Amino Zinc Enolate Carbocyclization Reactions. New Access to Polysubstituted Piperidine Derivatives

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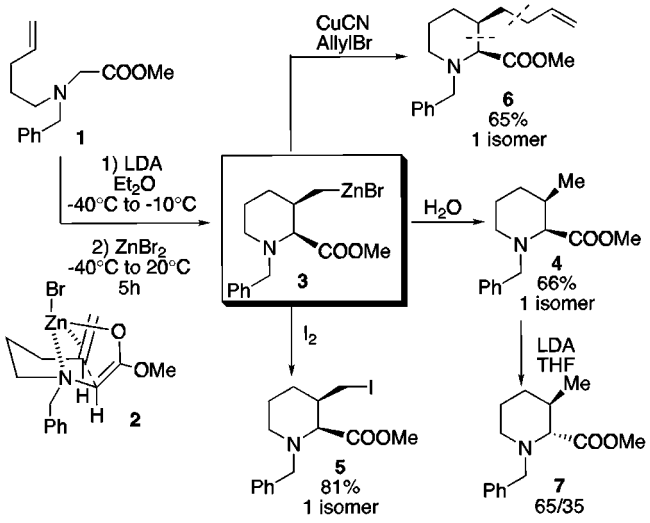
Received August 5, 1997

Various *N*-pent-4-enylglycine methyl esters have been submitted to carbocyclization of their zinc enolates onto the unactivated double bond. The cyclization to substituted pipecolic esters is highly stereoselective. In most cases, substitution of the pent-4-enyl moiety on various sites leads to a single isomer, hence a way to di-, tri-, tetra-, or pentasubstituted piperidines.

Introduction

Despite the extensive investigation of the intramolecular carbometalation reactions[1] of alkenes and alkynes, there are only few reports on the synthesis of six-membered rings by this strategy.[2] Indeed, the 6-exo-trig[6] cyclization of a 6-heptenylmetal to a (cyclohexylmethyl)-metal is much slower than the analogous 5-exo-trig carbocyclization.[2d] Recently, our attention turned to the carbocyclization of stabilized carbanions, for which only few reports were also described,[3] and we have described the first diastereoselective and enantioselective amino zinc enolate carbocyclization to give various polysubstituted pyrrolidine derivatives,[4] known to be conformationally restricted α-amino acids analogues.[5] This simple and straightforward intramolecular carbometalation of a zinc enolate toward an unfunctionalized double bond (the intramolecular olefinic aldol reaction[6]) for the creation of a five-membered ring led us to consider the possibility to prepare some polysubstituted piperidines.[7]

Scheme 1



Results and Discussion

The starting material **1**, easily prepared in two steps,[8] is metalated with LDA in Et_2O[9] and transmetalated with zinc bromide to give the corresponding *Z*-amino zinc enolate **2**.[10] After warming to room temperature and stirring for 5 h, a 6-exo-trig cyclization occurs to give the metalated piperidine **3** as described in Scheme 1. Hydrolysis of the reaction mixture afforded **4** in 66% yield as single diastereomer. The cis stereochemistry of the *β*-methyl pipecolic derivative **4** was established, first by using standard ^1H, ^{13}C, and COSY NMR techniques and then differencial nuclear Overhauser effects. Moreover, treatment of **4** with LDA in THF gives the trans isomer **7**.

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(4) (a) Lorthiois, E.; Marek, I.; Normant, J. F. *Tetrahedron Lett*. **1997**, *38*, 89−92. (b) Lorthiois, E.; Marek, I.; Normant, J. F. *J. Org. Chem*. **1997**, submitted. (c) Karoyan, P.; Chassaing, G. *Tetrahedron Lett.* **1997**, *38*, 85−88. (d) Karoyan, P.; Chassaing, G. *Tetrahedron Asymmetry* **1997**, *3*, 2025−2032.

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(6) Nakamura, E.; Kubota, K. *J. Org. Chem*. **1997**, *62*, 792−793.

(7) For the synthesis of piperidines via an anionic cyclization, see: (a) Van Der louw, J.; Van Der Baan, J. L.; Stieltjes, H.; Bickelhaupt, F.; Klumpp, G. P. *Tetrahedron Lett*. **1987**, *28*, 5929−5932. (b) Oppolzer, W.; Gaudin, J. M.; Bedoya-Zurita, M.; Hueso-Rodriguez, J.; Raynham, T. M.; Robyr, C. *Tetrahedron Lett*. **1988**, *29*, 4709−4712. (c) Oppolzer, W.; Swenson, R. E.; Gaudin, J. M. *Tetrahedron Lett*. **1988**, *29*, 5529−5532. (d) Shanghnessy, K. H.; Waymouth, R. M. *J. Am. Chem. Soc.* **1995**, *117*, 5873−5874. (e) Takacs, J. M.; Weidner, J. J.; Newsone, P. W.; Takacs, B. E.; Chidambaram, R.; Shonaker, R. *J. Org. Chem*. **1995**, *60*, 3473−3486. (f) Solé, D.; Cancho, Y.; Llebaria, A.; Delgado, J. M. A. *J. Org. Chem*. **1996**, *61*, 5895−5904.

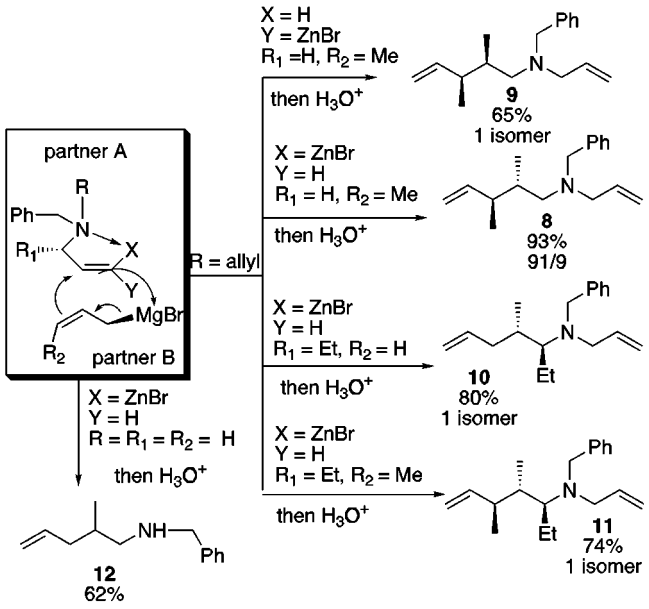
(8) See experimental procedure.

(9) The lithium enolate is unable to cyclize at room temperature.

(10) Van Der Steen, F. H.; Kleijn, H.; Britovsek, G. J. P; Jastrzebski, J. T. B. H.;Van Koten, G. *J. Org. Chem*. **1992**, *57*, 3906−3916.

S0022-3263(97)01449-7 CCC: $15.00
Published on Web 01/22/1998

Scheme 2



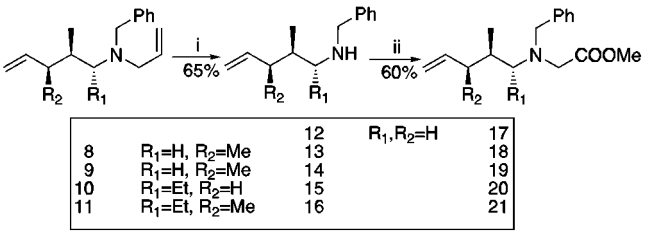
The formation of the functionalized organometallic derivative was also checked by iodinolysis or by reaction with allyl bromide after transmetalation into an organocopper derivative[11] to give respectively **5** and **6** in good overall yield as unique diastereomers (Scheme 1). The cis relative configuration of **4** can be explained by a chairlike transition state in which the electrophilic double bond occupies a pseudoaxial position (the *Z*-α-amino zinc enolate and the double bond are gauche to each other, see **2** in Scheme 1).

To confirm this chairlike transition state and also since no stereochemical studies were described in the literature for the synthesis of six-membered ring by anionic cyclization, we have decided to study the stereochemical influence of substituents on the starting linear substrate. For the preparation of the several starting materials, we have used the geminated organodimetallics chemistry, recently reviewed.[12] Indeed, by using the allylmetalation or crotylmetalation of vinylmetals, we have been able to obtain the corresponding organogembismetallic derivatives, as described in Scheme 2.

By combination of the controlled metalotropic equilibrium of the crotylmetal[13] (partner B) at low temperature and the diastereofacial choice of the allylmetalation on the heterosubstituted chelated vinylmetal[14] (partner A), the creation of one to three stereogenic centers is easily performed with a very high diastereoselectivity in a single-pot operation. After deallylation of the nitrogen atom according to Genet methodology[15] and alkylation with the methyl α-bromoacetate, as described in the general Scheme 3,[8] a detailed study of the stereochemical outcome in the six-membered ring carbocyclization of these starting materials was undertaken.

When the substrate **17** (derived from **12**) is submitted to our cyclization conditions (metalation with LDA transmetalation with $ZnBr_2$ cyclization at room temperature in 5 h), we obtain the corresponding cyclic organozinc bromide, as a unique isomer,[16] and then **22** after hydrolysis or **23** after reaction with NBS, as described in Scheme 4.

