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Stereoselective Synthesis of New Chiral *N*-Tertiary Tetrasubstituted *β*-Enamino Ester Piperidines through an Ammonia-Catalyzed Process

Sandrine Calvet-Vitale, Corinne Vanucci-Bacqué,* Marie-Claude Fargeau-Bellassoued, and Gérard Lhommet*

Université Pierre et Marie Curie, Institut de Chimie Moléculaire FR 2769, Laboratoire de Chimie Organique, UMR 7611, Equipe de Chimie des Hétérocycles, 4 Place Jussieu, 75252 Paris Cedex 05, France

vanucci@ccr.jussieu.fr; lhommet@ccr.jussieu.fr

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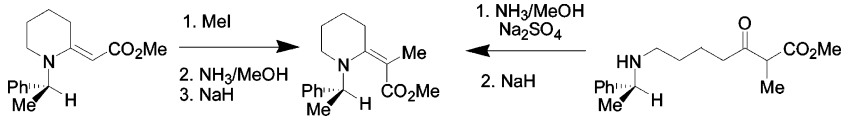
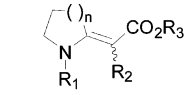


We report here two approaches for the preparation of new *N*-substituted *β*-enamino ester piperidines featuring an exocyclic tetrasubstituted double bond, based either on the direct alkylation of piperidine *β*-enamino esters bearing an exocyclic trisubstituted double bond or on the intramolecular cyclization of linear amino *β*-keto esters. The target compounds were obtained as unusual (*Z*)-stereoisomers in high yields. The key role of ammonia as reagent, acting both as a nucleophile and a base, was underlined. The diastereoselective formation of the products was rationalized on the basis of an ammonia addition−*syn* elimination catalytic process.

Introduction

Considering the outstanding interest of heterocyclic *β*-enamino esters as intermediates in the total syntheses of alkaloids,[1] we have developed a program aimed at preparing various chiral pyrrolidine and piperidine *β*-enamino esters.[2] In particular, *β*-enamino esters **1** and **2** featuring both an exocyclic tetrasubstituted double bond ($R_2 \neq H$) and a chiral auxiliary on the nitrogen atom ($R_1 \neq H$) have attracted our attention (Figure 1) as a way to access chiral pyrrolidines and piperidines following the stereocontrolled reduction of the double bond, which would simultaneously create two stereogenic centers. A general method for the preparation of pyrrolidines **1**[2a] relied upon Eschenmoser



R_1 and $R_2 \neq H$ n = 1: **1** n = 2: **2**

FIGURE 1.

reaction between the corresponding thiolactam and secondary α-bromo esters to lead to a mixture of (*E*)- and (*Z*)-isomers, the latter being always minor (Scheme 1). In contrast, when applied to piperidine-2-thiones,[3] the same procedure was reported to lead either to tetrahydrothieno[2,3-*b*]pyridin-3-ones **3a** or to thiazolidinones **3b** (depending on the nature of R_1), instead of the expected piperidine enamino esters **2** (Scheme 1). The only known preparation of a compound of type **2** (R_1 and $R_2 \neq H$) by Eschenmoser condensation involves the reaction of α-bromobutyrolactone with chiral piperidine thiolactam **4**[4]

(1) See, for example: (a) Fujimoto, R.; Kishi, Y. *Tetrahedron Lett.* **1981**, *22*, 4197−4198. (b) Hart, D. J.; Kanai, K. *J. Am. Chem. Soc.* **1983**, *105*, 1255−1263. (c) Cook, G. R.; Beholz, L. G.; Stille, J. R. *Tetrahedron Lett.* **1994**, *35*, 1669−1672. (d) Hernández, A.; Marcos, M.; Rapoport, H. *J. Org. Chem.* **1995**, *60*, 2683−2691. (e) Michael, J. P.; Gravestock, D. *Synlett* **1996**, 981−982. (f) Michael, J. P.; Gravestock, D. *Eur. J. Org. Chem.* **1998**, 865−870.

(2) (a) David, O.; Blot, J.; Bellec, C.; Fargeau-Bellassoued, M.-C.; Haviari, G.; Célérier, J.-P.; Lhommet, G.; Gramain, J.-C.; Gardette, D. *J. Org. Chem.* **1999**, *64*, 3122−3131. (b) David, O.; Fargeau-Bellassoued, M.-C.; Lhommet, G. *Tetrahedron Lett.* **2002**, *43*, 3471−3474. (c) Calvet S.; David, O.; Vanucci-Bacqué, C.; Fargeau-Bellassoued M.-C.; Lhommet, G. *Tetrahedron* **2003**, *59*, 6333−6339. (d) David, O.; Calvet, S., Chau, F.; Vanucci-Bacqué, C.; Fargeau-Bellassoued, M.-C.; Lhommet, G. *J. Org. Chem.* **2004**, *69*, 2888−2891.

