Diastereoselective and Enantioselective Intramolecular Amino−Zinc−Enolate Carbometalation Reactions. A New Polysubstituted Pyrrolidines Synthesis

Edwige Lorthiois, Ilane Marek,* and Jean F. Normant*

Laboratoire de Chimie des Organoéléments, Université P. et M. Curie, 4 Place Jussieu, 75252 Paris Cedex 05-France

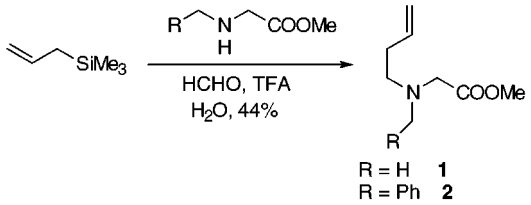
Received May 6, 1997

The amino−zinc−enolate cyclization allowed a new and straightforward route to polysubstituted pyrrolidines from simple starting materials. From this study, we have been able to determine, for the first time, the stereochemical influence of the substituents on the ring in the carbocyclization reaction. The diastereoselectivity thus obtained was explained by a chairlike amino−zinc−enolate transition state.

Introduction

Despite the extensive investigation of the intramolecular carbometalation reactions[1] of alkenes and alkynes, there are very few reports on the carbocyclization of *stabilized* carbanions. Indeed, the first carbocyclization reaction across activated alkynes (alkylthio- and alkoxyalkynes) via such lithium species was recently reported by Funk and co-workers[2] as a source of functionalized carbocycles. Moreover, the intramolecular carbometalation of (η^4-diene)Fe(CO)$_3$ complexes by a lithium enolate,[3] the palladium-catalyzed carbocyclization of δ-unsaturated malonates,[4] the catalyzed Conia's ene reaction,[5] and very recently the carbometalation of cyclopropene with zincated amides, esters, and hydrazones[6] were also described. However, the *simple* intramolecular carbometalation of a metal enolate toward an unfunctionalized or non strained double bond has never received attention. In the course of our research in the intramolecular carbometalation of propargyl (or allenyl) zinc derivatives, via the metallo−ene−allene reaction,[7] we have been interested to study the addition of an enolate moiety across a double bond for the synthesis of 3-substituted pyrrolidines,[8] known to be conformationally restricted α-amino acids analogues.[9] Here, are reported our results of the amino−zinc−enolate carbocyclizations with a complete study of the stereochemical influence of substituents on the pyrrolidine ring.

Scheme 1



Results and Discussion

The starting materials **1** and **2** were prepared either by a three-component condensation in a one-step procedure in moderate yield as described in Scheme 1 or in the already known two-step procedure.[10] In the former case, treatment of the allylsilane with an *N*-alkyliminium ion (generated by mixing the corresponding amine and

* Fax: 01 44 27 75 67. E-mail: normant@moka.ccr.jussieu.fr.

(1) (a) Knochel, P. *Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Eds.; New York, Pergamon Press: 1991; Vol. 4, pp 865−911. (b) Marek, I.; Normant, J. F. *Cross Coupling Reactions*; Diederich, D., Stang, P., Eds.; VCH: New York, 1998.

(2) Funk, R. L.; Botton, G. L.; Brummond, K. M.; Ellestad, K. E.; Stallman, J. B. *J. Am. Chem. Soc.* **1995**, *115*, 7023−7024.

(3) Yeh, M.-C. P.; Chuang, L.-W.; Ueng, C. H. *J. Org. Chem.* **1996**, *61*, 3874−3877.

(4) Cavicchioli, M.; Sixdenier, E.; Derrey, A.; Bouyssi, D.; Balme, G. *Tetrahedron Lett.* **1997**, *38*, 1763−1766.

(5) (a) Stammler, R.; Malacria, M. *Synlett* **1994**, 92−92. (b) Cruciani, P.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1994**, *35*, 6677−6680. (c) Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699−2708.

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

(7) (a) Meyer, C.; Marek, I.; Courtemanche, G.; Normant, J. F. *J. Org. Chem.* **1995**, *60*, 863−871. (b) Meyer, C.; Marek, I.; Normant, J. F.; Platzer, N. *Tetrahedron Lett.* **1994**, *35*, 5645−5648. (c) Meyer, C.; Marek, I.; Normant, J. F. *Tetrahedron Lett.* **1996**, *37*, 857−860. (d) Lorthiois, E.; Marek, I.; Meyer, C.; Normant, J. F. *Tetrahedron Lett.* **1995**, *36*, 1263−1266. (e) Lorthiois, E.; Marek, I.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1997**, *134*, 333−341.

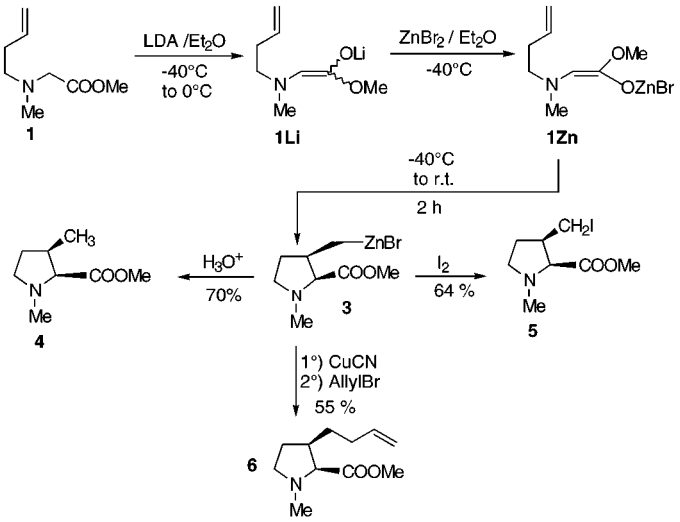
(8) For the more recent publications on the synthesis of pyrrolidines via an anionic cyclization, see: (a) Fujita, H.; Tokuda, M.; Nitta, M.; Suginome, H. *Tetrahedron Lett.* **1992**, *33*, 6359−6362. (b) Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981−2984. (c) Coldham, I. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1275−1276. (d) Pearson, W. H.; Jacobs, V. A. *Tetrahedron Lett.* **1994**, *35*, 7001−7004. (e) Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1994**, *59*, 5662−5671. (f) Pearson, W. H.; Lovering, F. E. *Tetrahedron Lett.* **1994**, *35*, 9173−9176. (g) Coldham, I.; Hugton, R. *Tetrahedron Lett.* **1995**, *36*, 2157−2160. (h) Pearson, W. H.; Lovering, F. E. *J. Am. Chem. Soc.* **1995**, *117*, *7*, 12336−12337. (i) Barluenga, J.; Canteli, R. M.; Florez, J. *J. Org. Chem.* **1996**, *61*, 3753−3757. (j) Solé, D.; Cancho, Y.; Llebaria, A.; Moreto, J.; Delgado, A. *J. Org. Chem.* **1996**, *61*, 5895−5904. For a palladium-mediated cyclization, see: Van der Louw, J.; Van der Baan, J. L.; Stichter, H.; Out, G. J. J.; Bickelhaupt, F.; Klumpp, G. W. *Tetrahedron Lett.* **1988**, *29*, 3579−3580. For the more recent publications on the synthesis of 3-substituted pyrrolidines via a cyclization of carbon-centered glycine radicals, see: (a) Esch, P. M.; Hiemstra, H.; De Boer, R. F.; Speckamp, W. N. *Tetrahedron* **1992**, *48*, 4659−4676. (b) Udding, J. H.; Tuijp, C. J. M.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 1907−1918 and references therein. (c) Schulze, R.; Beckhaus, H. D.; Rüchardt, C. *Chem. Ber.* **1993**, *126*, 1031. (d) Bachi, M. D.; Frolow, F.; Hoornaert, C. *J. Org. Chem.* **1983**, *48*, 1841. (e) Bachi, M. D.; De Mesmaeker, A.; Stevenart-De Mesmaeker, N. *Tetrahedron Lett.* **1987**, *28*, 2887−2890.