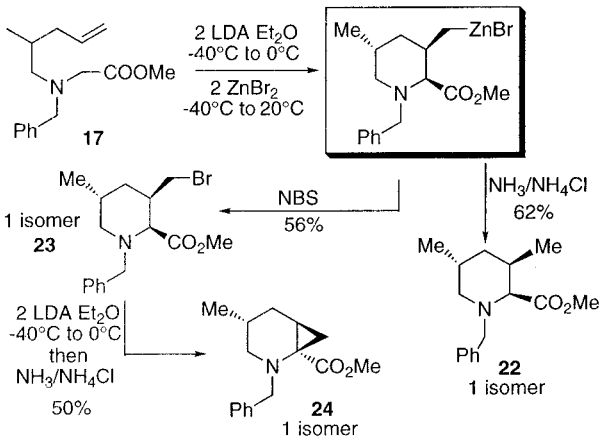
Scheme 3[a]



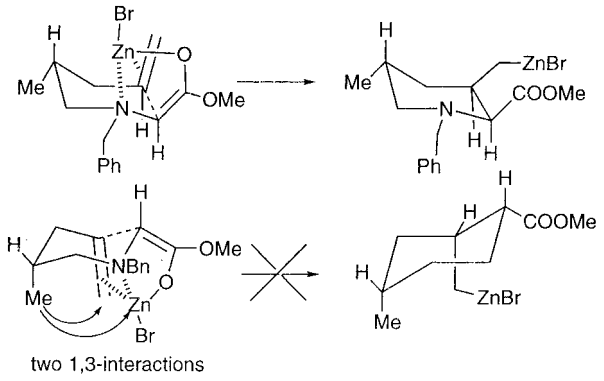
		12	R_1,R_2=H	17
8	R_1=H, R_2=Me	13		18
9	R_1=H, R_2=Me	14		19
10	R_1=Et, R_2=H	15		20
11	R_1=Et, R_2=Me	16		21

[a] (i) 5% $Pd(dba)_2$, dppb, mercaptobenzoic acid, THF, rt. (ii) NaH, DMF, 0 °C then $BrCH_2COOMe$.

Scheme 4



Scheme 5



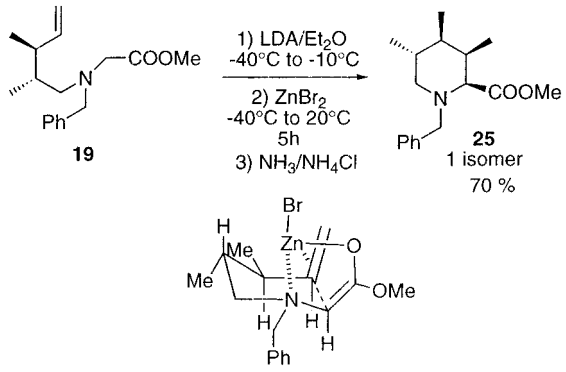
The relative configuration of **22** was assigned by NOE's and can be explained by a chairlike transition state in which the methyl substituent preferentially occupies a pseudoequatorial position (see Scheme 5). It should be noted that, even when the methyl substituent is far from the two reacting centers, only one isomer is formed in this process, to minimize the 1,3-interactions with the electrophilic double bond which is located in the pseudoaxial position as well as with the zinc moiety of the amino zinc enolate.

Moreover, the bromo derivative **23** can serve as a source of bicyclo[4.1.0]heptane amino ester **24**, which is

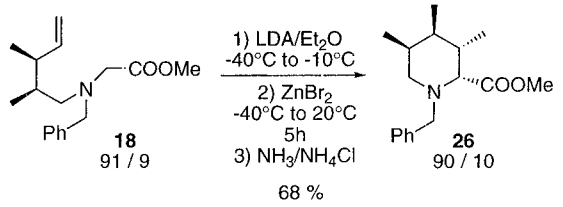
(11) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117−2188.
(12) Marek, I.; Normant, J. F. *Chem. Rev.* **1996**, *96*, 3241−3267.
(13) Marek, I.; Lefrançois, J-M.; Normant, J. F. *J. Org. Chem.* **1994**, *59*, 4154−4161.
(14) Brasseur, D.; Marek, I.; Normant, J. F. *Tetrahedron* **1996**, *52*, 7235−7250.
(15) Lemaire-Audoire, S.; Savignac, M.; Dupuis, C.; Genet, J. P. *Bull. Soc. Chim. Fr.* **1995**, *132*, 1157−1166.

(16) As determined by ^1H and ^{13}C NMR on the crude reaction mixture.

Scheme 6



Scheme 7



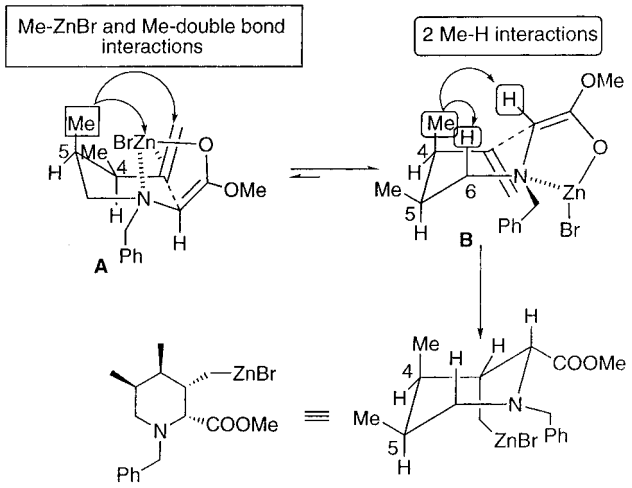
also an interesting constrained amino ester, by treatment with LDA as described in Scheme 4.[17]

If now we start from **19** (derived from **9**), according to our experimental conditions of metalation−transmetalation, the carbocyclization of the *Z*-α-amino zinc enolate across the double bond leads to the tetrasubstituted piperidine also as single diastereomer[16] in 70% yield. The relative configuration of **25** was established by analyzing the coupling patterns between each hydrogen and can be explained by a chairlike transition state in which the two methyl substituents preferentially occupy a pseudoequatorial position (match pair) as described in Scheme 6.

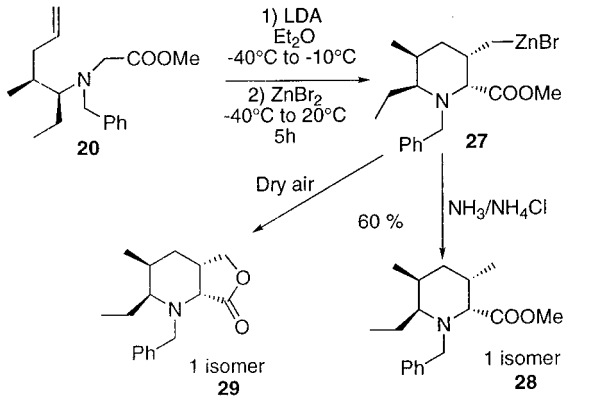
However, if we consider the carbocyclization of the mismatched pair, namely the carbocyclization of **18** (derived from **8**), with a diastereomeric ratio of 91/9 for **18**/**19**, we should be able to determine which substituent is able to fix the stereochemical outcome of the carbocyclization. Then, the substrate **18** was subjected to our metalation−transmetalation−cyclization procedure, to give, after hydrolysis, the tetrasubstituted piperidine **26** in 68% yield as two diastereomers in a ratio of 90/10 (see Scheme 7). As we started from a 91/9 ratio of **18**/**19**, the carbocyclization is, here again, highly diastereoselective.[16]

The stereochemistry of the major isomer was determined by analyzing the coupling constants of the piperidine protons of **26**. The relative configuration of the minor isomer (10%) is identical with that of **25** (Scheme 6), which means that this other diastereomer results from the presence of 9% of **19** at the start. The stereochemistry of **26** can be explained by a chairlike transition state of the *Z*-amino zinc enolate in which the methyl at C_4 (see Scheme 8) is preferentially axial and the methyl at C_5 is equatorial, rather than the opposite. Indeed, in the former case, two axial 1,3-interactions exist with the two hydrogens (as described in B), whereas in the latter case, two stronger 1,3-interactions exist, one with the double bond and the second one with the zinc moiety of the zinc enolate (as described in A).

Scheme 8



Scheme 9



We can conclude from these studies (Scheme 8) that the substituent in the homoallylic position (C_5) has a major impact on the stereochemical outcome of the carbocyclization. So, we were interested in preparing a second mismatched pair, still with a substituent in the homoallylic position (C_5) but now with a substituent in position α to the nitrogen atom (C_6, see Scheme 9). Indeed, during the chairlike transition state of the carbocyclization step, we will still have one of these two substituents in an axial position and the other one in an equatorial position, and it was interesting to see which one determines the diastereoselectivity of the carbocyclization in a six-membered ring synthesis.

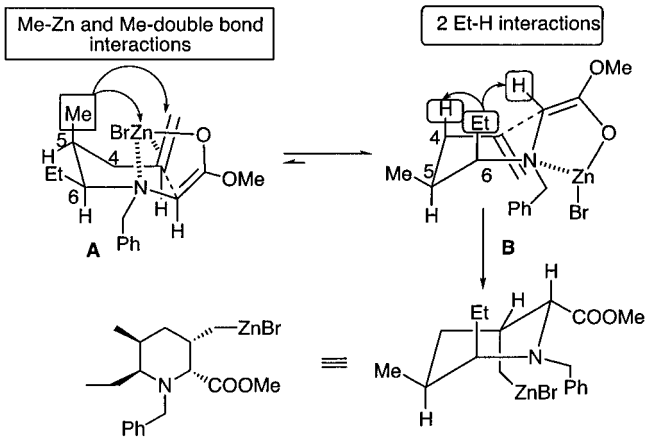
Having in our hands the starting material **20**, prepared according to Scheme 3 from **10** (see Scheme 2), we have submitted it to the carbocyclization condition (metalation−transmetalation−cyclization) to give the corresponding cyclic organozinc bromide **27** as described in Scheme 9. This can be hydrolyzed and oxidized by slow introduction of dry air[18] to give, respectively, **28** and **29** as single diastereomers.[16]

Both **28** and **29** have the same stereochemistry as determined by the analysis of the coupling constants. This stereochemistry can always be explained by the

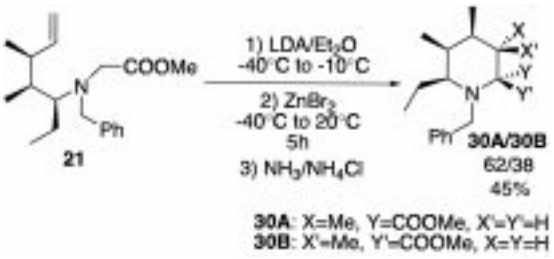
(17) (a) Hanessian, S.; Reinhold, U.; Ninkovic, S. *Tetrahedron Lett.* **1996**, *37*, 8967−8970. (b) Hanessian, S.; Ninkovic, S.; Reinhold, U. *Tetrahedron Lett.* **1996**, *37* , 8971−8974.

