–7.42 (5H, m, Ph). δ_C (125 MHz, $CDCl_3$) 22.9 and 23.7, 30.0 and 30.3, 30.6 and 31.0, 35.3, 36.9, 37.2, 46.2 and 46.6, 56.9 and 57.5, 66.4 and 66.8, 127.6 and 127.8, 128.0, 128.4, 137.1, 155.2, 172.7. HRMS [M + Na^+] calculated for $C_{17}H_{24}N_2O_3Na$, 327.1679; found: 327.1671.

Benzyl 2-(3-ethoxy-3-oxoprop-1-enyl)pyrrolidine-1-carboxylate (11e)

Following the general procedure, the one-pot reaction of *N*-acylcarbamate **10** with ethyl propiolate afforded **11e**[9b] in 74% (*Z*/*E* = 42/58) yield as a colorless oil. The physical and spectral data are in agreement with those reported in ref. 9*b*.

(*E*)-1-(Benzyloxycarbonyl)-2-[4-(methyloxycarbonyl)but-2-enyl]pyrrolidine (11f)

Following the general procedure, the one-pot reaction of *N*-acylcarbamate **10** with methyl penta-2,4-dienoate afforded **11f** (73%) as a colorless oil. υ_{max}/cm^{-1} (film): 3030, 2951, 2921, 1738, 1698, 1587, 1410, 1356, 1099, 1029; δ_H (500 MHz, $CDCl_3$) 1.64–1.98 (4H, m), 2.04–2.24 (1H, m), 2.32–2.64 (1H, m), 2.94–3.10 (2H, m, $COCH_2$), 3.32–3.54 (2H, m, NCH_2), 3.66 (3H, s, OMe), 3.82–3.95 (1H, m, NCH), 5.06–5.24 (2H, m, OCH_2Ph), 5.38–5.64 (2H, m, CH=CH), 7.22–7.48 (5H, m, Ph). δ_C (125 MHz, $CDCl_3$) δ 22.8 and 23.6, 29.1 and 23.0, 36.5, 37.5 and 37.8, 46.4 and 46.8, 51.6, 56.7 and 57.2, 66.4 and 66.6, 124.4, 127.7, 128.4, 130.5 and 130.6, 137.1, 154.7, 172.2. HRMS [M + Na^+] calculated for $C_{18}H_{23}NO_4Na$, 340.1519; found: 340.1514.

(2*S*,5*S*/*R*)-1-(Benzyloxycarbonyl)-2-[(*t*-butyldiphenylsilyloxy) methyl]-5-[2-(methyloxycarbonyl)ethyl]pyrrolidine (14a)

Following the general procedure, the one-pot reaction of *N*-acylcarbamate **12** with methyl acrylate afforded **14a** (86%) as a colorless oil, dr = 85 : 15, determined by HPLC: Shim-pack VP-ODS (150 × 4.6), CH_3CN/H_2O 75 : 25, 1.5 mL min^{-1}, λ = 220 nm, t_1 = 23.6 min (15.0%), t_2 = 24.9 min (85.0%). υ_{max}/cm^{-1} (film): 3066, 2949, 2854, 1736, 1697, 1406; δ_H (500 MHz, $CDCl_3$) 1.02 and 1.04 (9H, 2 s br, *t*-Bu), 1.52–1.74 (2H, m), 1.91–2.42 (6H, m), 3.48 (0.5H, m, NCH), 3.60 and 3.65 (3H, 2 s, OMe), 3.72 (0.5H, m, NCH), 3.74–4.06 (3H, m, NCH and OCH_2), 4.89–5.15 (2H, m, OCH_2Ph), 7.07–7.15 (1H, m, Ph), 7.16–7.43 (10H, m, Ph), 7.58–7.68 (4H, m, Ph); δ_C (125 MHz, $CDCl_3$) 19.1 and 19.2, 25.7, 26.3, 26.7 and 26.8, 28.1, 29.4, 31.3 and 31.4, 51.4 and 51.5, 57.5, 58.1, 58.5, 59.0, 63.3, 64.0, 66.5 and 66.6 and 66.7, 127.5 and 127.6 and 127.7 and 127.8 and 127.8 and 127.9 and 128.0, 128.3 and 128.4, 129.5 and 129.6, 133.4 and 133.5 and 133.6, 135.4 and 135.5, 136.0 and 136.8, 154.1, 173.4 and 173.6. HRMS [M + H^+] calculated for $C_{33}H_{42}NO_5Si$, 560.2832; found: 560.2843.