(9) (a) Sasaki, N. A.; Dockner, M.; Chiaroni, A.; Riche, C.; Potier, P. *J. Org. Chem.* **1997**, *62*, 765−770 and references therein. (b) Carpes, M. J. S.; Miranda, P. C. M. L.; Correia, C. R. D. *Tetrahedron Lett.* **1997**, *38*, 1869−1872.

(10) Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 1028−1030, followed by the reaction of the amino derivative with the bromo ester as described in Scheme 4.

S0022-3263(97)00813-X CCC: $15.00
Published on Web 03/21/1998

Scheme 2

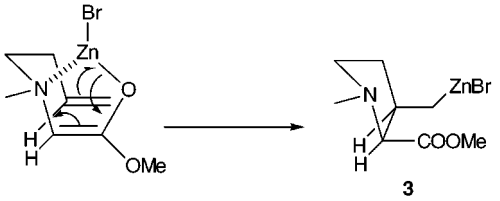


formaldehyde in acidic water) provides directly the homoallylamine (44%).

With these precursors in hand, we initiated a study of the carbocyclization reaction. Thus, **1** was cleanly metalated by treatment with 1.5 equiv of LDA in Et_2O at −40 °C, and after 2 h of stirring at room temperature, no cyclization of the corresponding lithium amino−enolate was observed. However, addition of 1.5 equiv of zinc salt at −40 °C to **1Li** led to the amino−zinc−enolate **1Zn** and resulted in a virtually quantitative 5-exo-Trig cyclization[11] reaction after 1 h at room temperature to give the cyclic product **3** (Scheme 2). Hydrolysis of the reaction mixture afforded **4** (70%) as a *single* diastereomer. The cis stereochemistry of the β-methylproline derivative was established first by using standard COSY techniques to determine unambiguously the ^{1}H and ^{13}C NMR chemical shifts, followed by the differential nuclear Overhauser effect. The formation of a new functionalized organometallic was checked by iodinolysis or by reaction with allyl bromide, after transmetalation of the resulting organozinc bromide into an organocopper reagent.[12]

Recent studies on the properties and structures of pure α-amino−(organo−zinc) ester enolates have shown that such enolates have exclusively the *Z*-configuration both in solution and in the solid-state.[13] The *Z*-configuration of these zinc enolates is imposed by an intramolecular Zn−N chelation. Then, the cis relative configuration of **3** was attributed to a chairlike transition state in which the *Z*-α-amino−zinc−enolate was in a plane parallel to that of the olefinic residue[7,14,15] (Scheme 3). Thus, from two sp^2 prochiral centers, two sp^3 stereogenic centers were created in a single-pot operation.

Scheme 3



Polysubstituted Pyrrolidines Synthesis. The starting material **9** with an alkyl group α to nitrogen was synthesized by the reaction of allylmagnesium bromide with the imine **7** at room temperature in a mixture of toluene/Et_2O (3/1) leading to the corresponding amine **8**. The reaction of the sodium salt of **8** in DMF with the α-bromoester gave the starting material **9** (70%) (Scheme 4).

We then studied the stereochemical outcome of the carbocyclization of **9**. Metalation of the amino−ester with LDA in Et_2O at low temperature, followed by a transmetalation into the amino−zinc−enolate, resulted, upon warming to room temperature, in a highly diastereoselective cyclization reaction (Scheme 5).

The *single* exclusive relative configuration in **10**, determined on the crude reaction mixture by ^{1}H and ^{13}C NMR, was assigned on the basis of differential NOE effects. The pure cis stereochemistry can be easily explained by the chairlike amino−zinc−enolate transition state, in which the ethyl group (R_2) preferentially occupies a pseudoequatorial position (Scheme 6).

Interestingly, the total stereoselection generated on the ethyl position is in sharp contrast with the diastereoselectivity obtained in the zinca−ene−allene reaction[7] as well as in the intramolecular carbolithiations[15b] (around 80/20, Scheme 7).

The discrepancy between these diastereomeric ratios can be explained, in the former case, by a minimum of 1,3-steric interactions between the ethyl group and the benzyl substituent on the nitrogen atom (Scheme 6). The transition state leading to the pseudoaxial position of the ethyl group would be disfavored by the repulsion between these two groups (Scheme 6). Thus, three stereogenic centers on a pyrrolidine have been easily created with complete diastereocontrol.

Another interesting substituted amino−ester with an alkyl group in the allylic position was then studied. According to our *metalation−transmetalation* procedure, the amino−zinc−enolate derived from **11**[16] undergoes a diastereoselective intramolecular carbocyclization (Scheme 5). Hydrolysis of the resulting organometallic afforded, respectively, the cyclic products **12a** and **12b** as a mixture of two diastereomers in a 80/20 ratio. The ^{1}H and ^{13}C NMR chemical shifts of **12a** and **12b** were established by using standard COSY techniques, and unambiguous configurational assignments were demonstrated on the basis of differential nuclear Overhauser effect spectra.

The relative configuration of the major isomer **12a** was attributed to steric interactions in the amino−zinc−enolate transition state that favor a geometry in which the methyl substituent preferentially occupies a pseudoequatorial position (R'_3) (Scheme 6). However, the

(11) (a) Lorthiois, E.; Marek, I.; Normant, J. F. *Tetrahedron Lett.* **1997**, *38*, 89−92. (b) Karoyan, P.; Chassaing, G. *Tetrahedron Lett.* **1997**, *38*, 85−88.

(12) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117−2188.

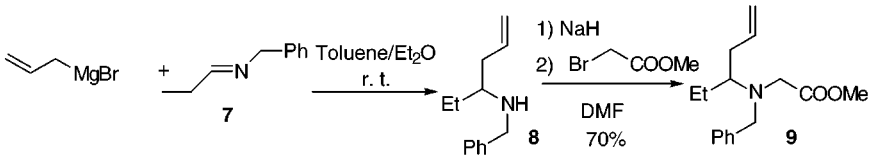
(13) Van Der Steen, F. H.; Kleijn, H.; Britovsek, G. J. P.; Jastrzebski, J. T. B. H.; Van Koten, G. *J. Org. Chem.* **1992**, *57*, 3906−3916.

(14) (a) St Denis, J.; Oliver, J. P.; Smart, J. B. *J. Organomet. Chem.* **1972**, *44*, C32−C36. (b) Albright, M. J.; St Denis, J.; Oliver, J. P. *J. Organomet. Chem.* **1977**, *125*, 1−8. (c) Hoaland, A.; Lehmkuhl, H.; Nehl, H. *Acta Chem. Scand.* **1984**, *38*, 547−553. (d) St Denis, J.; Oliver, J. P.; Dolzine, T. W.; Smart, J. B. *J. Organomet. Chem.* **1974**, *71*, 315−323. (e) Okninska, E.; Starowieyski, K. B. *J. Organomet. Chem.* **1989**, *376*, 7−13.

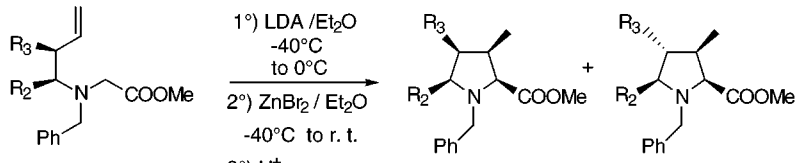
(15) (a) Houk, K. N.; Rondan, N. G.; Schleyer, P. v. R.; Kaufmann, E.; Clark, T. *J. Am. Chem. Soc.* **1985**, *107*, 2821. (b) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K.; Ovaska, T. V.; Rossi, K.; Thiel, Y.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 5720.

(16) The starting material was prepared via a Michael addition of benzylamine to ethyl methacrylate,[17] followed by the reduction of the ester into the aldehyde,[18] olefination[19] with the Wittig reagent, and reaction of the secondary amine with the α-bromoester as previously described in Scheme 4.