(3) (a) Marchand, P.; Bellec, C.; Fargeau-Bellassoued, M.-C.; Nezry, C.; Lhommet, G. *Heterocycles* **1996**, *43*, 63−70. (b) Michael, J. P.; de Koning, C. B.; van der Westhuyzen, C. W.; Fernandes, M. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2055−2062. (c) Russowsky, D.; da Silveira Neto, B. A. *Tetrahedron Lett*. **2003**, *44*, 2923−2926. (d) Russowsky, D.; da Silveira Neto, B. A. *Tetrahedron Lett.* **2004**, *45*, 1437−1440.

(4) David, O.; Bellec, C.; Fargeau-Bellassoued M.-C.; Lhommet, G. *Heterocycles* **2001**, *55*, 1689−1701.

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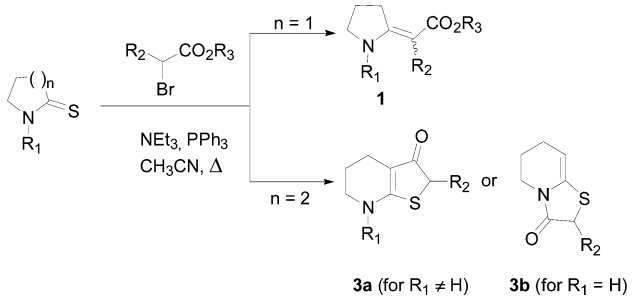
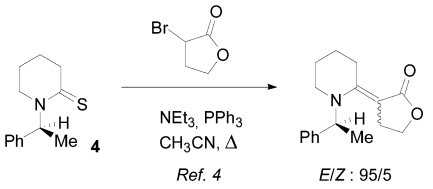
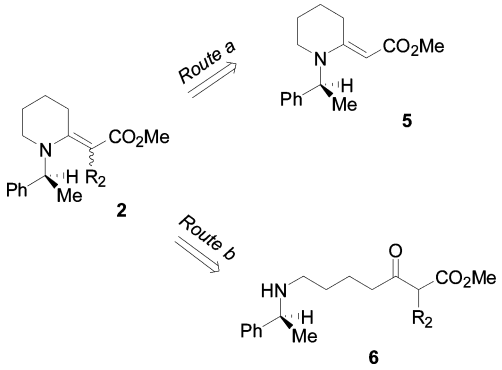
SCHEME 1



SCHEME 2



SCHEME 3



(Scheme 2). An access to piperidine **2** ($R_1 = R_2 =$ Me; $R_3 =$ Et) by condensation of ethyl bromoacetate with lactim ether under Reformatsky conditions has moreover been described.[5] However, to our knowledge, a general method to access piperidines **2** (R_1 and $R_2 \neq$ H) has never been reported. We wish now to report the first general synthesis of compounds **2** displaying various alkyl substituents R_2 on the double bond and the (*S*)-phenylethyl moiety as the chiral auxiliary attached to the nitrogen atom.

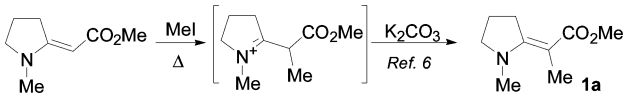
Results and Discussion

Access to the target compounds **2** was envisioned according to two strategies, relying either on the direct alkylation of chiral *β*-enamino ester **5** (Scheme 3, route a) or on the intramolecular cyclization of α-substituted *ω*-amino *β*-keto ester **6** (Scheme 3, route b).

We initially focused our attention on route a. We previously reported the synthesis of pyrrolidine **1a** ($R_1 = R_2 = R_3 =$ Me) by reacting methyl (1-methylpyrrolidin-2-ylidene)acetate in refluxing methyl iodide followed by the addition of potassium carbonate (Scheme 4).[6]

As an extension of this procedure, compound **5**[2c] was refluxed in methyl iodide to afford an iminium intermediate **Ia** (Scheme 5). The latter, shown by NMR to consist of a 70:30 mixture of

SCHEME 4



isomers, was first deprotonated by treatment with excess aqueous saturated potassium carbonate. Surprisingly, the NMR spectrum of the resulting reaction mixture showed that this two-step procedure had not generated the expected enamino ester, but a mixture consisting mainly of the endocyclic enamine **7a** as a 70:30 mixture of diastereoisomers (as determined by ^{1}H NMR), along with various amounts (10−30%) of the linear amino *β*-keto ester **6a**[7] (Scheme 5). Isolation of **7a** turned out to be particularly troublesome, since aqueous workup as well as chromatography on silica gel[8] quantitatively transformed **7a** into *β*-keto ester **6a**. Alternative treatment of iminium **Ia** with sodium hydride in THF (1.5 equiv) or triethylamine in MeOH (1.5 equiv) as the base resulted in the same outcome (Scheme 5). We finally thought to deprotonate crude iminium **Ia** with an anhydrous 7 N methanolic ammonia solution. After 48 h, the expected *β*-enamino ester **2a** was obtained along with keto ester **6a** in a 80:20 ratio as determined by ^{1}H NMR in $CDCl_3$.[9]