(2*S*,5*S*/*R*)-1-(Benzyloxycarbonyl)-2-[(*t*-butyldiphenylsilyloxy) methyl]-5-[(*E*)-5-(methyloxycarbonyl) pent-2-enyl]pyrrolidine (14b)

Following the general procedure, the one-pot reaction of *N*-acylcarbamate **12** with methyl penta-2,4-dienoate afforded **14b** (77%) as a colorless oil, dr > 99 : 1, determined by HPLC: Shim-pack VP-ODS (150 × 4.6), CH_3CN/H_2O 75 : 25, 1.5 mL min^{-1}, λ = 220 nm, t_1 = 10.9 min (99.7%), t_2 = 16.7 min (0.3%). υ_{max}/cm^{-1} (film): 3029, 2917, 2856, 1740 1691, 1590, 1385, 1111, 1029; δ_H (500 MHz, $CDCl_3$) 0.92–1.14 (9H, m, *t*-Bu), 1.60–1.74 (1H, m), 1.82–2.20 (4H, m), 2.36–2.68 (1H, m), 2.84–3.12 (2H, m, $COCH_2$), 3.42–4.12 (7H, m, NCH NCH OCH_2 and OMe), 4.88–5.24 (2H, m, OCH_2Ph), 5.34–5.64 (2H, m, CH=CH), 7.08–7.48 (11H, m, Ph), 7.54–7.72 (4H, m, Ph). δ_C (125 MHz, $CDCl_3$) 19.2 and 19.3, 25.5, 26.2 and 26.5, 26.8 and 26.9, 27.8, 29.7, 35.6, 37.9 and 38.0, 51.8, 57.7 and 58.1, 58.0 and 59.3, 63.4 and 64.1, 66.5, 124.4, 124.5, 127.6, 127.68, 127.73, 127.8, 127.9, 128.0, 128.4, 128.5, 129.6, 129.7, 130.9, 131.0, 133.4, 133.6, 135.5, 135.6, 136.8, 154.1, 172.3. HRMS [M + Na^+] calculated for $C_{35}H_{43}NO_5SiNa$, 608.2803; found: 608.2806.

(2*S*,5*S*/*R*)-1-(*t*-Butyloxycarbonyl)-2-[(*t*-butyldiphenylsilyl) oxymethyl]-5-[2-(methyloxycarbonyl)ethyl]pyrrolidine (15a)

Following the general procedure, the one-pot reaction of *N*-acylcarbamate **13** with methyl acrylate afforded **15a**[9b] in 81% yield as a colorless oil, dr = 90 : 10, determined by HPLC: Shim-pack VP-ODS (150 × 4.6), CH_3CN/H_2O 75 : 25, 1.5 mL min^{-1}, λ = 220 nm, t_1 = 31.1 min (10.0%), t_2 = 33.5 min (90.0%). The physical and spectral data are in agreement with those reported in ref. 9*b*.

(2*S*,5*S*/*R*)-1-(*t*-Butyloxycarbonyl)-2-[2-(*t*-butyloxycarbonyl) ethyl]-5-[(*t*-butyldiphenylsilyl)oxymethyl]-pyrrolidine (15b)

Following the general procedure, the one-pot reaction of *N*-acylcarbamate **13** with *t*-butyl acrylate afforded **15b**[9b] in 92% yield as a colorless oil, dr = 93 : 7, determined by HPLC: Shim-pack VP-ODS (150 × 4.6), CH_3CN/H_2O 75 : 25, 1.5 mL min^{-1}, λ = 220 nm, t_1 = 80.3 min (6.8%), t_2 = 89.9 min (93.2%). The physical and spectral data are in agreement with those reported in ref. 9*b*.