Scheme 4

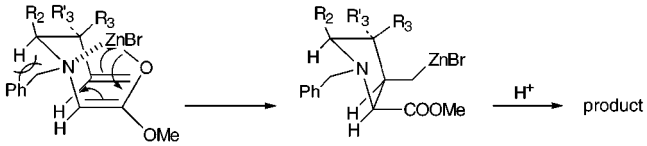


Scheme 5



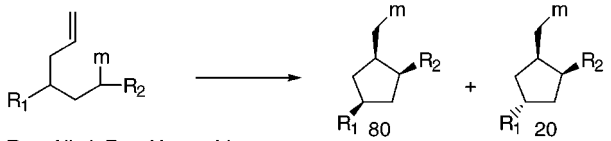
R_2=Et, R_3=H	**9**	Yield	60% : **10**	-
R_2=H, R_3=Me	**11**	"	65% : **12b** (20)	**12a** (80)
R_2=H, R_3=OMOM	**13**	"	75% : **14a** (85)	**14b** (15)
R_2=Et, R_3=Me	**16** (d. r.=96/4)	"	62% : **17** (d. r.=95/5)	-

Scheme 6



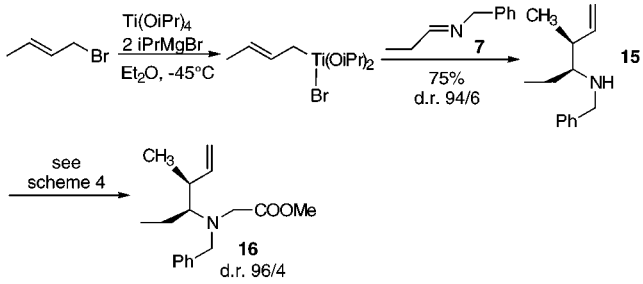
R_2=Et, R_3=R'_3=H	**10**
R_2=H, R_3=H, R'_3=Me	**12a**
R_2=H, R_3=Me, R'_3=H	**12b**
R_2=H, R_3=OMOM, R'_3=H	**14a**
R_2=H, R_3=H, R'_3=OMOM	**14b**
R_2=Et, R_3=Me, R'_3=H	**17**

Scheme 7



R_1 = Alkyl, R_2 = H, m = Li
R_1 = Alkyl, R_2 = alkynyl, m = ZnBr

Scheme 8



reason for the obtention of two diastereomers in a 80/20 ratio in this carbocyclization reaction is still not clear (we expected only one diastereomer according to our previous studies on the zinca−ene−allene cyclizations).[7] The same reaction applied to the heterosubstituted starting material[20] **13** led to a reverse stereochemical outcome as described in Scheme 5. In this case, due to the intramolecular chelation, the methoxy methyl group (OMOM), now, occupies a pseudoaxial position (R_3) in the amino−zinc−enolate transition state (Scheme 6).

Finally, we turned our attention to the synthesis of tetrasubstituted pyrrolidines. For this study, it was necessary to prepare a starting material with two stereogenic centers in a definite relationship, one in allylic position and the second one in homoallylic position. Both may be on the same side or on the opposite side of the chairlike amino−zinc−enolate transition state. For obvious reasons, and considering the diastereoselection obtained for the synthesis of **10** and **12** (Scheme 5), we decided to examine only the case in which we have a substituent in axial position whereas the other is in equatorial position (mismatch pair) instead of the case where the two substituents are located in pseudoequatorial position (match pair). Indeed, in the former case, it was interesting to determine which substituent was able to fix the stereochemical outcome of the carbocyclization process. The starting material was prepared by reaction of the crotyl titanium compound[21] with the imine **7** to afford the α,*β*-disubstituted homoallylamine (Scheme 8) with high diastereoselectivity (Cram-syn isomer in the ratio of 94/6).

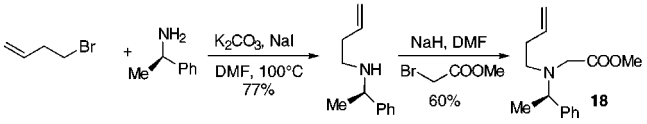
After reaction of **15** with the α-bromoester according to the experimental procedure described in Scheme 4 to produce **16**, the latter (mixture 96/4) was subjected to our *metalation−transmetalation−cyclization* procedure, and after hydrolysis, the tetrasubstituted pyrrolidine was obtained (62%) with a diastereomeric ratio of 95/5, determined on the crude reaction mixture (see Scheme 5).

The stereochemistry of **17** was, again, assigned on the basis of differential NOE effects, and the major isomer was attributed to the cis isomer with all substituents located on the same face (Scheme 5). The stereochemistry of the tetrasubstituted pyrrolidines can be rationalized by the chairlike amino−zinc−enolate transition state in which the ethyl group (R_2) occupies a pseudoequatorial position, thereby fixing the transition state in order to minimize the 1,3-steric interaction with the substituent

(17) David, S.; Sinay. P. *Bull. Soc. Chim. Fr.* **1965**, 2301.
(18) Meyer, C.; Marek, I.; Normant, J. F. *Synlett* **1993**, 386−388.
(19) Boland, W.; Ney, P.; Jaenicke, L. *Synthesis* **1980**, 1115.
(20) Reaction of butadiene with HBrO: Masuda, H.; Takase, K.; Nishio, M.; Hasegawa, A.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1994**, *59*, 5550−5555. Protection of the alcool moiety into the methoxy methyl derivative: Gras, J. L.; Ko Win Chan, Y.; Guerin, A. *Synthesis* **1985**, 74−75. For alkylation of this latter with the amino derivative, see ref 10.

(21) Gao, Y.; Sato, F. *J. Org. Chem.* **1995**, *60*, 8136−8137.

Scheme 9



on the nitrogen atom (Scheme 6). The methyl substituent in allylic position occupies the pseudoaxial position (R_3) in this transition state (due to the initial relationship between this two substituents, Scheme 8).

Thus, during this study we have been able to determine the different stereochemical factors which are responsible for the diastereoselective synthesis of polysubstituted pyrrolidines. With these results in mind, we turned our attention to the enantioselective synthesis of such pyrrolidines. For this purpose, we examined the chiral substrate **18**, easily prepared from the commercially available (*R*)-1-phenylethylamine as described in Scheme 9.

Following the *metalation−transmetalation−cyclization* procedure previously described, the chiral cyclic organozinc bromide was diastereoselectively formed, and after hydrolysis, the chiral β-methyl proline derivative was obtained as single cis diastereoisomer with a 98/2 diastereomeric ratio (93%) (Scheme 10).

The (2*R*,3*S*) absolute configuration of **19** was established by P. Karoyan and G. Chassaing[11b] who reached the same conclusion after hydrogenolysis to the secondary amine **20**, saponification, and comparison of the optical rotation of **21** with the known value for (2*R*,3*S*)-β-methylproline[22] (Scheme 11).

Whereas the enantioselectivity of this reaction is 96% when 2 equiv of zinc salt is used, a lower diastereoselection is obtained (50%) when the reaction is performed with only 1 equiv of zinc salt (but still the cis diastereomer). Moreover, if the aromatic ring of the chiral inductor is replaced by a cyclohexyl ring, no diastereoselection is obtained as described in Scheme 10.

In view of the above results, one can postulate a π-chelation between the aromatic ring and the amino−zinc−enolate in the transition state. Knowing that some π-chelations between organozinc derivatives and unsaturated systems are described in the literature,[14,23] the excess of zinc salt, which is necessary for the high diastereoselection, acts as a stabilizer between the aromatic ring and the amino−zinc−enolate as described in Scheme 12.

From this simplistic point of view, the chiral inductor adopts a position in which the methyl group bound to the chiral center has a lowered eclipsing strain with the two hydrogens in the α position, when one face of the carbon−carbon double bond is concerned rather than the other one.

We were also interested in the stereochemical effect of substituents on the carbon skeleton. For this reason, the corresponding chiral starting material **24** was prepared with a 90% diastereomeric excess[21] (see Scheme 13). Thus, the use of the (*R*)-1-phenylethylamine as the chiral source gave, after hydrolysis, the product **24** in which the carbon bearing the ethyl substituent has the *S* absolute configuration.[21]

However, according to the proposed model in Scheme 12, the carbocyclization reaction with the chiral (*R*)-1-phenylethylamine will put the ethyl substituent in a pseudoaxial position in the chairlike transition state (Et instead of H_a), which is not a favorable transition state (mismatched pair[24] in our cyclization reaction). Indeed, after reaction of the sodium salt of **24** with the α-bromoester as described in Scheme 4 to give **25**, the latter was submitted to our *metalation−transmetalation−cyclization* reaction conditions (Scheme 10). Two isomers were obtained in a 60/40 ratio, determined after a differential nuclear Overhauser effect.