Subsequently, we found that successive treatment of the crude iminium **Ia** with the ammonia solution (15 min) and then with sodium hydride allowed to reduce the reaction time and to generate compound **2a** as the sole product according to the ^{1}H NMR spectrum of the reaction mixture. This compound was relatively unstable and moisture sensitive, which prevented any aqueous workup. Moreover, attempted silica gel column chromatography delivered compound **6a** as the major compound. Finally, bulb-to-bulb distillation afforded **2a** in 89% yield as a single isomer. The stereochemistry of the double bond was assigned as (*Z*) on the basis of NOE experiments that showed interactions between the methyl group on the double bond (δ 1.74) and the C-3′ (δ 2.19) hydrogens. This result was unexpected since *N*-substituted pyrrolidine and piperidine *β*-enamino esters bearing an exocyclic double bond had been previously obtained generally as the (*E*)-isomer, with at worst the (*Z*)-isomer as a minor product.[2a,4,10]

Attempted extension of this procedure to various R_2 groups (ethyl, allyl, benzyl) invariably failed, the formation of iminium ions **Ib**−**d** being not even observed. Therefore, we moved to the second strategy based on the intramolecular cyclization of α-substituted *ω*-amino *β*-keto esters **6** (Scheme 3, route b). Preparation of compound **6a** ($R_2 =$ Me) was carried out starting from methyl 7-chloro-3-oxoheptanoate.[2c] The latter was treated with methyl iodide in the presence of potassium carbonate[11] to cleanly afford compound **9a** in 96% yield (Scheme 6). Direct condensation of (*S*)-1-phenylethylamine on keto ester **9a**, under different reaction conditions,[12] gave rise to the expected product **6a** as the minor component, along with the starting material and side products resulting from the reaction of the amine on the ketone.[13] At this point, we reasoned that initial protection of the keto function of **9a** would prevent these concurrent

(5) Jain, S.; Jain, R.; Singh, J.; Anand, N. *Tetrahedron Lett.* **1994**, *35*, 2951−2954.

(6) Célérier, J.-P.; Deloisy-Marchalant, E.; Lhommet, G. *J. Heterocycl. Chem.* **1984**, *21*, 1633−1635.

(7) It is noteworthy that NMR spectra of enamine **7a** in $CDCl_3$ always show the presence of amino keto ester **6a**. Thus, **7a** can never be observed in pure form. Moreover, we have observed that NMR sample of **7a** in $CDCl_3$ was totally converted into **6a** over 6 h.

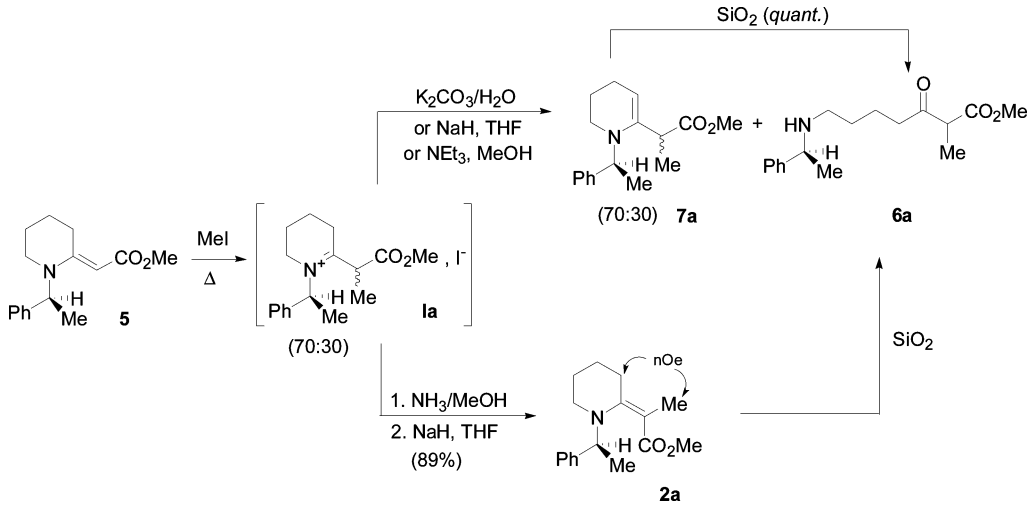
(8) The obtention of **6a** was also observed using deactivated silica gel which prevented any further purification.

(9) It is of note that enamino ester **2a** was not converted into **6a** in $CDCl_3$.

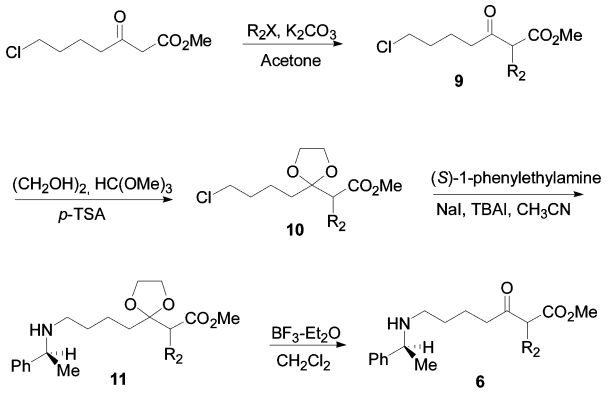
(10) Shiosaki, K. In *Comprehensive Organic Chemistry*; Trost B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, pp 865−892.