(2*S*,5*S*/*R*)-1-(*t*-Butyloxycarbonyl)-2-[(*t*-butyldiphenylsilyl) oxymethyl]-5-[2-(benzylaminocarbonyl)ethyl]pyrrolidine (15c)

Following the general procedure, the one-pot reaction of *N*-acylcarbamate **13** with *N*-benzylacrylamide afforded **15c** (74%) as a colorless oil, dr > 99 : 1, determined by HPLC: Shim-pack VP-ODS (150 × 4.6), CH_3CN/H_2O 75: 25, 1.5 mL min^{-1}, λ = 220 nm, t_1 = 64.4 min (0.3%), t_2 = 69.3 min (99.7%). υ_{max}/cm^{-1} (film): 3305, 3030, 2917, 1643, 1384, 1260, 1111, 1030; δ_H (500 MHz, $CDCl_3$) δ 1.08 (9H, s, *t*-Bu), 1.28 (9H, s, *t*-Bu), 1.44–1.62 (2H, m), 2.03–2.40 (4H, m), 3.44–3.87 (4H, m, NCH NCH and OCH_2), 4.39–4.56 (2H, m, OCH_2Ph), 7.25–7.47 (11H, m, Ph), 7.64–7.67 (4H, m, Ph). δ_C (125 MHz, $CDCl_3$) 19.2, 26.0, 26.9, 28.3, 28.6, 28.9, 33.6, 43.6, 57.5, 58.5, 63.7, 79.7, 127.1, 127.7, 127.8, 128.1, 128.5, 128.7, 129.6, 129.7, 133.4, 135.5, 135.5, 138.7, 154.2, 172.2. HRMS [M + Na^+] calculated for $C_{36}H_{48}N_2O_4SiNa$, 623.3276; found: 623.3283.

(2*S*,5*S*/*R*)-1-(*t*-Butyloxycarbonyl)-2-[(*t*-butyldiphenylsilyl) oxymethyl]-5-[2-(dimethylaminocarbonyl)ethyl]pyrrolidine (15d)

Following the general procedure, the one-pot reaction of *N*-acylcarbamate **13** with *N,N*-dimethylacrylamide afforded **15d** (84%) as a colorless oil, dr = 90 : 10, determined by HPLC: Shim-pack VP-ODS (150 × 4.6), CH_3CN/H_2O 60 : 40, 2.0 mL min^{-1}, λ = 220 nm, t_1 = 34.6 min (10.2%), t_2 = 69.3 min (89.8%). υ_{max}/cm^{-1} (film): 3030, 2916, 2850, 1650, 1384, 1090, 1031; δ_H (500 MHz, $CDCl_3$) 1.06 (9H, s, *t*-Bu), 1.30 and 1.47 (9H, 2 s br, *t*-Bu), 1.75–1.77 (2H, m), 2.00–2.43 (6H, m), 2.94–3.03 (6H, 2d, NMe_2), 3.44–3.97 (4H, m, NCH NCH and OCH_2), 7.37–7.43 (6H, m, Ph), 7.64–7.66 (4H, m, Ph). δ_C (125 MHz, $CDCl_3$) 19.2, 19.3, 26.0, 26.2, 26.8, 27.2, 28.3, 28.6, 29.0, 29.8, 30.8, 30.9, 31.1, 35.3, 35.4, 35.6, 37.3, 57.8, 58.4, 58.6, 63.6, 63.9, 79.1, 79.2, 127.4, 127.6, 127.7, 127.7, 127.8, 129.5, 129.6, 133.4, 133.6, 133.7, 135.5, 135.5, 153.8, 172.4, 172.8. HRMS [M + H^+] calculated for $C_{31}H_{47}N_2O_4Si$, 539.3300; found: 539.3292.

(2*S*,5*S*/*R*)-1-(*t*-Butyloxycarbonyl)-2-[(*t*-butyldiphenylsilyl) oxymethyl]-5-[2-(ethyloxycarbonyl)ethenyl]pyrrolidine (15e)