The major isomer **26a** resulted from a transition state in which the ethyl substituent preferentially occupied the pseudoequatorial position (identical to Scheme 6) whereas the minor isomer **26b** came from a transition state imposed by the (*R*)-1-phenylethylamine chiral inductor (see product **19**, Scheme 10). Thus, from this experiment, we can deduce that the ethyl substituent has a stronger effect on the stereochemical outcome than the chiral substituent on the nitrogen (% of **26a** > % of **26b**), and we may surmise that the diastereomer of **25** would give rise to a single isomer of **26** although we did not embark on its lengthy preparation. Finally, we turned our attention to the synthesis of homochiral tetrasubstituted pyrrolidines according to the strategy developed in Scheme 8 starting from a chiral (*R*)-phenylethylamine. For this reason, we prepared the starting material **27** with three chiral centers as described in Scheme 14 and subjected it to the intramolecular carbometalation (Scheme 10).

An examination of the NMR spectra of the crude reaction mixture indicates that the diastereoselection is very high (dr > 95/5). From the differential nuclear Overhauser effect studies, it was determined that the pyrrolidine **28** had all substituents located on the same side (Scheme 10). From this result, we deduced that the stereochemical outcome of the carbocyclization resulted from the substituents on the ring and not from the chiral phenyl ethyl amino group. Here again the stereochemistry of the tetrasubstituted pyrrolidine is rationalized by the chairlike amino−zinc−enolate transition state in which the ethyl group occupies a pseudoequatorial position and the methyl group, an axial position, as described for **17** (see Scheme 5). The chiral substituent on the nitrogen only serves in the first step of this reaction, namely, the enantioselective preparation of **27**, and not in the carbocyclization step, since the same stereochemistry in **17** (Scheme 5) and **28** (Scheme 10) is obtained whereas in **19** (Scheme 10) the two new chiral centers are formed in an opposite configuration with the same chiral inductor.

Conclusion

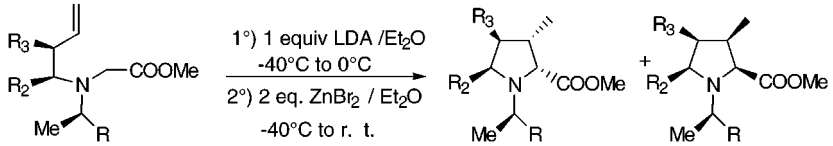
The amino−zinc−enolate cyclization allowed a new and straightforward route to polysubstituted pyrrolidines from simple starting materials. From this study, we have been able to determine for the first time the stereochemical influence of the substituents on the ring in the carbocyclization reaction. The diastereoselectivity thus

(22) Delaney, N. G.; Madison, V. *J. Am. Chem. Soc.* **1992**, *104*, 6635−6641.

(23) (a) Beruben, D.; Marek, I.; Normant, J. F.; Platzer, N. *J. Org. Chem.* **1995**, *60*, 2488. (b) Marek, I.; Beruben, D.; Normant, J. F. *Tetrahedron Lett.* **1995**, *36*, 3695−3698.

(24) In the match pair, the two substituents will be in the pseudoequatorial positions.

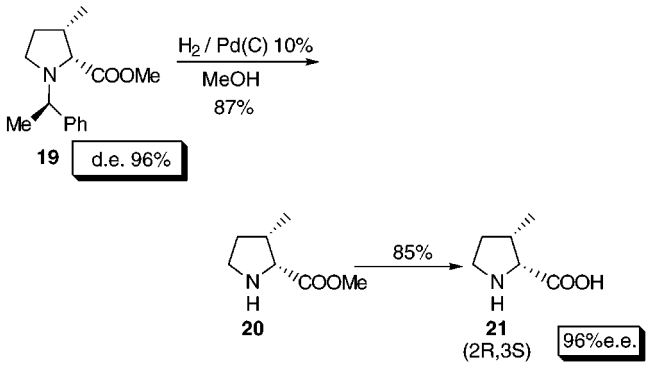
Scheme 10



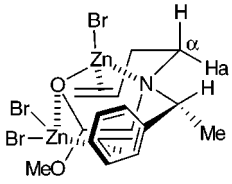
R=Ph	R_2=R_3=H	**18**	yield	93%	**19** (dr > 98/2)	-
R=chex	R_2=R_3=H	**22**	"	60%	**23a** (59)*	**23b** (41)*
R=Ph	R_2=Et, R_3=H	**25** (d. r.>95/5)	"	69%	**26b** (40)	**26a** (60)
R=Ph	R_2=Et, R_3=Me	**27** (d. r.>95/5)	"	65%	-	**28** (d. r.>95/5)

* or the reverse (undetermined)

Scheme 11



Scheme 12



obtained was explained by a chairlike amino−zinc−enolate transition state.

Experimental Section

***N*-Benzylglycinate Methyl Ester.** A solution of benzylamine (50 mmol, 5.35 g) in dry DMSO (70 mL) was stirred at room temperature as a mixture of triethylamine (5.05 g, 50 mmol) and methyl bromoacetate (7.65 g, 50 mmol) was added slowly. After being stirred for 1 h at room temperature, the reaction mixture was treated with a solution of NH_4Cl/NH_4OH 2/1. Ether was added, and the layers were separated, the aqueous 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 silicagel (eluent: dichloromethane/methanol 93/7) to give 5.85 g (65%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 3.82 (s, 2H), 3.74 (s, 3H), 3.44 (s, 2H), 1.95 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 139.6, 128.6, 128.4, 127.3, 53.4, 51.9, 50.0.

***N*-Benzyl-*N*-(But-3-enyl)glycinate Methyl Ester (2).** A solution of *N*-benzylglycinate methyl ester (1.67 mmol, 0.3 g), trifluoroacetic acid (1.67 mmol, 0.129 mL), aqueous formaldehyde (3.85 mmol, 0.312 g), and allyltrimethylsilane (1.84 mmol, 0.209 g) in water (30 mL) was heated at 50 °C during 60 h. The reaction mixture was treated with a solution of NH_4Cl/NH_4OH 2/1. Ether was added, and the layers were separated, the aqueous being extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give 0.173 g (44%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.28 (m, 5H), 5.95−5.85 (m, 1H), 5.15 (m, 2H), 3.83 (s, 2H), 3.71 (s, 3H), 3.36 (s, 2H), 2.71 (t, 2H, J = 7.3 Hz), 2.32−2.20 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 139.0, 136.6, 129.8, 129.0, 127.2, 115.7, 58.1, 54.0, 53.4, 51.3, 32.2.

***N*-Methyl-*N*-(But-3-enyl)glycinate Methyl Ester (1).** The title compound was prepared as described for the synthesis of **2**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78−5.68 (m, 1H), 5 (dd, J = 17.2, 1.4 Hz, 1H), 4.94 (d, J = 10.2 Hz, 1H), 3.65 (s, 3H), 3.21 (s, 2H), 2.51 (t, J = 7.3 Hz, 2H), 2.32 (s, 3H), 2.22−2.16 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 136.3, 115.0, 58.3, 56.4, 57.5, 42.3, 31.9.