(11) Lambert, P. H.; Vaultier, M.; Carrié, R. *J. Org. Chem.* **1985**, *50*, 5352−5356.

SCHEME 5



SCHEME 6



R_2	**9** (yield %)[a]	**10** (yield %)[a]	**11** (yield %)[a]	**6** (yield %)[a]
Me	**9a** (96)	**10a** (85)	**11a** (72)	**6a** (70)
Et	**9b** (60)	**10b** (86)	**11b** (77)	**6b** (77)
Allyl	**9c** (54)	**10c** (80)	**11c** (76)	**6c** (73)
Benzyl	**9d** (43)	**10d** (80)	**11d** (70)	**6d** (74)

[a] Isolated yields.

reactions. Compound **9a** was therefore readily converted into the corresponding dioxolane **10a** in 85% yield. Subsequent substitution of the halogen atom by (*S*)-1-phenylethylamine was achieved in refluxing acetonitrile to give amino ester **11a**, which was deprotected upon treatment with boron trifluoride etherate[2c] to lead to the expected amino *β*-keto ester **6a** in 70% isolated yield.[14]

We next turned our attention toward the cyclization of compound **6a** (Scheme 7), considering only dehydrating reaction conditions that would require no aqueous workup. Compound **6a** was first reacted with zinc perchlorate and magnesium sulfate[15] to afford iminium **Ia** as a 1:1 mixture of isomers, as determined by ^{1}H NMR. On the other hand, in refluxing methylene chloride and in the presence of sodium sulfate, **6a** led to enamine **7a** as a 1:1 mixture of isomers. Based on our previous study on the direct alkylation of enamino ester **5** (Scheme 3, route a), we treated in parallel iminium **Ia**, ClO_4^-, and compound **7a** with ammonia in methanol and then with sodium hydride (Scheme 7). Under these conditions, *β*-enamino ester **2a** was obtained in, respectively, 55% and 72% crude yield from **6a**. Finally, cyclization conditions were improved by reacting **6a** directly in the presence of sodium sulfate and ammonia in refluxing methanol followed by treatment with sodium hydride. This one-pot procedure afforded **2a** in 71% isolated yield, once again as the only (*Z*)-isomer.

To explore the scope of this methodology, we prepared various substituted *ω*-amino *β*-keto esters **6b** (R_2 = ethyl), **6c** (R_2 = allyl), and **6d** (R_2 = benzyl) according to the procedure developed for **6a** (Scheme 6). The alkylation step leading to compounds **9b**−**d**, using less reactive alkyl halide than methyl iodide, proceeded with lower yields compared to **9a**, due to the competitive formation of dialkylated derivatives. The subsequent protection−substitution−deprotection sequence efficiently led to amino keto esters **6b**−**d** in good yields. Compounds **6b**−**d** were then reacted under the optimized conditions previously developed for the preparation of **2a** to afford the expected corresponding piperidines **2b**, **2c**, and **2d** in, respectively, 75%, 77%, and 79% isolated yields[16] as the only (*Z*)-isomers (Scheme 8). The stereochemistry of the double bonds was assigned on the basis of ^{1}H NMR data. The chemical shifts of the hydrogen atoms at C-3′ of **2a**−**d** appeared in the range 2.10−2.15 ppm,[17,3c] shielded compared to the corresponding one observed in compounds with the (*E*)-stereochemistry (*δ* above 3 ppm[2b,4]). These results confirmed that our strategy based on the cyclization of compounds **6** efficiently and stereoselectively afforded variously substituted compounds **2**.

To rationalize our results, we will now discuss the mechanistic and stereochemical outcome of the involved reactions. We will mainly base our analysis on the methyl-substituted compounds. Iminium ion **Ia** (R_2 = CH_3) is the key intermediate to explain the formation of the different products we isolated. According

(12) Among the different reaction conditions screened: (a) condensation without solvent at 110 °C; (b) Na_2CO_3, NaI, cat. TBAI in refluxing CH_3CN; (c) Na_2SO_4, NaH_2PO_4, cat. I_2 at 65 °C; (d) $Zn(ClO_4)_2{\cdot}6H_2O$, $MgSO_4$ in refluxing CH_2Cl_2.

(13) *ω*-Chloro and/or *ω*-amino enamino esters were obtained as side products depending on the reaction conditions.