(18) (a) Chemla, F.; Normant, J. F. *Tetrahedron Lett.* **1995**, *36*, 3157−3160. (b) Klement, I.; Lutjens, H.; Knochel, P. *Tetrahedron Lett.* **1995**, *36*, 3161−3163. (c) Klement, I.; Lutjens, H.; Knochel, P. *Tetrahedron* **1997**, *53*, 9135−9144.

Scheme 10



Scheme 11



chairlike transition state, and the ethyl substituent in the α-position to the nitrogen atom (C_6) occupies a pseudoaxial position, whereas the substituent in a homoallylic position (C_5) occupies the pseudoequatorial position (see Scheme 10). Indeed, the 1,3-steric interactions between the ethyl substituent with the two hydrogens in **B** are less destabilizing than the 1,3-steric interactions between the methyl group at C_5 with the electrophilic double bond and with the zinc moiety of the zinc enolate as described in **A** in Scheme 10.

So, here again, the substituent in the C_5 position (homoallylic position) is able to control the stereochemical outcome of the carbocyclization, regardless of the presence of a mismatched substituent at C_4 (Scheme 8) or C_6 (Scheme 10) position.

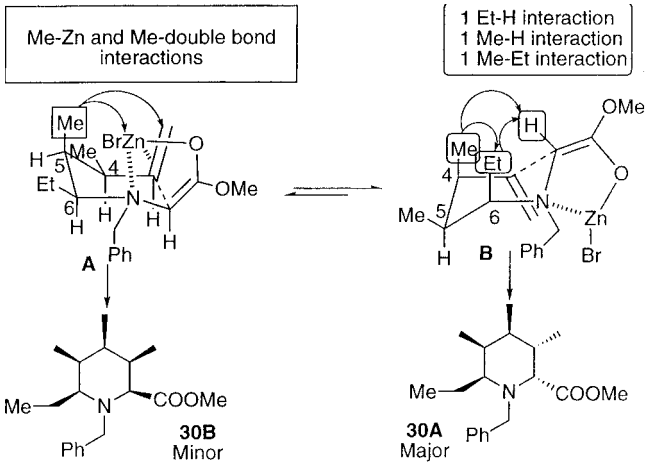
Finally, we decided to study the combination of these two substituents (C_4 and C_6) toward the substituent at C_5 in the stereoselectivity of the carbocyclization. The amino ester **21** (prepared from **11**, see Scheme 2) was submitted to the metalation−transmetalation−cyclization conditions to give, after 7 h at room temperature and hydrolysis, the pentasubstituted piperidine **30A** and **30B** in moderate chemical yield[19] as a mixture of two diastereomers in a ratio of 62/38 (see Scheme 11).

The relative configurations of these two piperidines **30A** and **30B** were determined by analyzing the coupling constants.[20] When the effect of the homoallylic substituent at C_5 is opposite to the combined effects of the substituents at C_4 and C_6, the diastereoselectivity of the carbocyclization becomes lower. The former substituent (C_5) is now not able to control totally the stereochemical outcome of the cyclization reaction. Indeed, if we examine the two following chairlike transition state **A** and **B**,

(19) The balance being the starting material.

(20) Although **30B** could not be well-separated from **30A** and from the starting material, the characteristic signals for $H_{1,2,3}$ and H_5 (see experimental part) and their NOE effect could be detected.

Scheme 12



we have in the former case **A** two 1,3-interactions, one with the double bond and one with the zinc moiety of the zinc enolate, whereas in the latter case **B**, we have three 1,3-interactions: the major one is an axial interaction between the methyl and the ethyl groups, and the two others are two alkyl−hydrogen interactions (see Scheme 12). These two transition states are not different enough in energy, and the two diastereomers are formed.

Conclusion

The zinc enolate cyclization allows the easy and straightforward preparation of piperidines with excellent control of the diastereoselectivity. During the synthesis of tri- to pentasubstituted piperidines, we have been able to determine, for the first time, that the stereochemical outcome of this carbocyclization was mainly due to the presence of a substituent in the homoallylic position (C_5). Extension of this chemistry to the stereocontrolled preparation of various heterocycles, as well as to the enantioselective synthesis, is currently underway.

Experimental Section

***N*-Benzyl-*N*-pent-4-enylamine.** A solution of benzylamine (30 mmol, 3.21 g), 5-bromopent-1-ene (39 mmol, 5.8 mL), sodium iodide (90 mmol, 13.5 g), and K_2CO_3 (90 mmol, 16.4 g) in dry DMF (100 mL) was stirred at 100 °C during 20 h. The reaction mixture was then treated with H_2O (40 mL) and extracted with ether (2 × 100 mL). The combined extracts were washed with satured NaCl (3 × 50 mL), dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography from the dialkylated product (eluent, CH_2Cl_2/MeOH 95/5) to give 1.42 g (27%) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.28 (m, 5H), 5.88−5.81 (m, 1H), 5.06−4.96 (m, 2H), 3.61 (s, 2H), 2.48 (t, J = 7.2 Hz, 2H), 2.13−2.07 (m, 2H), 1.65−1.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 138.6, 128.5, 128.2, 127.0, 114.8, 53.4, 48.9, 31.7, 29.3.

***N*-Allyl-*N*-benzyl-*N*-(3-iodo-prop-2(*Z*)-enyl)amine.** (*Z*)-1-Iodo-1-propen-3-ol is obtained in two steps according to the literature[21] method and is further converted into the (*Z*)-1-iodo-3-bromo-1-propene.[14] *N*-Allyl-*N*-benzylamine (7.25 mmol, 1 g), K_2CO_3 (8.7 mmol, 1.2 g), and (*Z*)-1-iodo-3-bromo-1-propene (7.98 mmol, 1.97 g) in dry DMF (25 mL) was stirred at room temperature during 3 h. The reaction mixture was then treated with H_2O (20 mL) and extracted with ether (2 × 25 mL). The organic layer was washed with saturated NaCl (3

(21) Marek, I.; Meyer, C.; Normant, J. F. *Org. Synth.* **1996**, *74*, 194−204.

× 50 mL), dried over $MgSO_4$, and concentrated to give 1.66 g (73%) of the title compound which was not further purified: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.27 (m, 5H), 6.43−6.37 (m, 2H), 5.98−5.88 (m, 1H), 5.26 (d, J = 17.24 Hz, 1H), 5.22−5.20 (m, 1H), 3.64 (s, 2H), 3.23 (m, 2H), 3.14 (d, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 138.9, 135.7, 129.05, 128.4, 127.1, 118.0, 83.6, 58.2, 57.6, 57.0.

***N*-Allyl-*N*-benzyl-*N*-(3-iodoprop-2(E)-enyl)amine.** This compound was prepared according to Lipschutz's[22] methodology starting from *N*-allyl-*N*-benzyl-*N*-propargylamine. $LiEt_3$-BH ("Super hydride", Aldrich, 1 M in THF, 7.3 mmol, 7.3 mL) was added dropwise over 5 min at room temperature to a solution of Cp_2ZrCl_2 (7.3 mmol, 2.13 g) in dry THF (10 mL). The solution was stirred, shielded from light, for 1 h at room temperature. After this time, *N*-allyl-*N*-benzyl-*N*-propargylamine (7.29 mmol, 1.35 g) in THF (5 mL) was slowly added and the mixture stirred for 10 min to provide a clear, yellow solution. Iodine (7.3 mmol, 1.85 g) in THF (5 mL) was then added and the resultant mixture was stirred for 5 min at room temperature. It was then poured into a solution of NH_4Cl/NH_4OH 2/1 and the mixture was filtered off on a pad of Celite. The layers were separated and the aqueous one was extracted with ether, washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/ether 95/5) to give 1.22 g (54%) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.26 (m, 5H), 6.62 (dt, J = 14.4, 6.6 Hz, 1H), 6.24 (d, J = 14.4 Hz, 1H), 5.92−5.85 (m, 1H), 5.25−5.17 (m, 2H), 3.61 (s, 2H), 3.12−3.06 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 139.2, 135.8, 129.3, 128.9, 127.2, 117.8, 77.9, 57.8, 57.5, 56.7.

***N*-Benzyl-*N*-(1-ethyl-3-iodoprop-2(Z)-enyl)amine.** (*Z*)-1-Iodo-1-penten-3-ol is obtained in two steps according to the literature[21] method and is further converted into (*Z*)-1-iodo-3-bromo-1-pentene.[14] A solution of *N*-benzylamine (13.8 mmol, 1.5 g), K_2CO_3 (16.56 mmol, 2.28 g), and (*Z*)-1-iodo-3-bromo-1-pentene (13.8 mmol, 3.62 g) in dry DMF (30 mL) was stirred at room-temperature overnight. The reaction mixture was then treated with H_2O (25 mL) and extracted with ether (2 × 25 mL). The organic layer was washed with saturated NaCl (3 × 20 mL), dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/ether 60/40) to give 2.3 g (55%) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 6.44 (d, J = 7.5 Hz, 1H), 6.07 (t, J = 7.5 Hz, 1H), 3.84 (d, J = 13.0 Hz, 1H), 3.74 (d, J = 13.0 Hz, 1H), 3.51−3.46 (m, 1H), 1.68−1.61 (m, 1H), 1.59−1.51 (m, 1H), 1.37 (m, 1H, NH), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 140.6, 128.5, 128.4, 127.05, 83.4, 63.1, 51.7, 28.05, 10.3.