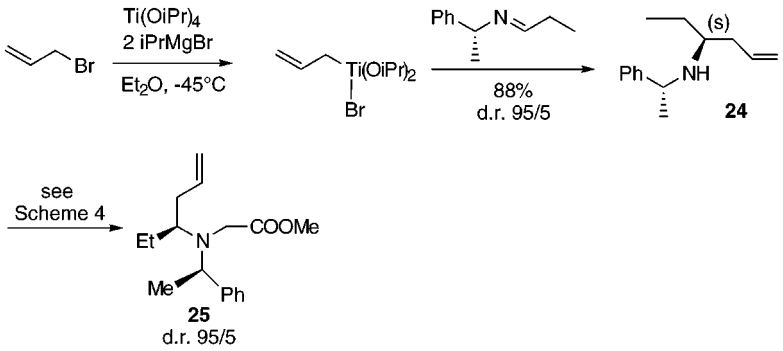
Typical Procedure for Cyclized Product 3. A solution of **1** (1 mmol, 0.157 g) in dry ether was cooled to −40 °C as LDA (2 M in THF/ heptane, 1.5 mmol, 0.75 mL) was added dropwise. The reaction mixture was then allowed to warm to 0 °C for 10 min and cooled to −40 °C as zinc bromide (1 M in ether, 1.5 mmol, 1.5 mL) was added dropwise. The reaction mixture was then allowed to warm to room temperature. The cyclized organozinc species is ready for further conversions.

(2*S,3*R**)-1,3-Dimethyl-2-carbomethoxy-*N*-methylpyrrolidine (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, in order to discard traces of zinc salts. The layers were separated, the aqueous 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: dichloromethane/methanol 90/10) to give 0.109 g (70%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.16−3.11 (m, 1H), 3.08 (d, 1H, J = 8.8 Hz), 2.57−2.53 (m, 1H), 2.36 (s, 3H), 2.38−2.30 (m, 1H), 2.07−2.02 (m, 1H), 1.57−1.52 (m, 1H), 0.95 (d, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 72.2, 55.65, 51.5, 41.1, 36.1, 32.7, 17.5. Anal. Calcd for $C_8H_{15}O_2N$: C, 61.12, H, 9.62, N, 8.91. Found: C, 61.35, H, 9.85, N, 8.44.

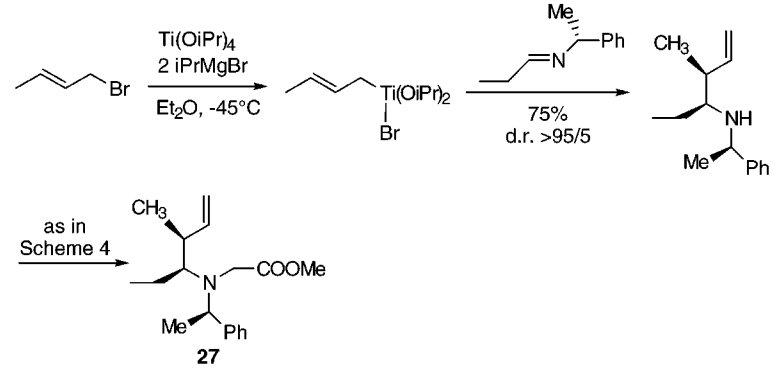
(2*S,3*R**)-1-Methyl-3-(iodomethyl)-2-carbomethoxy-*N*-methylpyrrolidine (5).** The cyclized product **3** was cooled to 0 °C as an excess of solid iodine (3 mmol, 0.762 g) was added. After the solution was stirred for 10 min at room temperature, a solution of NH_4Cl/NH_4OH 2/1 was added slowly. Ether was added, and the layers were separated, the aqueous 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 0.181 g (64%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.24−3.20 (m, 2H), 3.17−3.12 (m, 1H), 3.07 (dd, 1H, J = 10.1, 9.6 Hz), 2.91−2.86 (m, 1H), 2.49−2.42 (m, 1H), 2.36 (s, 3H), 2.21−2.16 (m, 1H), 1.77−1.67 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 71.4, 54.9, 52.0, 44.7, 40.8, 32.6, 7.5.

(2*S,3*R**)-1-Methyl-3-(but-3-enyl)-2-carbomethoxy-*N*-methylpyrrolidine (6).** The cyclized product **3** was cooled to −20 °C as copper cyanide (0.134 g, 1.5 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 (0.363 g, 3 mmol) was injected into

Scheme 13



Scheme 14



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 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 dried over $MgSO_4$ and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether 40/60) to give 0.108 g (55%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80−5.71 (m, 1H), 5.03−4.93 (m, 2H), 3.74 (s, 3H), 3.19 (d, 1H, J = 8.9 Hz), 3.13−3.09 (m, 1H), 2.45−2.39 (m, 2H), 2.37 (s, 3H), 2.17−2.05 (m, 1H), 2.02−1.98 (m, 2H), 1.66−1.61 (m, 1H), 1.39−1.32 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 138.2, 114.9, 71.5, 55.2, 51.5, 41.2, 40.6, 31.95, 31.0, 30.5. Anal. Calcd for $C_{11}H_{19}O_2N$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.83; H, 9.86; N, 7.32.

4-(Benzylamino)-1-hexene (8). To a solution of imine **7** (40.8 mmol, 6 g) in dry toluene (130 mL) was added at room temperature allylmagnesium bromide (1.38 M in ether, 81.6 mmol, 59.1 mL). The reaction mixture was stirred at room temperature for 60 h. It was then treated with a solution of NH_4Cl/NH_4OH 2/1. The layers were separated, the aqueous 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 70/30) to give 2.7 g (35%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.24 (m, 5H), 5.87−5.76 (m, 1H), 5.15−5.09 (m, 2H), 3.82 (d, 1H, J = 13.0 Hz), 3.78 (d, 1H, J = 13.0 Hz), 2.60−2.57 (m, 1H), 2.32−2.27 (m, 1H), 2.22−2.17 (m, 1H), 1.56−1.28 (m, 2H), 0.94 (t, 3H, J = 7.4 Hz).

General Procedure for the Alkylation with Methyl Bromoacetate: Preparation of *N*-Benzyl-*N*-(but-1-ethyl-3-enyl)glycinate Methyl Ester (9). To a solution of NaH (50%, 2.54 mmol, 0.12 g) in dry DMF was added 4-(benzylamino)-1-hexene (**8**) (1.95 mmol, 0.37 g) at 0 °C. The reaction mixture was stirred at 0 °C during 10 min, and methyl bromoacetate (2.34 mmol, 0.36 g) was added. The reaction mixture was stirred for 2 h and treated with a solution of NH_4Cl/NH_4OH 2/1. Ether was added, and the layers were separated, the aqueous 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 70/30) to give 0.356 g (70%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.25 (m, 5H), 5.94−5.84 (m, 1H), 5.11−5.04 (m, 2H), 3.86 (d, 1H, J = 13.8 Hz), 3.77 (d, 1H, J = 13.8 Hz), 3.68 (s, 3H), 3.38 (d, 1H, J = 16.7 Hz), 3.32 (d, 1H, J = 16.7 Hz), 2.65−2.61 (m, 1H), 2.45−2.38 (m, 1H), 2.11−2.04 (m, 1H), 1.54−1.42 (m, 2H), 0.99 (t, 3H, J = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 139.9, 137.3, 129.0, 128.25, 127.0, 116.0, 62.05, 54.65, 51.5, 51.4, 35.05, 24.0, 11.7.

General Procedure for the Metalation−Transmetalation−Cyclization of the Racemic Substrate. Preparation of (2*S,3*R**,5*S**)-5-Ethyl-3-methyl-2-carbomethoxy-*N*-benzylpyrrolidine (10).** A solution of **9** (0.66 mmol, 0.174 g) in dry ether was cooled to −40 °C as LDA (2 M in THF/heptane, 1.32 mmol, 0.66 mL) was added dropwise. The reaction mixture was then allowed to warm to 0 °C for 10 min and cooled to −40 °C as zinc bromide (1 M in ether, 1.32 mmol, 1.32 mL) was added dropwise. The reaction mixture was then allowed to warm to room temperature and stirred for 3 h. The reaction mixture was cooled to 0 °C as a solution of NH_4Cl/NH_4OH 2/1 was added slowly. 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 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 (60%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.21 (m, 5H), 3.97 (d, 1H, J = 13.8 Hz), 3.64 (d, 1H, J = 13.8 Hz), 3.47 (s, 3H), 3.39 (d, 1H, J = 9.4 Hz), 2.70−2.64 (m, 1H), 2.39−2.30 (m, 1H), 2.07−2.01 (m, 1H), 1.85−1.78 (m, 1H), 1.48−1.41 (m, 1H), 1.38−1.28 (m, 1H), 0.95−0.91 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.25, 139.0, 129.9, 128.6, 127.5, 70.7, 65.9, 57.5, 51.6, 39.8, 34.9, 27.5, 16.7, 11.0. Anal. Calcd for $C_{16}H_{23}O_2N$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.62; H, 8.64; N, 5.44.