Following the general procedure, the one-pot reaction of *N*-acylcarbamate **13** with ethyl propiolate afforded **15e** (91%) as a colorless oil. For 2,5-*trans*-**15e** *Z*/*E* = 35/65, determined by ^1H NMR, dr = 92 : 8, determined by HPLC analysis after hydrogenation of the diastereomeric mixture. υ_{max}/cm^{-1} (film): 3030, 2917, 1693, 1591, 1384, 1260, 1110, 1030; δ_H (500 MHz, $CDCl_3$) 1.10 (9H, s, *t*-Bu), 1.26–1.48 (12H, m, 12H), 1.61–1.76 (m, 1H), 1.95–2.21 (m, 2H), 2.25–2.36 (m, 1H), 3.40–4.65 (m, 6H), 5.62–6.45 (m, 1H), 6.80–7.25 (m, 1H), 7.33–7.51 (6H, m, Ph), 7.63–7.76 (4H, m, Ph). δ_C (125 MHz, $CDCl_3$) 14.1, 19.08, 19.13, 26.7, 28.18, 28.24, 28.30, 29.7, 31.3, 31.4, 55.9, 56.6, 58.1, 58.6, 59.8, 60.1, 63.56, 63.64, 63.88, 79.2, 79.4, 79.6, 117.9, 118.6, 120.1, 127.5, 127.6, 129.5, 129.6, 133.16, 133.29, 133.39, 133.46, 135.4, 147.9, 148.6, 152.5, 153.3, 153.5, 153.8, 154.1, 154.3, 165.6, 166.3. HRMS [M + Na^+] calculated for $C_{31}H_{43}NO_5SiNa$, 560.2803; found: 560.2811.

(2*S*,5*S*/*R*)-1-(*t*-Butyloxycarbonyl)-2-[(*t*-butyldiphenylsilyl) oxymethyl]-5-[(*E*)-5-(methyloxycarbonyl)pent-2-enyl] pyrrolidine (15f)

Following the general procedure, the one-pot reaction of *N*-acylcarbamate **13** with methyl penta-2,4-dienoate afforded **15f** (86%) as a colorless oil, dr = 91 : 9, determined by HPLC: Shim-pack VP-ODS (150 × 4.6), CH_3CN/H_2O 75 : 25, 2.0 mL min^{-1}, λ = 220 nm, t_1 = 34.0 min (8.95%), t_2 = 69.3 min (91.1%). υ_{max}/cm^{-1} (film): 3030, 2917, 2856, 1740, 1691, 1590, 1385, 1259, 1166, 1030; δ_H (500 MHz, $CDCl_3$) 1.06 and 1.08 (9H, 2 s, *t*-Bu), 1.24–1.48 (9H, m, *t*-Bu), 1.60–1.76 (1H, m), 1.90–2.20 (4H, m), 2.40–2.65 (1H, m), 2.80–3.15 (2H, m, $COCH_2$), 3.60–4.05 (7H, m, NCH, NCH, OCH_2 and OMe), 5.40–5.80 (2H, m, HC═CH), 7.35–7.55 (6H, m, Ph), 7.60–7.75 (4H, m, Ph). δ_C (125 MHz, $CDCl_3$) 19.15, 19.21, 25.9, 26.3, 28.3, 28.5, 35.7, 37.2, 37.8, 37.9, 38.0, 51.4, 51.6, 57.5, 57.7, 58.7, 63.6, 63.9, 78.97, 79.03, 124.0, 124.1, 127.55, 127.60, 127.64, 129.4, 129.6, 131.2, 133.4, 133.6, 133.7, 135.43, 135.46, 153.6, 153.7, 172.2. HRMS [M + Na^+] calculated for $C_{32}H_{45}NO_5SiNa$, 574.2959; found: 574.2959.

(3*S*,9*aR*)-3-[(*t*-Butyldiphenylsilyloxy)methyl]hexahydro-1H-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (16)

A suspension of compound **14b** (40 mg, 0.07 mmol), 20% $Pd(OH)_2/C$ (4 mg) in MeOH (2 mL) was stirred at rt under 1 atm of hydrogen for 20 h. The reaction mixture was filtered through Celite and washed with MeOH. The combined filtrates were concentrated under reduced pressure. The residue was dissolved in toluene (40 mL) and NEt_3 (0.06 mL) was added. The solution was heated at reflux for 16 h. Then, the resulting mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel (eluent: EtOAc: hexanes 1 : 2) to furnish **16** (20 mg, 70%) as a pale yellow oil. $[\alpha]_D^{20}$ −29.4 (*c* 0.9 in $CHCl_3$); υ_{max}/cm^{-1} (film): 3029, 2917, 2856, 1740, 1691, 1371, 1353, 1130, 1103; δ_H (500 MHz, $CDCl_3$) 1.06 (9H, s, *t*-Bu), 1.48–1.70 (5H, m), 1.76–1.85 (1H, m), 1.96–2.05 (3H, m) 2.25–2.46 (3H, m), 3.64 (1H, dd, *J* 6.8, 9.8, H_{10}), 3.76 (1H, app. t, *J* 9.2, H_{9a}), 3.76 (1H, dd, *J* = 3.3, 9.8, $H_{10'}$), 4.25–4.35 (1H, m, H_3), 7.31–7.45 (6H, m, Ph), 7.60–7.70 (4H, m, Ph); δ_C (125 MHz, $CDCl_3$) δ 19.2, 23.3, 25.4, 26.9, 29.7 32.6, 36.0, 38.4, 59.5, 59.6, 63.2, 127.58, 127.61, 129.5 129.6, 133.7, 133.8, 135.6, 174.0. HRMS [M + H^+] calculated for $C_{26}H_{36}NO_2Si$, 422.2510; found: 422.2515.