***N*-Allyl-*N*-benzyl-*N*-(1-ethyl-3-iodoprop-2(Z)-enyl)amine.** A solution of *N*-benzyl-*N*-(1-ethyl-3-iodoprop-2(*Z*)-enyl)amine (5.15 mmol, 1.55 g), allyl bromide (7.72 mmol, 0.93 g), and K_2CO_3 (7.72 mmol, 1.06 g) in dry DMF (30 mL) was stirred at room temperature for 2 h, treated with a solution of NH_4Cl/NH_4OH (2/1) (20 mL), and extracted with ether (2 × 30 mL). The combined extracts were washed with satured NaCl (3 × 20 mL), dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/ether 70/30) to give 1.65 g (95%) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.25 (m, 5H), 6.49 (d, J = 7.5 Hz, 1H), 6.29 (dd, J = 9.0, 7.5 Hz, 1H), 5.92−5.84 (m, 1H), 5.25 (dt, J = 18.7, 1.7 Hz, 1H), 5.14 (d, J = 9.9 Hz, 1H), 3.89 (d, J = 14.2 Hz, 1H), 3.45 (d, J = 14.2 Hz, 1H), 3.49−3.44 (m, 1H), 3.32−3.26 (m, 1H), 3.0 (dd, J = 14.36, 7.56 Hz, 1H), 1.0 (t, J = 7.44 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 140.4, 136.9, 128.7, 128.2, 126.8, 117.0, 84.4, 64.7, 54.1, 53.3, 25.4, 10.9.

5-(Benzylamino)-4-methylpent-1-ene (12). A solution of benzyl allylamine (13.6 mmol, 2 g) in dry ether (15 mL) was cooled to −50 °C as *n*-butyllithium (1.6 M in hexanes, 16.32 mmol, 10.2 mL) was added dropwise. The resultant mixture was stirred at −30 °C during 20 min and then *tert*-butyllithium[23] (1.5 M in pentane, 13.6 mmol, 9 mL) was added dropwise and the mixture was stirred for 2 h at −20 °C. It was then cooled to −60 °C as allylmagnesium bromide (1.3 M in ether, 24.3 mmol, 18.7 mL) and zinc bromide (1 M in ether, 34 mmol, 34 mL) were added. The reaction mixture was allowed to warm to room temperature. After completion, a solution of NH_4Cl/NH_4OH (2/1) was added slowly at 0 °C. Ether was added and the mixture was stirred for at least 3 h with a few $Na_2S{\cdot}9H_2O$ crystals. The layers were separated, the aqueous one being extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/ether 50/50) to give 1.53 g (60%) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5H), 5.88−5.78 (m, 1H), 5.08−5.03 (m, 2H), 3.87 (d, J = 13.2 Hz, 1H), 3.77 (d, J = 13.2 Hz, 1H), 2.60 (m, 1H), 2.49 (dd, J = 11.6, 7.0 Hz, 1H), 2.21 (m, 1H), 1.96 (m, 1H), 1.78 (m, 1H), 0.95 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 137.3, 128.5, 128.2, 126.9, 116.0, 55.6, 54.3, 39.6, 33.4, 27.6.

***N*-Allyl-*N*-benzyl-*N*-(2(*S**),3(*S**)-dimethylpent-4-enyl)amine (8).** A solution of *N*-allyl-*N*-benzyl-*N*-(3-iodoprop-2(*Z*)-enyl)amine (5.29 mmol, 1.65 g) in dry ether (15 mL) was cooled to −80 °C as *tert*-butyllithium (1.5 M in pentane, 10.6 mmol, 7 mL) was added dropwise. The resultant mixture was stirred at −60 °C for 5 min as crotylmagnesium bromide (0.96 M in ether, 7.93 mmol, 8.3 mL) and zinc bromide (1 M in ether, 7.93 mmol, 7.93 mL) were added. The reaction mixture was stirred for 3 h at −40 °C. After completion, a solution of NH_4Cl/NH_4OH (2/1) was added slowly at −40 °C. Ether was added and the mixture was stirred for at least 3 h with a few $Na_2S{\cdot}9H_2O$ crystals. The layers were separated, the aqueous one being extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give 1.19 g (93%) of the title compound which was not further purified (dr = 91/9): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.25 (m, 5H), 5.95−5.88 (m, 1H), 5.74−5.67 (m, 2H), 5.21−5.14 (m, 2H), 4.98−4.92 (m, 2H), 3.62 (d, J = 13.68 Hz, 1H), 3.54 (d, J = 13.68 Hz, 1H), 3.12−3.05 (m, 2H), 2.43−2.37 (m, 2H), 2.20 (dd, J = 12.48, 7.64 Hz, 1H), 1.75−1.70 (m, 1H), 1.02 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 6.67 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 140.1, 136.3, 129.0, 128.2, 126.7, 117.1, 114.1, 58.8, 58.5, 57.2, 39.7, 36.2, 17.85, 14.2.

***N*-Allyl-*N*-benzyl-*N*-(2(*R**),3(*S**)-dimethylpent-4-enyl)amine (9).** A solution of *N*-allyl-*N*-benzyl-*N*-(3-iodoprop-2(*E*)-enyl)amine (3.91 mmol, 1.226 g) in dry ether (10 mL) was cooled to −80 °C as *tert*-butyllithium (1.5 M in pentane, 7.8 mmol, 5.22 mL) was added dropwise. The resultant mixture was stirred at −60 °C for 5 min as crotylmagnesium bromide (1.05 M in ether, 7.8 mmol, 7.46 mL) and zinc bromide (1 M in ether, 7.8 mmol, 7.8 mL) were added. The reaction mixture was stirred for 5 h at −40 °C. After completion, a solution of NH_4Cl/NH_4OH (2/1) was added slowly at −40 °C. Ether was added and the mixture was stirred for at least 3 h with a few $Na_2S{\cdot}9H_2O$ crystals. The layers were separated, the aqueous one being extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography (eluent, cyclohexane/ether 95/5) to give 0.62 g (65%) of the title compound as a unique isomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40−7.24 (m, 5H), 5.97−5.71 (m, 2H), 5.24−5.12 (m, 2H), 5.03−4.93 (m, 2H), 3.57 (s, 2H), 3.06 (d, J = 6.36 Hz, 2H), 2.47−2.30 (m, 2H), 1.22−1.12 (m, 1H), 1.80−1.73 (m, 1H), 0.88 (d, J = 6.84 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.2, 140.3, 136.5, 129.1, 128.3, 126.9, 117.2, 113.0, 59.0, 58.35, 57.45, 39.6, 35.9, 14.3 (2C).

***N*-Allyl-*N*-benzyl-*N*-(1(*S**)-ethyl-2(*S**)-methylpent-4-enyl)amine (10).** A solution of *N*-allyl-*N*-benzyl-*N*-(1-ethyl-3-iodoprop-2(*Z*)-enyl)amine (1.98 mmol, 0.677 g) in dry ether (10 mL) was cooled to −80 °C as *tert*-butyllithium (1.5 M in pentane, 4 mmol, 2.66 mL) was added dropwise. The resultant

(22) Lipshutz, B.; Keil, R.; Ellsworth, E. L. *Tetrahedron Lett.* **1990**, *31*, 7257−7260.

(23) Barluenga, J.; Gonzalez, R.; Fananas, F. J. *Tetrahedron Lett.* **1992**, *33*, 7573−7574.

mixture was stirred at −60 °C for 5 min as allylmagnesium bromide (1.38 M in ether, 6 mmol, 4.34 mL) and zinc bromide (1 M in ether, 6 mmol, 6 mL) were added. The reaction mixture was stirred for 3 h at −30 °C. After completion, a solution of NH_4Cl/NH_4OH (2/1) was added slowly at −30 °C. Ether was added and the mixture was stirred for at least 3 h with a few $Na_2S{\cdot}9H_2O$ crystals. The layers were separated, the aqueous one being extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography (eluent, cyclohexane/ether 95/5) to give 0.4 g (80%) of the title compound as a unique isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.25 (m, 5H), 5.93−5.81 (m, 2H), 5.21−5.01 (m, 4H), 3.83 (d, J = 14.16 Hz, 1H), 3.65 (d, J = 14.16 Hz, 1H), 3.23 (dd, J = 14.2, 5.48 Hz, 1H), 3.13 (dd, J = 14.2, 7.24 Hz, 1H), 2.44 (q, J = 6.2 Hz, 1H), 2.30−2.26 (m, 1H), 1.94−1.88 (m, 1H), 1.79−1.76 (m, 1H), 1.69−1.62 (m, 1H), 1.55−1.47 (m, 1H), 1.02 (t, J = 7.52 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.1, 138.4, 138.2, 128.85, 128.2, 126.7, 116.3, 115.55, 64.1, 54.8, 54.3, 39.0, 35.4, 20.4, 17.2, 13.5.