4-(Benzylamino)-3-methyl-1-butene. A solution of methyltriphenylphosphonium bromide (6.24 g, 17.5 mmol) in dry THF (50 mL) was cooled to 0 °C as *n*-butyllithium (11.8 mL,

18.9 mmol, 1.6 M in hexanes) was added dropwise. The red solution was then stirred for 15 min at 0 °C.

A solution of 3-methyl-*N*-benzylamino-2-methyl propionate (1.45 g, 7 mmol) in dry hexane was cooled to −78 °C as DIBALH (1 M in hexanes, 7.7 mmol, 7.7 mL) was added dropwise. The reaction mixture was stirred for 20 min at −65 °C as the Wittig reagent was added slowly at −65 °C. The resultant mixture was then slowly warmed to room temperature and stirred for 1 h. It was then poured into a 1 M solution of hydrochloric acid. The layers were separated, and the aqueous was treated with 6 M NaOH until pH > 10. The resulting aqueous layer was then extracted with ether. The organic extract was washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent: dichloromethane/methanol 90/10) to give 0,544 g (45%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.26 (m, 5H), 5.75−5.66 (m, 1H), 5.13−5.04 (m, 2H), 3.84 (d, 1H, J = 13.3 Hz), 3.80 (d, 1H, J = 13.3 Hz), 2.63−2.51 (m, 2H), 2.46−2.39 (m, 1H), 1.05 (d, 3H, J = 6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 140.6, 128.5, 128.2, 126.95, 114.6, 55.0, 54.0, 38.4, 18.4.

***N*-Benzyl-*N*-(2-methylbut-3-enyl)glycinate Methyl Ester (11).** A solution of 4-(benzylamino)-3-methyl-1-butene (0.54 g, 3.1 mmol) was treated following the general procedure for the alkylation with methyl bromoacetate as described for **9**. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether 70/30) to give 0.53 g (70%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.26 (m, 5H), 5.87−5.79 (m, 1H), 5.10−5.01 (m, 2H), 3.86 (s, 2H), 3.71 (s, 3H), 3.36 (s, 2H), 2.68−2.55 (m, 2H), 2.47−2.41 (m, 1H), 1.05 (d, 3H, J = 6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 143.1, 139.35, 129.0, 128.35, 127.15, 113.5, 60.2, 58.3, 54.2, 51.3, 36.4, 18.05. Anal. Calcd for $C_{15}H_{21}O_2N$: C, 72.84; H, 8.56; N, 5.66. Found: C, 73.02; H, 8.67; N, 5.43.

(2*S,3*R**,4*R**)-3,4-Dimethyl-2-carbomethoxy-*N*-benzylpyrrolidine (12).** A solution of **11** (0.81 mmol, 0.2 g) in Et_2O (20 mL) was treated following the metalation−transmetalation−cyclization−hydrolysis general procedure for racemic substrate. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether 80/20) to give 0.13 g (65%) of the title compound. **Major Diastereomer 12a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.24 (m, 5H), 3.75 (d, 1H, J = 12.8 Hz), 3.67 (d, 1H, J = 12.8 Hz), 3.62 (s, 3H), 3.47 (d, 1H, J = 8.9 Hz), 3.19 (dd, 1H, J = 8.7, 6.4 Hz), 2.20 (t, 1H, J = 8.9 Hz), 1.97−1.94 (m, 2H), 0.98 (d, 3H, J = 6.2 Hz), 0.88 (d, 3H, J = 7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 138.4, 129.5, 128.3, 127.3, 70.0, 61.05, 58.9, 51.3, 43.85, 39.7, 16.95, 14.6. **Minor Diastereomer 12b.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.24 (m, 5H), 3.88 (d, 1H, J = 13.1 Hz), 3.68 (s, 3H), 3.60 (d, 1H, J = 13.1 Hz), 3.59 (d, 1H, J = 7.4 Hz), 2.81−2.72 (m, 2H), 2.51 (sex, 1H, J = 7.3 Hz), 2.32−2.19 (m, 1H), 0.96 (d, 3H, J = 7,0 Hz), 0.88 (d, 3H, J = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 139.0, 129.2, 128.3, 127.1, 70.3, 58.95, 58.7, 51.45, 38.8, 35.5, 14.6, 11.1. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.37; H, 8.35; N, 5.49.

***N*-Benzyl-*N*-(2-((methoxymethyl)oxy)but-3-enyl)glycinate Methyl Ester (13).** A solution of 4-(benzylamino)but-1-ene 3-methoxymethyl ether (0.184 g, 0.83 mmol) was treated following the general procedure for the alkylation with methyl bromoacetate as described for **9**. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether 40/60) to give 0.18 g (74%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34−7.20 (m, 5H), 5.72 (ddd, 1H, J = 17.3, 10.22, 7.15 Hz), 5.25−5.16 (m, 2H), 4.66 (d, 1H, J = 6.6 Hz), 4.56 (d, 2H, J = 6.6 Hz), 4.18−4.13 (m, 1H), 3.87 (s, 2H), 3.65 (s, 3H), 3.42 (s, 2H), 3.35 (s, 3H), 2.90 (dd, 1H, J = 13.8, 6.8 Hz), 2.78 (dd, 1H, J = 13.8, 5.3 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.2, 139.2, 137.2, 129.1, 128.4, 127.3, 117.5, 94.4, 76.6, 59.1, 58.65, 56.0, 54.8, 51.3.

(2*S,3*R**,4*S**)-3-Methyl-2-carbomethoxy-4-((methoxymethyl)oxy)-*N*-benzylpyrrolidine (14a).** A solution of **13** (0.57 mmol, 0.167 g) in Et_2O (20 mL) was treated following the metalation−transmetalation−cyclization−hydrolysis general procedure for racemic substrate. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether 30/70) to give 0.125 g (75%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.23 (m, 5H), 4.63−4.58 (m, 2H), 4.18−4.14 (m, 1H), 3.89 (d, 1H, J = 13.1 Hz), 3.70 (s, 3H), 3.63 (d, 1H, J = 13.1 Hz), 3.51 (d, 1H, J = 8.24 Hz), 3.33 (s, 3H), 3.11 (dd, 1H, J = 10.1, 3.9 Hz), 2.80 (dd, 1H, J = 10.1, 6.3 Hz), 2.67−2.62 (m, 1H), 1.00 (d, 3H, J = 7.2 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.85, 138.4, 129.2, 128.35, 127.2, 96.0, 76.6, 68.1, 58.05, 57.4, 55.6, 51.4, 40.1, 10.3. Anal. Calcd for $C_{16}H_{23}O_4N$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.57; H, 7.94; N, 4.83.

(3*S,4*S**)-4-(Benzylamino)-3-methyl-1-hexene (15).** The starting material was prepared according to ref 20. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36−7.20 (m, 5H), 5.88−5.71 (m, 1H), 5.08−4.98 (m, 2H), 3.77 (s, 2H), 2.49−2.32 (m, 2H), 1.58−1.23 (m, 2H), 1.01 (d, 3H, J = 6.6 Hz), 0.91 (t, 3H, J = 7.4 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.15, 141.3, 128.4, 128.3, 126.9, 114.4, 62.8, 51.8, 39.8, 23.7, 15.55, 10.9.