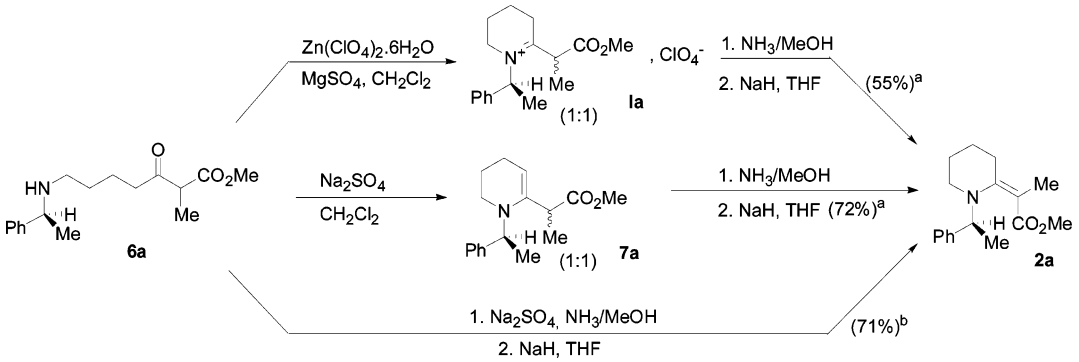
(14) One notes that contrary to what was observed for the unsubstituted compound **11** (R_2 = H),[2c] no in situ cyclisation of intermediate **6a** into compound **2a** occurred during the deprotection step.

(15) Bartoli, G.; Bosco, M.; Locatelli, M.; Marcantoni, E.; Melchiorre, P.; Sambri, L. *Synlett* **2004**, *2*, 239−242.

(16) Contrary to **2a**, silica gel column chromatography of compounds **2b**−**d** generates only a small amount of linear amines **6b**−**d**.

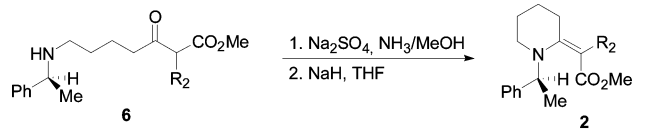
(17) Célérier, J.-P.; Deloisy, E.; Lhommet, G.; Maitte, P. *J. Org. Chem.* **1979**, *44*, 3089.

SCHEME 7[a]



[a] Key: (a) crude yields from **6a**; (b) isolated yield.

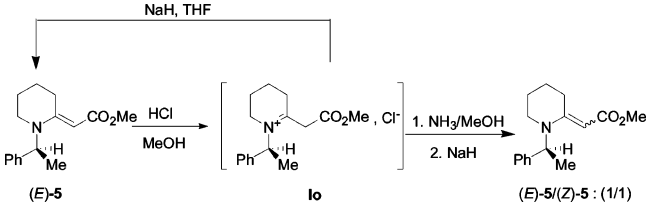
SCHEME 8



R_2	**6**	**2** (Yield %)[a]
Et	**6b**	**2b** (75)
Allyl	**6c**	**2c** (77)
Benzyl	**6d**	**2d** (79)

[a]Isolated yields

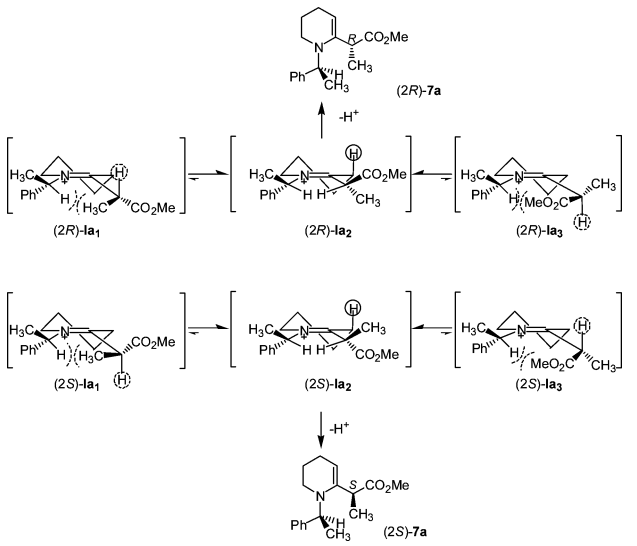
SCHEME 9



to the base used to deprotonate **Ia**, two different compounds **7a** or **2a** were obtained. The surprising formation of enamine **7a** in the presence of potassium carbonate, sodium hydride, or triethylamine sharply contrasts with what was observed with the *N*-substituted pyrrolidine analogue. In the latter case, deprotonation of the intermediate iminium exclusively occurred as expected at the more acidic site, α to the ester moiety, to generate an exocyclic double bond (Scheme 4).[6] This result demonstrates the influence of the ring size on the outcome of the reaction. Also noteworthy is the observation that reaction with sodium hydride of iminium ion **Io** (R_2 = H, formation confirmed by NMR) stemming from **5** returned compound **5** as the only (*E*)-isomer (Scheme 9), suggesting that deprotonation had taken place with the same regioselectivity α to the ester group. This observation underlines the key role of the R_2 substituent in the deprotonation process in the case of the piperidine compounds.