***N*-Allyl-*N*-benzyl-*N*-(2(*S**),3(*S**)-dimethyl-1*S**-ethylpent-4-enyl)amine (11).** A solution of *N*-allyl-*N*-benzyl-*N*-(1-ethyl-3-iodoprop-2(*Z*)-enyl)amine (4.85 mmol, 1.65 g) in dry ether (10 mL) was cooled to −80 °C as *tert*-butyllithium (1.5 M in pentane, 9.7 mmol, 6.5 mL) was added dropwise. The resultant mixture was stirred at −60 °C for 5 min as crotylmagnesium bromide (1.05 M in ether, 14.5 mmol, 13.8 mL) and zinc bromide (1 M in ether, 14.5 mmol, 14.5 mL) were added. The reaction mixture was stirred for 3 h at −30 °C. After completion, a solution of NH_4Cl/NH_4OH (2/1) was added slowly at −30 °C. Ether was added and the mixture was stirred for at least 3 h with a few $Na_2S{\cdot}9H_2O$ crystals. The layers were separated, the aqueous one being extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography (eluent, cyclohexane) to give 0.98 g (74%) of the title compound as a unique isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.25 (m, 5H), 5.87−5.82 (m, 1H), 5.78−5.69 (m, 1H), 5.17−5.06 (m, 2H), 4.99−4.95 (m, 2H), 3.88 (d, J = 14.2 Hz, 1H), 3.60 (d, J = 14.2 Hz, 1H), 3.29−3.24 (m, 1H), 3.12 (dd, J = 14.28, 7.64 Hz, 1H), 2.56−2.53 (m, 1H), 2.44−2.39 (m, 1H), 1.64−1.54 (m, 3H),1.03−0.99 (m, 6H), 0.93 (d, J = 6.92 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 141.4, 138.3, 128.9, 128.2, 126.6, 116.0, 114.1, 62.1, 55.1, 54.5, 41.6, 38.8, 21.2, 19.7, 13.5, 12.7.

General Procedure for Genet Deallylation Methodology.[15] *N*-Benzyl-*N*-(2(*S),3(*S**)-dimethylpent-4-enyl) amine (13).** A mixture of $Pd(dba)_2$ (0.24 mmol, 0.14 g, 5 mol %) and 1,4-bis(diphenylphosphino)butane (2.67 mmol, 0.1 g, 5 mol %) in THF (0.5 mL) was stirred at room temperature under an argon atmosphere, for 10 min. The preformed catalyst and 2-mercaptobenzoic acid (5.39 mmol, 0.82 g, 1.1 equiv) were added to a solution of *N*-allyl-*N*-benzyl-*N*-(2*S**,3*S**-dimethylpent-4-enyl)amine (**8**) (1.19 g, 4.9 mmol) in THF (10 mL) and the reaction mixture was stirred under an argon atmosphere at 20 °C. After completion, the mixture was treated with a solution of HCl 10% and extracted by AcOEt to eliminate the byproduct and the catalyst in the organic layer. The aqueous layer containing the protonated amine was basified with a solution of 1 M NaOH and extracted by AcOEt. The organic layer was dried over $MgSO_4$ and concentrated. The crude material was purified by chromatography on silica gel (eluant: cyclohexane/ether 50/50) to give 0.665 g (67%) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.25 (m, 5H), 5.80−5.72 (m, 1H), 5.02−4.98 (m, 2H), 3.81 (s, 2H), 2.65 (dd, J = 11.66, 6.08 Hz, 1H), 2.45 (dd, J = 11.66, 7.36 Hz, 1H), 2.33−2.28 (m, 2H), 1.71−1.65 (m, 1H), 2.20 (dd, J = 12.48, 7.64 Hz, 1H), 1.75−1.70 (m, 1H), 1.03 (d, J = 6.84 Hz, 3H), 0.91 (d, J = 6.67 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 140.85, 128.5, 128.2, 126.9, 114.1, 54.3, 53.7, 40.45, 38.2, 17.75, 14.6.

***N*-Benzyl-*N*-(2(*R**),3(*S**)-dimethylpent-4-enyl)amine (14).** *N*-Allyl-*N*-benzyl-*N*-(2(*R**),3(*S**)-dimethylpent-4-enyl)-amine (**9**) (0.387 g, 1.59 mmol) was treated according to the general procedure for Genet deallylation methodology[15] (see above for **13**). The crude material was purified by chromatography on silica gel (eluant, cyclohexane/ether 70/30) to give 0.205 g (64%) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.25 (m, 5H), 5.83−5.74 (m, 1H), 5.02−4.97 (m, 2H), 3.83 (d, J = 16.92 Hz, 1H), 3.78 (d, J = 16.92 Hz, 1H), 2.68 (dd, J = 11.64, 5.6 Hz, 1H), 2.45 (dd, J = 11.64, 7.88 Hz, 1H), 2.26−2.21 (m, 1H), 1.71−1.65 (m, 1H), 1.36 (m, 1H, NH), 0.97 (d, J = 6.84 Hz, 3H), 0.91 (d, J = 6.76 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 141.1, 128.5, 128.2, 127.0, 113.4, 54.4, 53.8, 40.6, 38.0, 15.5, 14.8.

***N*-Benzyl-*N*-(1(*S**)-ethyl-2(*S**)-methylpent-4-enyl)-amine (15).** *N*-Allyl-*N*-benzyl-*N*-(1(*S**),(2*S**)-dimethylpent-4-enyl)amine (**10**) (0.4 g, 1.55 mmol) was treated according to the general procedure for Genet deallylation methodology[15] (see above for **13**). The crude material was purified by chromatography on silica gel (eluant, cyclohexane/ether 70/30) to give 0.15 g of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.18 (m, 5H), 5.86−5.65 (m, 1H), 5.03−4.93 (m, 2H, H_1), 3.81 (d, J = 13 Hz, 1H), 3.71 (d, J = 13 Hz, 1H), 2.35 (td, J = 6.37, 3.72 Hz, 1H), 2.27−2.20 (m, 1H), 1.90−1.83 (m, 1H), 1.78−1.70 (m, 1H), 1.50−1.36 (m, 2H), 1.13 (m, 1H, NH), 0.89 (t, J = 7.33 Hz, 3H), 0.85 (d, J = 6.75 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.6, 138.5, 128.5, 128.4, 127.0, 115.6, 62.6, 52.4, 37.8, 35.0, 24.0, 14.9, 11.3.

***N*-Benzyl-*N*-(2(*S**),3(*S**)-dimethyl-1(*S**)-ethylpent-4-enyl)amine (16).** *N*-Allyl-*N*-benzyl-*N*-(2(*S**),3(*S**)-dimethyl-1(*S**)-ethylpent-4-enyl)amine (**11**) (0.768 g, 2.84 mmol) was treated according to the general procedure for Genet deallylation methodology[15] (see above for **13**); 0.445 g (68%) of the title compound was thus obtained: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.27 (m, 5H), 5.81−5.72 (m, 1H), 5.04−4.96 (m, 1H), 3.90 (d, J = 12.84 Hz, 1H), 3.70 (d, J = 12.84 Hz, 1H), 2.55−2.51 (m, 1H), 2.35−2.27 (m, 1H), 1.72−1.65 (m, 1H), 1.51−1.43 (m, 2H), 1.15 (m, 1H, NH), 0.99 (d, J = 6.72 Hz, 3H), 0.93 (t, J = 7.44 Hz, 3H), 0.88 (d, J = 7.04 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 141.4, 128.4 (4C), 126.9, 113.7, 60.3, 52.25, 40.75, 39.9, 24.4, 19.4, 11.2, 10.8.

***N*-Benzyl-*N*-pent-4-enyl glycinate Methyl Ester (1).** To a solution of *N*-benzyl-*N*-pent-4-enylamine (8.11 mmol, 1.42 g) in dry DMSO (200 mL) were added methyl α-bromo acetate (9.73 mmol, 1.49 g) and triethylamine (9.73 mmol, 0.98 g). The resultant mixture was stirred for 5 h at room temperature and then treated with a solution of NH_4Cl/NH_4OH 2/1 (50 mL), extracted with ether (2 × 100 mL). The combined extracts were washed with satured NaCl (3 × 50 mL), dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/ether 70/30) to give 1.6 g (80%) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.27 (m, 5H), 5.86−5.79 (m, 1H), 5.05−4.95 (m, 2H), 3.81 (s, 2H), 3.70 (s, 3H), 3.35 (s, 2H), 2.68 (t, J = 7.3 Hz, 2H), 2.14−2.08 (m, 2H), 1.66−1.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 139.2, 138.6, 129.0, 128.4, 127.2, 114.7, 58.3, 54.1, 53.5, 51.35, 31.4, 26.9.

General Procedure for the Alkylation of Secondary Amines with Methyl α-Bromoacetate. *N*-Benzyl-*N*-(2-methylpent-4-enyl)glycinate Methyl Ester (17). To a solution of NaH (50% in grease, 6.3 mmol, 0.3 g) in dry DMF (20 mL) was added 5-(benzylamino)-4-methylpent-1-ene **12** (0.99 g, 5.24 mmol) at 0 °C. The reaction mixture was stirred at 0 °C during 10 min, and methyl α-bromoacetate (6.3 mmol, 0.96 g) was added. The reaction mixture was stirred for 6 h and treated with a solution of NH_4Cl/NH_4OH (2/1). Ether was added, and the layers were separated, the aqueous one being extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/ether 97/3) to give 0.93 g (68%) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4−7.27 (m, 5H), 5.86−5.75 (m, 1H), 5.06−5.00 (m, 2H), 3.82 (s, 2H), 3.72 (s, 3H), 3.33 (s, 2H), 2.56 (dd, J = 12.7, 7.16 Hz, 1H), 2.46 (dd, J = 12.7, 7.24 Hz, 1H), 2.32−2.27 (m, 1H), 1.88−1.83 (m, 1H), 1.79−1.75 (m, 1H), 0.93 (d, J = 6.56 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 139.5, 135.5, 129.0, 128.4, 127.1, 115.9, 60.5, 58.5, 54.4, 51.3, 39.2, 31.6, 17.85.