Benzyl 2-(hydroxymethyl)-5-(3-methoxy-3-oxopropyl) pyrrolidine-1-carboxylate (2*S*,5*R*-17) and (2*S*,5*S*-18)

To a solution of compound **14a** (150 mg, 0.27 mmol) in THF (5 mL) was added a 1 M THF solution of *n*-Bu_4NF (0.4 mL, 0.4 mmol) at 0 °C, and the resulting solution was stirred at room temperature for 3 h. After removing the solvent under reduced pressure, the residue was purified by flash chromatography on

silica gel (eluent: EtOAc/petroleum ether 1 : 1) to afford (2*S*,5*R*)-**17** (13 mg, 15%) and (2*S*,5*S*)-**18** (74 mg, 85%).

(2*S*,5*R*)-**17** (more polar diastereomer): yield: 15% Colorless oil: $[\alpha]_D^{20}$ −11.9 (*c* 1.1 in $CHCl_3$). υ_{max}/cm^{-1} (film): 3408, 3030, 2973, 2921, 1745, 1680, 1407, 1365, 1164, 1029; δ_H (500 MHz, $CDCl_3$) 1.50–2.16 (m, 6H), 2.20–2.58 (2H, m, $COCH_2$), 3.46–3.66 (4H, m, OCH and OMe), 3.70–3.84 (1H, m, NCH), 3.88–4.06 (2H, m, NCH and OCH), 4.28–4.48 (1H, s br, OH), 5.00–5.22 (2H, m, OCH_2Ph), 7.22–7.42 (5H, m, Ph). δ_C (125 MHz, $CDCl_3$) 26.3, 29.5, 30.1, 31.0, 51.5, 58.4, 61.7, 66.9, 67.3, 127.9, 128.0, 128.4, 136.2, 157.3, 173.6. HRMS [M + H^+] calculated for $C_{17}H_{24}NO_5$, 322.1648, found: 322.1643.

(2*S*,5*S*)-**18** (less polar diastereomer): yield: 85%. Colorless oil: $[\alpha]_D^{20}$ −41.5 (*c* 1.0 in $CHCl_3$). υ_{max}/cm^{-1} (film): 3435, 3030, 2973, 2921, 1738, 1688, 1593, 1365, 1029; δ_H (500 MHz, $CDCl_3$) 1.50–1.75 (m, 3H), 1.85–2.10 (m, 3H), 2.12–2.50 (2H, m, $COCH_2$), 3.35–3.80 (5H, m, NCH OCH_2 and OMe), 3.80–3.90 (1H, s br, OH), 3.92–4.05 (1H, m, NCH), 5.02–5.22 (2H, m, OCH_2Ph), 7.25–7.50 (5H, m, Ph). δ_C (125 MHz, $CDCl_3$) 26.5 and 27.0, 28.0 and 28.1, 29.0, 31.2 and 31.4, 51.6, 58.0 and 58.8, 60.4, 66.1, 66.8 and 67.2, 128.03, 128.07, 128.5, 136.4, 156.1, 173.3. HRMS [M + H^+] calculated for $C_{17}H_{24}NO_5$, 322.1648; found: 322.1650.