In the case of iminium ion **Ia** (R_2 = CH_3), based on simple pK_a considerations, one could suppose that deprotonation would occur at the more acidic carbon α to the ester group to give compound **2a**, which in turn could isomerize under basic conditions to yield enamine **7a**. However, we showed that enamino ester **2a** when reacted with sodium hydride did not give rise to **7a**, but remained unchanged. The formation of enamine **7a** may be rationalized on the basis of orbital and conformational factors (Scheme 10). We have drawn in Scheme 10 the reactive conformations of iminium ions (2*R*)-**Ia** and (2*S*)-

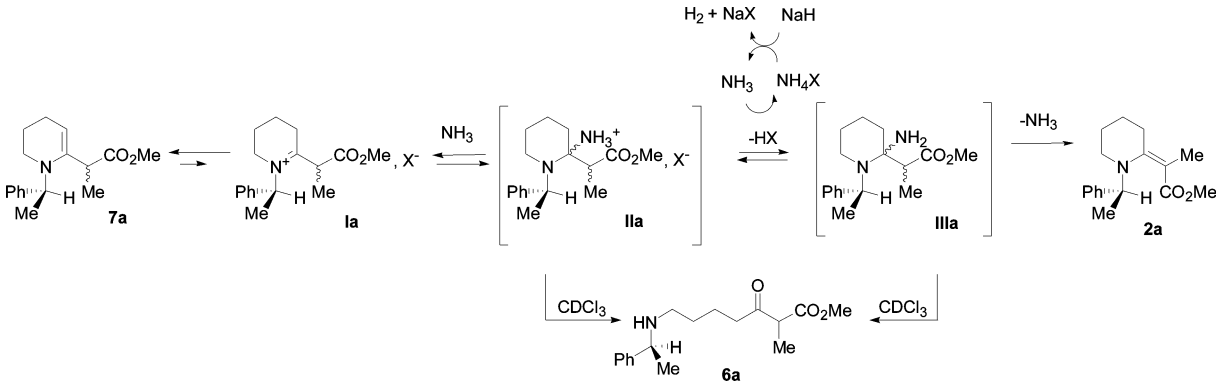
SCHEME 10. Proposed Mechanism for the Formation of 7a from Iminium Ion Ia



Ia that allow hydrogen abstraction (C−H bond nearly parallel to the π-orbital of the iminium double bond).[18] For conformations (2*R*)-$\mathbf{Ia}_2$ and (2*S*)-$\mathbf{Ia}_2$ in which the allylic 1,3-strains are both minimized, only the axial hydrogen atom at C-3′ is in an adequate position to be abstracted. This leads to the isolated enamines **7a** as a mixture of isomers in the same ratio as iminium ion **Ia**. Conversely, conformations $\mathbf{Ia}_1$ and $\mathbf{Ia}_3$ that would lead to the expected β-enamino ester **2a** by abstraction of the hydrogen α to the ester group appear strongly disfavored due to developing allylic 1,3-strains. Because of the absence of these allylic 1,3-strains in the case of iminium ion **Io** (R_2 = H), conformation $\mathbf{Io}_1$ is no longer disfavored compared to $\mathbf{Io}_2$. Therefore, deprotonation in the presence of NaH occurs as expected at the most acidic carbon to generate **5** as the (*E*)-isomer. In the case of the pyrrolidine iminium analogue to **I**, hydrogen abstraction at C-3′ is not stereoelectronically favored compared to piperidine iminium **Ia**, due to the pseudoaxial orientation of the C3′-H bond, while allylic 1,3-strains would not be as important as in the six-membered ring case. Combined with the reluctance of a five-membered ring to accommodate an endocyclic double bond, these reasons would explain formation of **1a** via deprotonation α to the ester function (Scheme 4).

(18) Deslongchamps, P. In *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York, 1983; Vol. 1, pp 209−290.

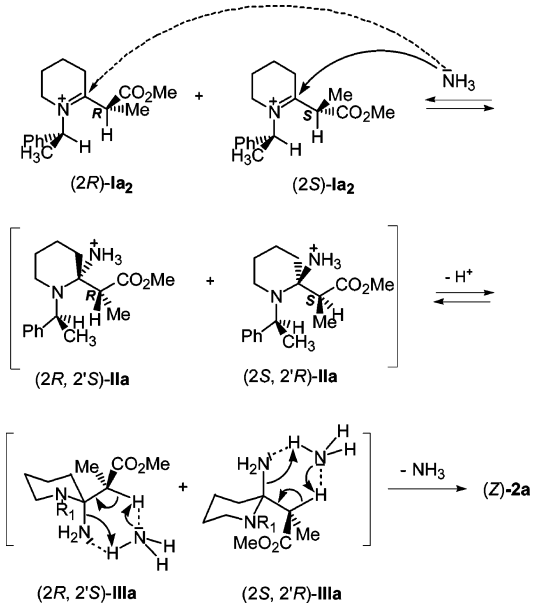
SCHEME 11. Proposed Mechanism for the Formation of 2a via Iminium Ia in NH_3/MeOH