***N*-Benzyl-*N*-((1*S**,2*S**)-1-ethyl-2-methylbut-3-enyl)glycinate Methyl Ester (16).** A solution of (3*S**,4*S**)-4-(benzylamino)-3-methyl-1-hexene (**15**) (0.39 g, 1.92 mmol) was treated following the general procedure for the alkylation with methyl bromoacetate as described for **9**. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether 70/30) to give 0.32 g (61%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.24 (m, 5H), 5.80−5.72 (m, 1H), 5.05 (dd, 1H, J = 17.1, 1.7 Hz), 4.97 (dd, 1H, J = 10.2, 2.0 Hz), 3.90 (d, 1H, J = 13.8 Hz), 3.85 (d, 1H, J = 13.8 Hz), 3.66 (s, 3H), 3.42 (s, 2H), 2.48−2.37 (m, 2H), 1.57−1.47 (m, 2H), 1.10 (d, 3H, J = 6.6 Hz), 1.00 (t, 3H, J = 7.4 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.2, 143.2, 140.0, 129.3, 128.3, 127.1, 114.25, 66.8, 56.2, 52.5, 51.6, 41.8, 22.1, 19.6, 13.2. Anal. Calcd for $C_{17}H_{25}O_2N$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.32; H, 9.28; N, 5.18.

(2*S,3*R**,4*S**,5*S**)-3,4-Dimethyl-5-ethyl-2-carbomethoxy-*N*-benzylpyrrolidine (17).** A solution of **16** (0.54 mmol, 0.15 g) was treated following the metalation−transmetalation−cyclization−hydrolysis general procedure for racemic substrate. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether 80/20) to give 0.093 g (62%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.20 (m, 5H), 3.98 (d, 1H, J = 13.56 Hz), 3.50 (d, 1H, J = 13.6 Hz), 3.45 (d, 1H, J = 10.7 Hz), 3.42 (s, 3H), 2.70−2.65 (m, 1H), 2.48−2.42 (m, 1H), 2.09−2.03 (m, 1H), 1.75−1.69 (m, 1H), 1.50−1.45 (m, 1H), 0.97−0.91 (m, 6H), 0.86 (d, 3H, J = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 138.5, 129.7, 128.0, 127.0, 70.0, 69.2, 57.35, 51.0, 38.4, 38.0, 22.45, 12.1, 10.95, 8.6. Anal. Calcd for $C_{17}H_{25}O_2N$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.01; H, 8.86; N, 5.28.

***N*-(*R*)-1-(Phenylethyl)-*N*-(but-3-enyl)amine.** A solution of 4-bromo-1-butene (52.5 mmol, 7.08 g), (*R*)-(+)-α-methylbenzylamine (35 mmol, 4.27 g), K_2CO_3 (105 mmol, 14.5 g), and NaI (105 mmol, 15.75 g) was heated at 100 °C in dry DMF (30 mL) for 12 h. A solution of NH_4Cl/NH_4OH 2/1 and ether were then added. The layers were separated, the aqueous 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: dichloromethane/methanol 90/10) to give 4.7 g (77%) of the title compound. $[\alpha]_D$ = −36.8 (0.0417, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.24 (m, 5H), 5.82−5.72 (m, 1H), 5.12−4.96 (m, 2H), 3.79 (q, J = 6.6 Hz, 1H), 2.63−2.5 (m, 2H), 2.28−2.18 (m, 2H), 1.60 (m, 1H),1.37 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 136.6, 128.5, 127.0, 126.7, 116.5, 58.4, 46.8, 34.4, 24.4.

***N*-(*R*)-1-(Phenylethyl)-*N*-(but-3-enyl)glycinate Methyl Ester (18).** A solution of *N*-(*R*)-1-(phenylethyl)-*N*-(but-3-enyl)amine (5.92 g, 33.8 mmol) was treated following the general procedure for the alkylation with methyl bromoacetate as described for **9**. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether 60/40) to give 5 g (60%) of the title compound. $[\alpha]_D$ = +33.4 (0.0312, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.24 (m, 5H), 5.82−5.72 (m, 1H), 5.12−4.97 (m, 2H), 3.79 (q, 1H, J = 6.6 Hz), 2.63−2.50 (m, 2H), 2.28−2.18 (m, 2H), 1.37 (d, 3H, J = 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 136.7, 128.6, 127.0, 126.7, 115.4, 58.4, 46.8, 34.5, 24.4.

General Procedure for the Metalation−Transmetalation−Cyclization for the Chiral Substrate. Preparation of (2*R*,3*S*)-3-Methyl-2-carbomethoxy-*N*-(*R*)-1-phenylethyl)pyrrolidine (19). A solution of **18** (0.5 mmol, 0.123 g) in dry ether was cooled to −40 °C as LDA (2 M in THF/*n*-heptane, 0.55 mmol, 0.275 mL) was added dropwise. The reaction mixture was then allowed to warm to 0 °C for 10 min and cooled to −40 °C as zinc bromide (1 M in ether, 1.1 mmol, 1.1 mL) was added dropwise. The reaction mixture was then allowed to warm to room temperature and stirred for 3 h. The reaction mixture was cooled to 0 °C as a solution of NH_4Cl/NH_4OH 2/1 was added slowly. 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 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 0.114 g (93%) of the title compound. $[\alpha]_D = +79.45$ (0.0507, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.23 (m, 5H), 3.71 (q, 1H, J = 6.6 Hz), 3.63 (s, 3H), 3.36 (d, 1H, J = 8.6 Hz), 3.03 (dt, 1H, J = 8.9, 2.9 Hz), 2.88−2.80 (m, 1H), 2.46−2.42 (m, 1H), 1.99−1.96 (m, 1H), 1.65−1.60 (m, 1H), 1.37 (t, 3H, J = 6.7 Hz), 0.92 (d, 3H, J = 6.7 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.1, 144.6, 128.4, 127.6, 127.2, 67.7, 62.1, 50.9, 50.7, 36.7, 32.1, 22.6, 15.8. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.91; H, 8.55; N, 5.59.

***N*-(*S*)-(+)-1-(Cyclohexylethyl)-*N*-(but-3-enyl)amine.** A solution of 4-bromo-1-butene (18.84 mmol, 2.54 g), (*S*)-(+)-1-cyclohexylethylamine (15.7 mmol, 2 g), K_2CO_3 (47.2 mmol, 6.5 g), and NaI (47.2 mmol, 7.08 g) was heated at 100 °C in dry DMF (30 mL) for 12 h. A solution of NH_4Cl/NH_4OH 2/1 and ether were then added. The layers were separated, the aqueous 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 70/30) to give 1.56 g (55%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76−5.65 (m, 1H), 5.03−4.94 (m, 2H), 2.67−2.60 (m, 1H), 2.53−2.47 (m, 1H), 2.37−2.32 (m, 1H), 2.18−2.14 (m, 2H), 1.69−1.58 (m, 5H), 1.16−1.06 (m, 4H), 0.94−0.89 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 116.3, 57.8, 46.6, 43.0, 34.65, 30.1, 28.1, 26.9, 26.8, 26.6, 16.9.

***N*-(*S*)-(+)-1-(Cyclohexylethyl)-*N*-(but-3-enyl)glycinate Methyl Ester (22).** A solution of *N*-(*S*)-(+)-1-(cyclohexylethyl)-*N*-(but-3-enyl)amine (1.56 g, 8.62 mmol) was treated following the general procedure for the alkylation with methyl bromoacetate as described for **9**. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether 70/30) to give 1.11 g (51%) of the title compound. $[\alpha]_D = +49.2$ (0.026, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88−5.78 (m, 1H), 5.05−4.95 (m, 2H), 3.67 (s, 2H), 3.29 (d, 1H, J = 16.8 Hz), 3.16 (d, 1H, J = 16.8 Hz), 2.62−2.51 (m, 2H), 2.43−2.36 (m, 1H), 2.19−2.13 (m, 3H), 1.72−1.65 (m, 4H), 1.25−1.12 (m, 4H), 0.91−0.83 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 137.2, 115.4, 61.5, 52.4, 51.5, 51.35, 41.9, 33.5, 31.0, 30.5, 26.8, 26.7, 26.5, 11.5.