***N*-Benzyl-*N*-(2(*S**),3(*S**)-dimethylpent-4-enyl)glycinate Methyl Ester (18).** A solution of *N*-allyl-*N*-benzyl-*N*-(2(*S**),3(*S**)-dimethylpent-4-enyl)amine (**13**) (0.665 g, 3.27 mmol) was treated following the general procedure for the alkylation of secondary amines with methyl α-bromoacetate. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/ether 97/3) to give 0.83 g (92%) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.25 (m, 5H), 5.75−5.66 (m, 1H), 4.99−4.93 (m, 2H), 3.83 (d, J = 13.64 Hz, 1H), 3.78 (d, J = 13.64 Hz, 1H), 3.70 (s, 3H), 3.32 (s, 2H), 2.63 (dd, J = 12.7, 7.04 Hz, 1H), 2.44−2.38 (m, 2H), 1.72−1.66 (m, 1H),1.02 (d, J = 7.0 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.25, 141.3, 139.5, 129.0, 128.4, 127.1, 114.4, 59.0, 58.4, 54.2, 51.3, 39.6, 36.5, 18.0, 13.9.

***N*-Benzyl-*N*-(2(*R**),3(*S**)-dimethylpent-4-enyl)glycinate Methyl Ester (19).** A solution of *N*-allyl-*N*-benzyl-*N*-(2(*R**),(3*S**)-dimethylpent-4-enyl)amine (**14**) (0.205 g, 1 mmol) was treated following the general procedure for the alkylation of secondary amines with methyl α-bromoacetate. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/ether 70/30) to give 0.163 g (59%) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.25 (m, 5H), 5.84−5.74 (m, 1H), 5.0−4.96 (m, 2H), 3.82 (d, J = 13.92 Hz, 1H), 3.78 (d, J = 13.92 Hz, 1H), 3.71 (s, 3H), 3.32 (s, 2H), 2.67 (dd, J = 12.8, 6.84 Hz, 1H), 2.40 (dd, J = 12.8, 7.88 Hz, 1H), 2.36−2.31 (m, 1H), 1.77−1.70 (m, 1H), 0.89 (d, J = 6.84 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 144.0, 139.5, 129.1, 128.4, 127.2, 113.2, 58.6, 58.55, 54.4, 51.3, 39.4, 35.9, 14.3, 14.0.

***N*-Benzyl-*N*-(1(*S**)-ethyl-2(*S**)-methylpent-4-enyl)glycinate Methyl Ester (20).** A solution of *N*-benzyl-N -(1(*S**)-ethyl-2(*S**)-methylpent-4-enyl)amine **15** (0.094 g, 0.43 mmol) was treated following the general procedure for the alkylation of secondary amines with methyl α-bromoacetate. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/ether 70/30) to give 0.062 g (50%) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.23 (m, 5H), 5.80−5.71 (m, 1H), 5.04−4.97 (m, 2H), 3.89 (d, J = 13.84 Hz, 1H), 3.81 (d, J = 13.84 Hz, 1H), 3.64 (s, 3H), 3.40 (d, J = 16.76 Hz, 1H), 3.24 (d, J = 16.76 Hz, 1H), 2.41 (q, J = 6.28 Hz, 1H), 2.26−2.20 (m, 1H), 1.92−1.86 (m, 1H), 1.75−1.70 (m, 1H), 1.65−1.60 (m, 1H), 1.57−1.50 (m, 1H), 0.99 (t, J = 7.36 Hz, 3H), 0.97 (d, J = 6.76 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.25, 140.05, 138.1, 129.2, 128.3, 127.1, 115.8, 66.5, 56.3, 53.0, 51.5, 38.7, 36.0, 21.4, 16.9, 13.2.

***N*-Benzyl-*N*-(2(*S**),3(*S**)-dimethyl-1(*S**)-ethylpent-4-enyl)glycinate Methyl Ester (21).** A solution of *N*-benzyl-*N*-(2(*S**),3(*S**)-dimethyl-1(*S**)-ethylpent-4-enyl)amine (**16**) (0.445 g, 1.92 mmol) was treated following the general procedure for the alkylation of secondary amines with methyl α-bromoacetate. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/ether 80/20) to give 0.294 g (51%) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.22 (m, 5H), 5.76−5.67 (m, 1H), 4.97 (d, J = 14.76 Hz, 1H), 4.97 (d, J = 12.4 Hz, 1H), 3.93 (d, J = 13.72 Hz, 1H), 3.81 (d, J = 13.72 Hz, 1H), 3.61 (s, 3H), 3.41 (d, J = 16.6 Hz, 1H), 3.35 (d, J = 16.6 Hz, 1H), 2.53−2.47 (m, 1H), 2.45−2.37 (m, 1H), 1.65−1.50 (m, 3H), 1.02 (t, J = 7.36 Hz, 3H), 1.01 (d, J = 6.96 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 141.3, 140.0, 129.3, 128.2, 127.0, 114.3, 65.0, 56.85, 53.3, 51.4, 41.8, 38.95, 22.2, 19.7, 13.1, 12.3.

Typical Procedure of the Cyclization Reaction in the Synthesis of Polysubstituted Piperidine Derivatives. A solution of *N*-benzyl-*N*-(pent-4-enyl)glycinate methyl ester (**1**) (1 mmol, 0.25 g) in dry ether (15 mL) was cooled to −20 °C as LDA (2 M in THF/*n*-heptane, 2 mmol, 1 mL) was added dropwise. The reaction mixture was then allowed to warm to 10 °C for 10 min and cooled to −40 °C as zinc bromide (1 M in ether, 2 mmol, 2 mL) was added dropwise. The reaction mixture was then allowed to warm to 20 °C. The cyclized organozinc species **3** is ready for further conversions.

(2*S,3*R**)-1-Benzyl-2-carbomethoxy-3-methylpiperidine (4).** The cyclized product **3** was cooled to 0 °C as a solution of NH_4Cl/NH_4OH 2/1 was added slowly. Ether was added and the mixure was stirred for at least 3 h with a few $Na_2S{\cdot}9H_2O$ crystals. The layers were separated, the aqueous one being extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/ether 90/10) to give 0.163 g (66%) of the title compound as a unique isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H), 3.71 (s, 3H), 3.64 (d, J = 13.5 Hz, 1H), 3.59 (d, J = 13.5 Hz, 1H), 3.48 (d, J = 5.2 Hz, 1H), 3.02−2.96 (m, 1H), 2.55−2.51 (m, 1H), 2.09−1.99 (m, 1H), 1.75−1.68 (m, 1H), 1.62−1.46 (m, 3H), 0.92 (d, J = 7.04 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 139.1, 128.9, 128.3, 127.1, 66.3, 60.25, 50.55, 47.0, 33.25, 27.9, 25.2, 18.25; IR (neat) 2910, 2820, 1720, 1490, 1420, 1360, 1270, 1190, 1140, 1060, 1000, 740, 690. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.91; H, 8.56; N, 5.60.

(2*S,3*R**)-1-Benzyl-2-carbomethoxy-3-(iodomethyl)piperidine (5).** The cyclized product **3** was cooled to 0 °C as an excess of solid iodine (3 mmol, 0.76 g) was added. After stirring for 10 min at room temperature, a solution of NH_4Cl/NH_4OH 2/1 was added slowly. Ether was added, and the layers were separated, the aqueous one being extracted with ether. The combined extracts were diluted with saturated $Na_2S_2O_3$, washed with brine, and stirred for at least 3 h with a few $Na_2S{\cdot}9H_2O$ crystals. These were then removed by filtration and the organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent, dichloromethane/methanol 95/5) to give 0.303 g (81%) of the title compound as a unique isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 3.75 (s, 3H), 3.77−3.72 (m, 2H), 3.63 (d, J = 13.6 Hz, 1H), 3.17 (dd, J = 10.0, 7.2 Hz, 1H), 3.09 (dd, J = 10.0, 7.3 Hz, 1H), 2.94−2.87 (m, 1H), 2.55−2.51 (m, 1H), 2.26−2.21 (m, 1H), 1.85−1.81 (m, 1H), 1.72−1.69 (m, 1H), 1.63−1.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 138.9, 128.7, 128.4, 127.2, 64.8, 59.95, 50.9, 46.6, 42.1, 26.5, 25.0, 8.5; IR (neat) 2920, 2820, 1710, 1490, 1450, 1360, 1240, 1190−1140, 990, 730, 690. Anal. Calcd for $C_{15}H_{20}NO_2I$: C, 48.27; H, 5.4; N, 3.75. Found: C, 48.47; H, 5.6; N, 3.75.

(2*S,3*R**)-1-Benzyl-2-carbomethoxy-3-but-3-enylpiperidine (6).** The cyclized product **3** was cooled to −20 °C as copper cyanide (0.18 g, 2 mmol) in THF (10 mL) was added. The resultant mixture was slowly allowed to rise to −5 °C and stirred for 15 min. It was then cooled to −40 °C as allyl bromide (0.36 g, 3 mmol) was injected into the flask. The reaction mixture was slowly allowed to warm to room temperature overnight and was subsequently quenched with a solution of NH_4Cl/NH_4OH (2/1). The layers were separated and the aqueous one was extracted with ether. The combined extracts were washed with brine and stirred for at least 3 h with a few $Na_2S{\cdot}9H_2O$ crystals. These were then removed by filtration, and the organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/ether 90/10) to give 0.186 g (65%) of the title compound as a unique isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.24 (m, 5H), 5.84−5.73 (m, 1H), 5.02−4.94 (m, 2H), 3.71 (s, 3H), 3.66 (d, J = 13.45 Hz, 1H), 3.56 (d, J = 13.45 Hz, 1H), 3.55 (d, J = 5.12 Hz, 1H), 2.97 (td, J = 11.36, 8.4 Hz, 1H), 2.58−2.54 (m, 1H), 2.13−2.08 (m, 2H), 1.88−1.85 (m, 1H), 1.73−1.68 (m, 1H), 1.60−1.51 (m, 3H), 1.39−1.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 139.15, 138.7, 128.9, 128.4, 127.1, 114.85, 64.9, 60.3, 50.6, 46.6, 38.1, 32.2, 31.4, 25.4, 25.2.