Striking is the different behavior of iminium ion **Ia** in the presence of methanolic ammonia (with or without the subsequent treatment with sodium hydride), that afforded selectively the expected compound **2a** as a single isomer. To show the key role of ammonia, iminium ion **Ia** was successively treated with pure methanol and then with NaH in THF: this sequence delivered enamine **7a**. Moreover, reaction of iminium ion **Io** (R_2 = H) with NH_3/MeOH and then NaH led to **5** as a 1:1 mixture of the (*E*)-isomer and of the unprecedented (*Z*)-isomer (Scheme 9),[19] which again stresses the key role of ammonia. We suppose that ammonia would react first as a base to give enamine **7a** as previously observed. To account for the obtention of **2a**, we reasoned that ammonia would react also as a nucleophile, adding on the double bond of iminium ion **Ia**,[20] which is believed to result from an underlying enamine-iminium equilibrium under the protic conditions of the reaction[21] (Scheme 11) The existence of such an equilibrium is supported by the transformation of enamine **7a** into enamino ester **2a** following successive treatment with ammonia in methanol and then with sodium hydride (Scheme 7). The resulting intermediate ammonium **IIa** would deprotonate under the basic reaction conditions to generate amine **IIIa**. The latter would undergo ammonia elimination involving a formal hydrogen abstraction at the more acidic carbon α to the ester group, through a diasteroconvergent mechanism, to afford exocyclic β-enamino ester **2a** (Scheme 11). The formation of compound **6a** along with **2a** (as shown by NMR) following treatment of iminium ion **Ia** with ammonia in methanol for 48h, might be due to the opening of instable intermediate species **IIa** and/or **IIIa** during workup. The role of sodium hydride, added at the end of the process, would be to complete the reaction by quenching the acid species and hence to displace the equilibrium toward formation of the amine **IIIa** and ultimately that of compound **2a**.

Concerning the stereochemical outcome of this reaction that afforded **2a** as a single (*Z*)-isomer from an isomeric mixture of iminium **Ia**, we postulate a diastereocontrolled addition of ammonia on iminium **Ia**. If selectivity were induced by the (*S*)-1-phenylethyl auxiliary, ammonia would add *anti* to the bulky phenyl group of both isomers of iminium $\mathbf{Ia}_2$ to afford, following ammonia elimination via aminals (2*R*, 2′*R*)-**IIIa** and (2*S*, 2′*R*)-**IIIa**, a mixture of (*Z*)-**2a** and (*E*)-**2a** isomers in the same ratio

SCHEME 12. Proposed Mechanism for the Stereoconvergent Formation of (*Z*)-2a from Iminium Ions Ia



as that observed for iminium **Ia**. Since this result is not observed, we have to suppose that the stereogenic center α to the ester group control the facial selectivity of the addition of ammonia. To account for the formation of **2a**, we ruled out an E_2 mechanism because elimination of the amide ion appears unlikely. We rather propose a *syn* elimination mechanism. To rationalize the isolation of the sole isomer (*Z*)-**2a**, we postulate addition of ammonia *anti* to the carbomethoxy group of the most stable conformation $\mathbf{Ia}_2$ of each isomer (Scheme 12). The resulting amines (2*R*, 2′*S*)-**IIIa** and (2*S*, 2′*R*)-**IIIa** would undergo elimination of ammonia through the same concerted bimolecular process catalyzed by ammonia. We suggest that hydrogen bonding between intermediates **IIIa** and a second molecule of ammonia would allow a *syn* elimination process via a possible six-membered ring transition state[22] to give rise to (*Z*)-**2a** (Scheme 12). Although we could not isolate any intermediate in this reaction, the above original mechanism accounts for both the stereoconvergence of the reaction and the unusual (*Z*) stereochemistry of the double bond of **2a**. Furthermore, the mechanistic analysis developed for the formation of (*Z*)-**2a** can be extended to account for the formation of the variously substituted β-enamino esters **2b**−**d**.

(19) The 1:1 mixture of (*E*) and (*Z*) isomers of **5** slowly isomerized (3 days) into the (*E*)-isomer in $CDCl_3$.

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(22) (a) Ilieva, S.; Galabov B.; Musaev, D. G.. Morokuma, K.; Schaefer, H. F., III. *J. Org. Chem.* **2003**, *68*, 1496−1502. (b) Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1960**, *82*, 675−681.

Conclusions

In this paper, we have disclosed two related methods for the diastereoselective synthesis of the unprecedented chiral *N*-substituted β-enamino ester piperidines with a tetrasubstituted double bond. Direct alkylation of piperidine β-enamino ester **5** was efficient only in the case of the methyl substituent. On the other hand, intramolecular cyclization of ω-amino β-keto esters allowed the preparation of variously substituted compounds **2** in good yields. Our study showed that the common intermediate iminium **I** for these two approaches displayed different behavior depending on the nature of the base. Obtention of compounds **2** as a single unexpected (*Z*)-isomer was only possible using ammonia as the reagent. A stereoconvergent ammonia-assisted *syn* elimination was proposed to account for the observed high diastereoselectivity. Further work to develop the synthetic applications of these polyfunctional heterocycles is underway in our laboratory.