(2*R,3*S**)-3-Methyl-2-carbomethoxy-*N*-((*S*)-1-cyclohexylethyl)pyrrolidine (23).** A solution of **22** (0.79 mmol, 0.2 g) in Et_2O (20 mL) was treated following the metalation−transmetalation−cyclization general procedure for chiral substrate. 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 0.12 g (60%) of the title compound. **Major Diastereomer.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.58 (d, 1H, J = 8.4 Hz), 3.01 (ddd, 1H, J = 8.5, 6.2, 2.2 Hz), 2.85−2.80 (m, 1H), 2.44−2.30 (m, 2H), 1.91−1.83 (m, 1H), 1.73−1.60 (m, 3H), 1.37−1.31 (m, 1H), 1.26−1.10 (m, 6H), 0.97−0.85 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 67.9, 65.9, 61.0, 51.0, 50.9, 47.8, 42.0, 37.05, 32.0, 31.2, 27.7, 26.9, 15.3, 12.7. **Minor Diastereomer.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.54 (d, 1H, J = 8.8.Hz), 2.94 (ddd, 1H, J = 8.5, 6.2, 2.2 Hz), 2.70−2.63 (m, 1H), 2.44−2.30 (m, 2H), 1.91−1.83 (m, 1H), 1.73−1.60 (m, 3H), 1.37−1.31 (m, 1H), 1.26−1.10 (m, 6H), 0.97−0.85 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.75, 67.9, 65.9, 61.0, 51.0, 50.7, 47.8, 41.9, 36.5, 32.5, 31.1, 27.6, 26.6, 15.6, 12.3.

***N*-(*R*)-1-Phenylethyl-*N*-(1*S*)-(1-ethylbut-3-enyl)amine (24). 24** was prepared according to ref 21. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.24 (m, 5H), 5.88−5.77 (m, 1H), 5.14−5.08 (m, 2H), 3.95 (q, 1H, J = 6.60 Hz), 2.43−2.38 (m, 1H), 2.27−2.19 (m, 3H), 1.45−1.28 (m, 2H), 1.36 (d, 3H, J = 6.60 Hz), 0.87 (t, 3H, J = 7.48 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 135.6, 128.4, 126.8, 126.7, 117.1, 55.4, 55.1, 37.3, 27.4, 25.0, 10.5.

***N*-((*R*)-1-(Phenylethyl))-*N*-((1*S*)-1-ethylbut-3-enyl)glycinate Methyl Ester (25).** A solution of *N*-(*R*)-1-(phenylethyl)-*N*-(1*S*)-(1-ethylbut-3-enyl)amine (**24**) (0.568 g, 2.79 mmol) was treated following the general procedure for the alkylation with methyl bromoacetate as described for **9**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.22 (m, 5H), 5.71−5.63 (m, 1H), 4.97−4.92 (m, 2H), 4.09 (q, 1H, J = 6.6 Hz), 3.71 (s, 3H), 3.45 (d, 1H, J = 17.5 Hz), 3.34 (d, 1H, J = 17.5 Hz), 2.58−2.53 (m, 1H), 2.26−2.20 (m, 1H), 1.87−1.80(m, 1H), 1.39−1.30(m, 2H), 1.35 (d, 3H, J = 6.6 Hz), 0.90 (t, 3H, J = 7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 145.8, 137.4, 128.35, 127.9, 127.1, 115.9, 60.5, 60.1, 51.7, 47.6, 35.3, 25.15, 21.6, 11.55.

(2*S,3*R**,5*S*)-5-Ethyl-3-methyl-2-carbomethoxy-*N*-((*R*)-1-phenylethyl)pyrrolidine (26).** A solution of **25** (0.295 mmol, 0.0813 g) in Et_2O (20 mL) was treated following the metalation−transmetalation−cyclization general procedure for chiral substrate. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether 80/20) to give 0.056 g (69%) of the title compound. **Major Diastereomer.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (q, 1H, J = 6.7 Hz), 3.52 (d, 1H, J = 9.1 Hz), 3.34 (s, 3H), 3.09−3.03 (m, 1H), 2.21−2.15 (m, 1H), 2.05−1.96 (m, 1H), 1.72−1.83 (m, 1H), 1.55−1.47 (m, 1H), 1.41−1.34 (m, 1H), 1.37 (t, 3H, J = 6.7 Hz), 0.96−0.87 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 144.0, 128.3, 128.1, 126.7, 64.4, 62.9, 55.6, 50.8, 38.8, 36.5, 27.8, 15.0, 11.3, 10.55. **Minor Diastereomer.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (q, 1H, J = 6.7 Hz), 3.81 (d, 1H, J = 7.5 Hz), 3.65 (s, 3H), 3.25−3.21 (m, 1H), 1.48−1.43 (m, 1H), 1.91−1.87 (m, 1H), 1.72−1.83 (m, 1H), 1.62−1.58 (m, 1H), 1.41−1.34 (m, 1H), 1.37 (t, 3H, J = 6.7 Hz), 0.96−0.87 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 148.7, 128.3, 127.9, 122.2, 68.4, 63.4, 59.5, 50.9, 37.1, 34.6, 27.5, 21.4, 15.1, 10.3. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.34; H, 9.36; N, 5.28.

***N*-((*R*)-1-Phenylethyl-*N*-(1*S*,2*S*)-(1-ethyl-2-methylbut-3-enyl)amine.** The starting material was prepared according to ref 21. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.28 (m, 5H), 5.91−5.82 (m, 1H), 5.15−5.08 (m, 2H), 4.09 (q, 1H, J = 6.6 Hz), 2.60−2.56 (m, 1H), 2.25−2.21 (m, 2H), 1.50−1.45 (m, 1H), 1.37 (d, 3H, J = 6.6 Hz), 1.25 (m, 1H), 1.17−1.10 (m, 1H), 1.02 (d, 3H, J = 7.0 Hz), 0.90 (t, 3H, J = 7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 141.5, 128.35, 127.05, 126.8, 114.8, 60.6, 55.05, 39.3, 25.2, 23.6, 16.5, 11.35.

***N*-((*R*)-1-Phenylethyl)-*N*-((1*S*,2*S*)-1-ethyl-2-methylbut-3-enyl)glycinate Methyl Ester (27).** A solution of *N*-(*R*)-1-phenylethyl-*N*-(1*S*,2*S*)-(1-ethyl-2-methylbut-3-enyl)amine (0.4 g, 1.84 mmol) was treated following the general procedure for the alkylation with methyl bromoacetate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.23 (m, 5H), 5.76−5.66 (m, 1H), 5.01−5.91 (m, 2H), 4.13 (q, 1H, J = 6.76 Hz), 3.66 (s, 3H), 3.53 (d, 1H, J = 17.52 Hz), 3.39 (d, 1H, J = 17.52 Hz), 2.47−2.34 (m, 2H), 1.44−1.31 (m, 2H), 1.37 (d, 3H, J = 6.76 Hz), 0.98−0.89 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 145.7, 143.0, 128.25, 128.2, 127.05, 114.35, 64.2, 61.5, 51.6, 48.9, 41.5, 22.6, 21.05, 19.9, 12.5.

(2*S*,3*R*,4*S*,5*S*)-5-Ethyl-3,4-dimethyl-2-carbomethoxy-*N*-((*R*)-1-phenylethyl)pyrrolidine (28). A solution of **27** (0.207 mmol, 0.059 g) in Et_2O (20 mL) was treated following the metalation−transmetalation−cyclization general procedure for chiral substrate. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether 80/20) to give 0.041 g (69%) of the title compound. $[\alpha]_D = -25.8$ (0.0152, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.16 (m, 5H), 4.20 (q, 1H, J = 6.8 Hz),3.66 (d, 1H, J = 10.4 Hz), 3.21 (s, 3H), 2.96−2.91 (m, 1H), 2.40−2.36 (m, 1H), 2.09−2.03 (m, 1H), 1.71−1.65 (m, 1H), 1.49−1.42 (m, 1H), 1.32 (d, 3H, J = 6.8 Hz), 0.91 (d, 3H, J = 7.5 Hz), 0.92 (t, 3H, J = 7.9 Hz), 0.83 (d, 3H, J = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 143.55,

128.8, 127.8, 126.75, 66.45, 63.85, 55.3, 50.75, 38.9, 38.85, 22.85, 12.1, 11.2, 10.7, 8.5. Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.70; H, 9.39; N, 4.92.

Supporting Information Available: NMR spectra for compounds prepared (60 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.

JO970813E