(2*S,3*S**)-1-Benzyl-2-carbomethoxy-3-methylpiperidine (7).** A solution of (2*S**,3*R**)-1-benzyl-2-carbomethoxy-3-methylpiperidine (**4**) (0.34 mmol, 0.084 g) in dry ether (15 mL) was cooled to −20 °C as LDA (2 M in THF/*n*-heptane, 1.35 mmol, 0.68 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature for 20 min, it was then cooled to 0 °C as a solution of NH_4Cl/NH_4OH 2/1 was added slowly. Ether was added and the mixure was stirred for at least 3 h with a few $Na_2S{\cdot}9H_2O$ crystals. The layers were separated, the aqueous one being extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/

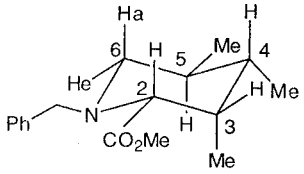
ether 90/10) to give 0.045 g (55%) of the title compound (cis/trans 35/65): ^{1}H NMR (400 MHz, $CDCl_3$) of the trans isomer δ 7.34−7.25 (m, 5H), 3.78 (s, 3H), 3.73 (d, J = 13.32 Hz, 1H), 3.27 (d, J = 13.32 Hz, 1H), 2.89 (dt, J = 11.28, 3.52 Hz, 1H), 2.66 (d, J = 9.2 Hz, 1H), 1.95−1.88 (m, 2H), 1.77−1.71 (m, 1H), 1.63−1.56 (m, 2H), 1.07−0.99 (m, 1H), 0.92 (d, J = 6.64 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.35, 137.7, 129.6, 128.3, 127.3, 73.75, 61.2, 51.85, 51.4, 34.4, 32.1, 24.6, 18.9.

(2*S,3*R**,5**R*)-1-Benzyl-2-carbomethoxy-3,5-dimethylpiperidine (22).** A solution of *N*-benzyl-*N*-(2-methylpent-4-enyl)glycinate methyl ester (**17**) (0.2 g, 0.77 mmol) was treated following the typical procedure for the cyclization reaction (as described for the preparation of **3**). The cyclized product was cooled to 0 °C as a solution of NH_4Cl/NH_4OH (2/1) was added slowly. Ether was added and the mixure was stirred for at least 3 h with a few $Na_2S{\cdot}9H_2O$ crystals. The layers were separated, the aqueous one being extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/ether 90/10) to give 0.123 g (62%) of the title compound as a unique isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 3.77 (d, J = 13.52 Hz, 1H), 3.75 (s, 3H), 3.35 (d, J = 13.52 Hz, 1H), 3.22 (d, J = 4.28 Hz, 1H), 2.95 (dd, J = 10.84, 3.2 Hz, 1H), 2.28−2.23 (m, 1H), 1.91−1.87 (m, 1H), 1.84−1.79 (m, 1H), 1.71−1.65 (m, 1H), 1.26−1.20 (m, 1H), 1.01 (d, J = 7.04 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 138.9, 129.1, 128.25, 127.1, 67.85, 60.35, 57.35, 51.2, 37.9, 30.6, 26.2, 19.2, 16.6; IR (neat) 2940, 2920, 1740, 1720, 1490, 1450, 1380, 1260, 1190, 1170, 1140, 1090, 1070, 1020, 740, 690. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.44; H, 8.85; N, 5.41.

(2*S,3*R**,5**R*)-1-Benzyl-5-(bromomethyl)-2-carbomethoxy-3-methylpiperidine (23).** A solution of *N*-benzyl-*N*-(2-methylpent-4-enyl)glycinate methyl ester (**17**) (0.33 g, 1.26 mmol) was treated by following the typical procedure for the cyclization reaction (as described for the preparation of **3**). The cyclized product was cooled to −30 °C as an excess of *N*-bromosuccinimide (2.52 mmol, 0.45 g) was added. After stirring for 10 min at room temperature, a solution of NH_4Cl/NH_4OH (2/1) was added slowly. Ether was added, and the layers were separated, the aqueous one being extracted with ether. The combined extracts were washed with brine and stirred for at least 3 h with a few $Na_2S{\cdot}9H_2O$ crystals. These were then removed by filtration and the organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/ether 90/10) to give 0.302 g (56%) of the title compound as a unique isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 3.78 (s, 3H), 3.73 (d, J = 13.48 Hz, 1H), 3.53−3.49 (m, 3H), 3.42 (d, J = 13.48 Hz, 1H), 2.93 (dd, J = 11.12, 3.4 Hz, 1H), 2.52−2.46 (m, 1H), 2.08−2.02 (m, 1H), 1.95−1.90 (m, 1H), 1.89−1.84 (m, 1H), 1.36−1.29 (m, 1H), 0.96 (d, J = 6.56 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 138.7, 128.9, 128.35, 127.2, 66.3, 60.1, 58.2, 51.5, 38.5, 34.6, 33.7, 26.3, 18.9.

***N*-Benzyl-2-carbomethoxy-2,3-methano-5-methylpiperidine (24).** A solution of (2*S**,3*R**,5**R*)-1-benzyl-5-(bromomethyl)-2-carbomethoxy-3-methylpiperidine (**23**) (0.27 g, 0.8 mmol) in dry ether (15 mL) was cooled to −40 °C as LDA (2 M in THF/*n*-heptane, 1.6 mmol, 0.8 mL) was added dropwise. The reaction mixture was then allowed to warm to room temperature for 30 min. After completion, the solution was cooled to 0 °C as a solution of NH_4Cl/NH_4OH (2/1) was added slowly. Ether was added, and the layers were separated, the aqueous one being extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/ether 80/20) to give 0.1 g (50%) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.24 (m, 5H), 3.80 (d, J = 13.48 Hz, 1H), 3.69 (s, 3H), 3.55 (d, J = 13.48 Hz, 1H), 2.39−2.36 (m, 1H), 2.15 (dd, J = 13.52, 10.44 Hz, 1H), 2.02−1.92 (m, 2H), 1.56−1.52 (m, 1H), 1.45−1.39 (m, 1H), 1.37 (dd, J = 9.8, 4.24 Hz, 1H), 1.06 (dd, J = 7.6, 4.24 Hz, 1H), 0.79 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 140.0, 129.3, 128.3, 127.1, 58.5, 53.5, 52.4, 44.2, 31.2, 25.65, 22.35, 18.8, 18.25; IR (neat) 2970, 2810, 1710, 1490, 1450, 1430, 1350, 1250, 1190, 1160, 1100, 740, 690; MS m/z 260 (MH^+).

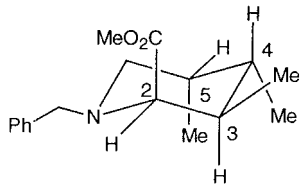
(2*S,3*R**,4*R**,5**R*)-1-Benzyl-2-carbomethoxy-3,4,5-trimethylpiperidine (25).** A solution of *N*-benzyl-*N*-(2(*R**),3(*S**)-dimethylpent-4-enyl)glycinate methyl ester (**19**) (0.16 g, 0.59 mmol) was treated following the typical procedure for the cyclization reaction (as described for the preparation of **3**). The cyclized product thus obtained was cooled to 0 °C as a solution of NH_4Cl/NH_4OH (2/1) was added slowly. Ether was added and the mixure was stirred for at least 3 h with a few $Na_2S{\cdot}9H_2O$ crystals. The layers were separated, the aqueous one being extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/ether 80/20) to give 0.113 g (70%) of the title compound as a unique isomer. The relative configuration was determined after irradiation of the methyl groups located on the C_3 and C_4 positions.



J2-3=Jae=3.5Hz
J3-4=Jea=3.5Hz
J4-5=Jaa=10.95Hz
J5-6a=Jaa=10.95Hz
J5-6e=Jae=3.2Hz
J6a-6e=Jgem=10.7Hz

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.24 (m, 5H), 3.95 (d, J = 13.28 Hz, 1H), 3.77 (s, 3H), 3.14 (d, J = 13.28 Hz, 1H), 3.12 (d, J = 3.5 Hz, 1H), 2.77 (dd, J = 10.7, 3.2 Hz, 1H), 2.02−1.99 (m, 1H), 1.59 (dd, J = 10.95, 10.7 Hz, 1H), 1.55−1.51 (m, 1H), 1.28−1.23 (m, 1H), 0.94 (d, J = 6.68 Hz, 3H), 0.93 (d, J = 6.12 Hz, 3H), 0.74 (d, J = 6.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 138.7, 129.4, 128.2, 127.05, 70.7, 61.0, 60.3, 51.7, 41.3, 38.5, 30.75, 17.1, 16.9, 9.0. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.1; H, 9.15; N, 5.09. Found: C, 74.1; H, 9.14; N, 5.09.

(2*S,3*R**,4*S**,5**R*)-1-Benzyl-2-carbomethoxy-3,4,5-trimethylpiperidine (26).** A solution of *N*-benzyl-*N*-(2(*S**),3(*S**)-dimethylpent-4-enyl)glycinate methyl ester (**18**) (0.2 g, 0.72 mmol) was treated following the typical procedure for the cyclization reaction (as described for the preparation of **3**). The cyclized product thus obtained was cooled to 0 °C as a solution of NH_4Cl/NH_4OH (2/1) was added slowly. Ether was added and the mixure was stirred for at least 3 h with a few $Na_2S{\cdot}9H_2O$ crystals. The layers were separated, the aqueous one being extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/ether 90/10) to give 0.136 g (68%) of the title compound (dr = 90/10). The coupling constants were assigned (in C_6D_6 solvent), after irradiation of the methyl group located on the C_4 and C_3 positions.