(2*S*,5*S*)-1-(*t*-Butyloxycarbonyl)-2-(hept-1-enyl)-5-[2-(methyl oxycarbonyl)ethyl]pyrrolidine (19)

A solution of sulfur trioxide–pyridine complex (594 mg, 3.74 mmol) in DMSO (3 mL) was added to a cooled solution (0 to 5 °C) of (2*S*,5*S*)-**18** (200 mg, 0.623 mmol) and triethylamine (0.26 mL, 1.87 mmol) in DMSO (2 mL). The mixture was stirred at rt for 30 min and then diluted with diethyl ether (10 mL). A 10% citric acid solution was added to the mixture to adjust the acidity to pH 4. The organic phase was separated, and the aqueous phase was extracted with diethyl ether (5 mL × 3). The combined organic layers were washed with brine, dried over with anhydrous Na_2SO_4, filtered and concentrated to give a colorless oil. To a solution of hexyltriphenylphosphonium bromide (533 mg, 1.25 mmol) in THF (10 mL) was added *n*-BuLi (2.5 M in hexane, 0.5 mL, 1.25 mmol) at −78 °C. After being stirred for 15 min at −78 °C and 15 min at rt, a solution of the above mentioned crude product in THF (4 mL) was added at −78 °C and the resulting mixture was stirred at −78 °C for 2 h. The reaction mixture was allowed to warm to rt and quenched with a saturated aqueous solution of NH_4Cl (3 mL). The organic layer was separated, and the aqueous phase extracted with diethyl ether (5 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: EtOAc/petroleum ether 1 : 5) to afford compound **19** (110 mg, 45%) as a colorless oil. υ_{max}/cm^{-1} (film): 3063, 3030, 1738, 1688, 1593, 1407, 1365, 1164; δ_H (500 MHz, $CDCl_3$) 0.80–0.96 (3H, m, Me), 1.05–1.50 (6H, m), 1.55–1.72 (3H, m), 1.77–2.45 (7H, m), 3.56 and 3.65 (3H, 2 s, OMe), 3.85–4.00 (1H, m, NCH), 4.55–4.70 (1H, m, NCH), 5.00–5.25 (2H, m, OCH_2Ph), 5.23–5.51 (2H, m, CH═CH), 7.24–7.38 (5H, m, Ph). δ_C (125 MHz, $CDCl_3$) 14.0, 22.5, 27.2, 27.5, 28.2, 28.8, 29.1 and 29.3, 30.4, 31.4 and 31.5, 51.6, 54.7, 57.5, 66.6, 127.7, 128.0, 128.2, 128.4, 130.1, 131.0, 136.9, 154.8, 173.7. HRMS [M + Na^+] calculated for $C_{23}H_{33}NO_4Na$, 410.2301; found: 410.2299.

(2*S*,5*R*)-1-(*t*-Butyloxycarbonyl)-2-(hept-1-enyl)-5-[2-(*N*-methyl-*N*-methyloxylaminecarbonyl)ethyl]pyrrolidine (20)

To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride salt (80 mg, 0.82 mmol) in CH_2Cl_2 (2 mL) at 0 °C was dropwise added $AlMe_3$ (0.82 mL of a 1 M solution in toluene, 0.82 mmol). After being stirred for 30 min, a solution of ester **19** (63 mg, 0.16 mmol) in CH_2Cl_2 (1 mL) was added. The mixture was stirred for 3 h at rt, then quenched with a saturate aqueous solution of $KHSO_4$ and filtered through Celite. The filtrate was extracted with EtOAc (5 mL × 3), dried over with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel (eluent: EtOAc/petroleum ether 1 : 2) to afford compound **20** (53 mg, 78%) as a colorless oil and recovered **19** (6 mg, 10%). υ_{max}/cm^{-1} (film): 3063, 3030, 2973, 2921, 1745, 1686, 1596, 1384, 1361, 1164, 1029; δ_H (500 MHz, $CDCl_3$) 0.80–0.96 (3H, m, Me), 1.15–1.35 (6H, m), 1.55–1.78 (3H, m, NMe), 1.80–2.25 (m, 5H), 2.30–2.60 (m, 2H), 3.08 and 3.15 (2 s br, 3H), 3.55 and 3.68 (3H, 2 s, OMe), 3.82–4.02 (1H, m, NCH), 4.51–4.70 (1H, m, NCH), 5.00–5.15 (2H, m, OCH_2Ph), 5.20–5.50 (2H, m, CH═CH), 7.20–7.42 (5H, m, Ph). δ_C (125 MHz, $CDCl_3$) δ 14.2, 22.6, 27.4, 27.8, 28.5 and 28.8, 29.3, 29.6, 30.6, 31.5 and 31.7, 32.4, 54.8 and 55.2, 57.42 and 57.43 and 58.01, 61.4, 66.7, 127.8, 128.0, 128.4, 128.6, 130.2, 130.7, 131.2, 131.3, 137.2, 154.4 and 154.9, 174.3. HRMS [M + Na^+] calculated for $C_{24}H_{36}N_2O_4Na$, 439.2567, found: 439.2570.