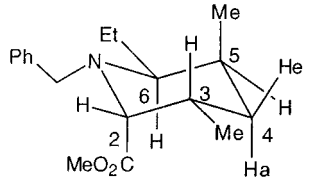
J2-3=Jea=5.24Hz
J3-4=Jaa=9.96Hz
J4-5=Jae=4.24Hz

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5H), 3.72 (s, 3H), 3.58 (s, 2H), 3.47 (d, J = 4.76 Hz, 1H), 3.11 (dd, J = 11.28, 3.4 Hz, 1H), 2.29 (dd, J = 11.28, 4.12 Hz, 1H), 1.97−1.88 (m, 2H), 1.85−1.81 (m, 1H), 0.95 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 6.56 Hz, 3H), 0.90 (d, J = 6.52 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.0, 139.4, 128.7, 128.3, 127.0, 66.25, 60.0, 53.5, 50.6, 34.6, 34.2, 33.0, 16.3, 15.9, 13.2.

^{1}H NMR (400 MHz, C_6D_6) δ 7.37 (d, J = 7.48 Hz, 2H), 7.19 (t, J = 7.36 Hz, 2H), 7.09 (t, J = 7.28 Hz, 1H), 3.59 (d, J = 13.4 Hz, 1H), 3.53 (d, J = 13.4 Hz, 1H), 3.43 (d, J = 5.24 Hz, 1H), 3.32 (s, 3H), 3.31−3.27 (m, 1H), 2.23 (dd, J = 11.2, 3.6 Hz, 1H), 1.98−1.94 (m, 1H), 1.79−1.75 (m, 1H), 1.65−1.61 (m,

1H), 0.87 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 6.92 Hz, 3H), 0.74 (d, J = 6.92 Hz, 3H); ^{13}C NMR (50 MHz, C_6D_6) δ 171.9, 139.6, 128.7, 127.2, 127.0, 66.2, 60.1, 53.3, 49.7, 34.2, 34.0, 33.25, 16.2, 15.6, 12.8. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74. 13; H, 9.12; N, 5.21.

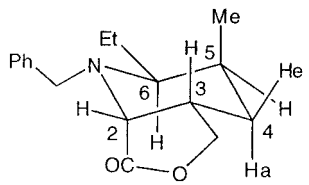
(2*S,3*R**,5**R*,6*R**)-1-Benzyl-2-carbomethoxy-3,5-dimethyl-6-ethylpiperidine (28).** A solution of *N*-benzyl-*N*-(1(*S**)-ethyl-2(*S**)-methylpent-4-enyl)glycinate methyl ester (**20**) (0.032 g, 0.11 mmol) was treated following the typical procedure for the cyclization reaction (as described for the preparation of **3**). The cyclized product **27** was cooled to 0 °C as a solution of NH_4Cl/NH_4OH (2/1) was added slowly. Ether was added and the mixure was stirred for at least 3 h with a few $Na_2S{\cdot}9H_2O$ crystals. The layers were separated, the aqueous one being extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/ether 90/10) to give 0.019 g (60%). The coupling constants were determined by irradiation of the methyl group located on the C_5 position.



J2-3=Jea=5.68Hz
J3-4a=Jaa=12.8Hz
J3-4e=Jae=3.72Hz
J4a-4e=Jgem=12.8Hz
J4a-5=Jae=4.44Hz
J4e-5=Jee=3.72Hz
J5-6=Jea=3.48Hz

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.21 (m, 5H), 4.07 (d, J = 14.68 Hz, 1H), 3.68 (s, 3H), 3.44 (d, J = 5.68 Hz, 1H), 3.35 (d, J = 14.68 Hz, 1H), 3.34−3.30 (m, 1H), 2.25−2.16 (m, 1H), 2.04−1.96 (m, 1H), 1.79 (td, J = 12.8, 4.44 Hz, 1H), 1.71−1.65 (m, 1H), 1.41 (dt, J = 12.8, 3.72 Hz, 1H), 1.18−1.12 (m, 1H), 1.01 (d, J = 6.88 Hz, 3H), 0.90 (t, J = 7.36 Hz, 3H), 0.83 (d, J = 7.04 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 143.3, 128.25, 128.1, 126.7, 65.8, 58.45, 54.5, 50.4, 36.1, 29.4, 27.2, 23.5, 18.45, 12.8, 11.1; IR (neat) 2950, 1730, 1600, 1490, 1450, 1380, 1190, 1140, 1090, 740, 690; MS m/z 290 (MH^+).

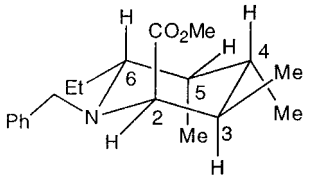
2-Benzyl-2-aza-3-ethyl-4-methyl-8-oxabicyclo[4.3.0]-nonan-9-one (29). A solution of *N*-benzyl-*N*-(1(*S**)-ethyl-2(*S**)-dimethylpent-4-enyl)glycinate methyl ester (**20**) (0.032 g, 0.11 mmol) was treated following the typical procedure for the cyclization reaction (as described for the preparation of **3**). The cyclized product **27** was oxydized with dry air. After completion, a solution of NH_4Cl/NH_4OH (2/1) was added slowly. Ether was added and the mixure was stirred for at least 3 h with a few $Na_2S{\cdot}9H_2O$ crystals. The layers were separated, the aqueous one being extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/ether 90/10) to give 0.022 g (60%) of the title compound. The coupling constants were determined by irradiation of the hydrogen atom located on the C_5 position.



J2-3=Jea=6.32Hz
J3-4a=Jaa=10.8Hz
J4a-4e=Jgem=10.8Hz
J4a-5=Jae=4.4Hz

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.23 (m, 5H), 4.21 (d, J = 14.24 Hz, 1H), 4.17−4.13 (m, 1H), 4.13 (d, J = 14.24 Hz, 1H), 3.96 (dd, J = 8.8, 1.88 Hz, 1H), 3.53 (d, J = 6.32 Hz, 1H), 2.71−2.66 (m, 1H), 2.59−2.54 (m, 1H), 1.97−1.92 (m, 1H), 1.82−1.73 (m, 2H), 1.62−1.57 (m, 1H), 1.29−1.24 (m, 1H), 0.98 (d, J = 7.0 Hz, 1H), 0.89 (t, J = 7.36 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 140.8, 128.5, 126.9, 70.5, 60.8, 59.4, 52.5, 32.1, 31.6, 29.9, 29.4, 12.6, 11.6; MS m/z 274 (MH^+).

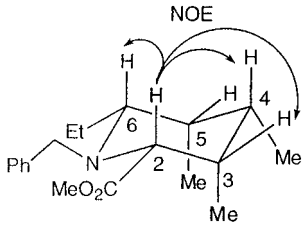
(2*S,3*R**,4*S**,5*R**,6*R**)-1-Benzyl-2-carbomethoxy-3,4,5-trimethyl-6-ethylpiperidine (30A)/(2*S**,3*R**,4*R**,5*S**,6*S**)-1-Benzyl-2-carbomethoxy-3,4,5-trimethyl-6-ethylpiperidine (30B).** A solution of *N*-benzyl-*N*-(2(*S**),3(*S**)-dimethyl-1(*S**)-ethylpent-4-enyl)glycinate methyl ester (**21**) (0.13 g, 0.42 mmol) was treated following the typical procedure for the cyclization reaction (as described for the preparation of **3**). The cyclized product thus obtained was cooled to 0 °C as a solution of NH_4Cl/NH_4OH (2/1) was added slowly. Ether was added and the mixure was stirred for at least 3 h with a few $Na_2S{\cdot}9H_2O$ crystals. The layers were separated, the aqueous one being extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent, cyclohexane/ether 90/10) to give 0.038 g (30%) of **30A** and 0.02 g (15%) of **30B**. The coupling constants of **30A** were determined by irradiation of the methyl groups located on the C_3 and C_4 positions.



J2-3=Jea=5.8Hz
J3-4=Jaa=11.8Hz
J4-5=Jae=3.88Hz

30A: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.22 (m, 5H), 4.08 (d, J = 14.64 Hz, 1H), 3.67 (s, 3H), 3.51−3.44 (m, 1H), 3.41 (d, J = 5.8 Hz, 1H), 3.30 (d, J = 14.64 Hz, 1H), 2.22−2.16 (m, 1H), 1.99−1.92 (m, 1H), 1.87−1.82 (m, 2H), 1.21−1.17 (m, 1H), 0.91−0.85 (m, 9H), 0.78 (d, J = 6.92 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 141.8, 128.3, 128.1, 126.8, 66.5, 60.2, 54.0, 50.3, 36.3, 35.35, 32.3, 24.05, 17.65, 10.9, 15.7, 5.5. Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.2; H, 9.63; N, 4.62. Found: C, 74.81; H, 9.66; N, 4.51.

The coupling constants[20] of **30B** were determined by irradiation of the methyl group located on the C_4 position, the hydrogen atom on the C5 position as well as the CH_2 of the ethyl groups.



J2-3=Jae=4.0Hz
J3-4=Jea ou Jee=4.0Hz
J4-5=Jae=4.0Hz
J5-6=Jea=3.2Hz

30B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.20 (m, 5H), 3.75 (d, J = 16.36 Hz, 1H), 3.66 (s, 3H), 3.58 (d, J = 16.36 Hz, 1H), 3.39 (d, J = 4.0 Hz, 1H), 2.24−2.20 (m, 1H), 2.04−1.98 (m, 1H), 1.84−1.80 (m, 1H), 1.66−1.60 (m, 2H), 1.04 (d, J = 7.16 Hz, 3H), 0.99 (d, J = 7.16 Hz, 3H), 0.97−0.92 (m, 1H), 0.88 (d, J = 6.84 Hz, 3H), 0.73 (d, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 142.2, 128.0, 127.8, 126.2, 70.6, 58.1, 51.5, 38.2, 37.6, 34.4, 29.9, 23.6, 17.4, 12.3, 10.6, 9.6.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of starting amines and of compounds **1**, **4**−**11**, **13**−**26**, **28**, **29**, and **30A** (67 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO971449M