(2*S*,5*R*)-1-(*t*-Butyloxycarbonyl)-2-(hept-1-enyl)-5-(3-oxobutyl)-pyrrolidine (21)

To a solution of 44 mg (0.11 mmol) of amide **20** in 2 mL of THF at −78 °C was added 0.46 mL (0.74 mmol) of a 1.6 M solution of MeLi in diethyl ether. After being stirred at −78 °C for 30 min, the reaction was quenched with 2 mL of saturated aqueous NH_4C1 and diluted with 25 mL of diethyl ether. The layers were separated and the aqueous phase extracted with diethyl ether (10 mL × 3). The combined organic layers were washed with brine, dried over with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/petroleum ether 1 : 2) to afford compound **21** (36 mg, 92%) as a colorless oil. υ_{max}/cm^{-1} (film): 3063, 3030, 2921, 2854, 1738, 1697, 1407, 1365, 1164, 1029; δ_H (500 MHz, $CDCl_3$) 0.81–0.94 (3H, m, Me), 1.15–1.34 (6H, m), 1.55–1.66 (3H, m), 1.80–2.22 (8H, m), 2.26–2.56 (2H, m, $COCH_2$), 3.80–3.95 (1H, m, NCH), 4.50–4.70 (1H, m, NCH), 5.00–5.55 (4H, m, OCH_2PH and CH═CH), 7.20–7.40 (5H, m, Ph). δ_C (125 MHz, $CDCl_3$) 14.2, 22.6, 27.4 and 27.6, 27.9 and 28.1, 28.6, 29.3 and 29.6, 29.9, 30.5, 31.5 and 31.7, 41.2, 54.9 and 55.2, 57.1 and 57.6, 66.8, 127.9, 128.1, 128.4, 128.6, 130.3, 130.5, 131.2, 137.1, 155.0, 208.8. HRMS [M + Na^+] calculated for $C_{23}H_{33}NO_3Na$ 394.2353; found: 394.2358.

(−)-Xenovenine (*ent*-6)

A suspension of compound **21** (40 mg, 0.11 mmol), 20% $Pd(OH)_2/C$ (7 mg) in MeOH (2 mL) was stirred at rt under 1 atm of hydrogen for 20 h. The reaction mixture was filtered through Celite and washed with CH_2Cl_2. The combined organic solvents were concentrated under reduced pressure. The residue was purified by column chromatography on basic alumina (eluent:

n-hexane: $Et_2O = 7:1$) to give (–)-xenovenine (*ent*-**6**) (19 mg, 80%) as a colorless oil. $[\alpha]_D^{20}$ –10.5 (*c* 1.4 in $CHCl_3$) {[38a] $[\alpha]_D^{26}$ –10.93 (*c* 1.45 in $CHCl_3$);[38c] $[\alpha]_D^{23}$ –11.4 (*c* 1.37 in $CHCl_3$)}; υ_{max}/cm^{-1} (film): 2955, 2925, 2855, 1461, 1371, 1353, 1130, 1103; δ_H (500 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.1, Me), 1.09 (3H, d, *J* 6.0, Me), 1.26–1.60 (m, 17H), 1.87–2.05 (m, 3H) 2.57–2.62 (1H, m, NCH), 2.71–2.78 (1H, m, NCH), 3.59 (1H, m, NCH); δ_C (125 MHz, $CDCl_3$) δ 14.0, 21.9, 22.6, 27.2, 29.3 29.9, 31.7, 31.8, 32.1, 32.4, 34.5, 37.1, 61.7, 65.0, 66.6. MS (ESI, *m/z*): 224 ($M + H^+$). HRMS [$M + H^+$] calculated for $C_{17}H_{24}NO_5$, 224.2373; found: 224.2379.

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