Experimental Section

General Procedure for the Preparation of Compounds 9. To a suspension of K_2CO_3 (14 mmol, 2 equiv) in dry acetone (25 mL) was added dropwise methyl 7-chloro-3-oxo-heptanoate (7 mmol, 1 equiv). The reaction mixture was stirred at room temperature for 30 min, and the alkyl halide (7.7 mmol, 1.1 equiv) was added dropwise. After being stirred for 12 h, the reaction mixture was concentrated in vacuo and the residue dissolved in CH_2Cl_2 (20 mL). The organic layer was washed with water, dried over Na_2SO_4, and concentrated in vacuo to afford after column chromatography on silica gel the expected compounds **9**.

7-Chloro-2-methyl-3-oxoheptanoic Acid Methyl Ester (9a). Compound **9a** was obtained as a colorless oil following the general procedure using methyl iodide as alkylating agent in 96% yield: R_f (cyclohexane/AcOEt 8/2) 0.3; IR (neat) 1745, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (d, J = 7 Hz, 3H), 1.71−1.90 (m, 4H), 2.57−2.64 (m, 2H), 3.52−3.62 (m, 3H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 12.4, 20.5, 31.4, 40.1, 44.3, 52.0, 52.2, 170.6, 204.9. Anal. Calcd for $C_9H_{15}ClO_3$: C, 52.30; H, 7.32. Found: C, 52.29; H, 7.21.

7-Chloro-2-ethyl-3-oxoheptanoic Acid Methyl Ester (9b). Compound **9b** was obtained as a colorless oil following the general procedure using ethyl iodide as alkylating agent in 60% yield: R_f (cyclohexane/AcOEt 8/2) 0.3; IR (neat) 1740, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.5 Hz, 3H), 1.69−1.81 (m, 4H), 1.82−1.91 (m, 2H), 2.51−2.72 (m, 2H), 3.39 (t, J = 7.5 Hz, 1H), 3.51−3.56 (m, 2H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 11.8, 20.5, 21.5, 31.6, 40.8, 44.5, 52.1, 60.2, 170.1, 204.6. Anal. Calcd for $C_{10}H_{17}ClO_3$: C, 54.42; H, 7.76. Found: C, 54.47; H, 7.93.

7-Chloro-2-allyl-3-oxoheptanoic Acid Methyl Ester (9c). Compound **9c** was obtained as a colorless oil following the general procedure using allyl bromide as alkylating agent in 54% yield: R_f (cyclohexane/AcOEt 8/2) 0.3; IR (neat) 1750, 1720, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.69−1.90 (m, 4H), 2.43−2.64 (m, 4H), 3.48−3.67 (m, 3H), 3.71 (s, 3H), 4.95−5.12 (m, 2H), 5.51−5.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.2, 31.2, 31.8, 41.4, 44.2, 51.8, 57.6, 116.9, 133.9, 169.1, 203.4. Anal. Calcd for $C_{11}H_{17}ClO_3$: C, 56.78; H, 7.36. Found: C, 56.80; H, 7.58.

7-Chloro-2-benzyl-3-oxoheptanoic Acid Methyl Ester (9d). Compound **9d** was obtained as a colorless oil following the general procedure using benzyl bromide as alkylating agent in 43% yield: R_f (cyclohexane/AcOEt 8/2) 0.35; IR (neat) 1750, 1720, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.51−1.66 (m, 4H), 2.21−2.40 (m, 1H), 2.65−2.77 (m, 1H), 3.11−3.17 (m, 2H), 3.42−3.51 (m, 2H), 3.67 (s, 3H), 3.80 (t, J = 7.5 Hz, 1H), 7.10−7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.4, 31.4, 34.1, 41.9, 44.2, 52.4, 60.1, 126.6, 128.3, 128.7, 138.0, 169.3, 204.0. Anal. Calcd for $C_{15}H_{19}ClO_3$: C, 63.71; H, 6.77. Found: C, 64.14; H, 7.16.

General Procedure for the Preparation of Compounds 10. A mixture of β-keto ester **8** (10 mmol, 1 equiv), methyl orthoformate (20 mmol, 2 equiv), ethylene glycol (50 mmol, 5 equiv), and *p*-TSA (1 mmol, 0.1 equiv) was stirred at room temperature for 48 h. A 5% aqueous solution of NaH_2PO_4 (3 mL) was added. The reaction mixture was stirred for 15 min, and Et_2O (40 mL) was added. The organic layer was successively washed with 5% NaH_2PO_4 solution (3 × 10 mL), water (15 mL), and brine (15 mL), dried over Na_2SO_4, and concentrated in vacuo. Column chromatography on silica gel gave pure compounds **10**.

2-[2-(4-Chlorobutyl)[1,3]dioxolan-2-yl]propionic Acid Methyl Ester (10a). Compound **10a** was obtained as colorless oil in 85% yield following the general procedure: R_f (cyclohexane/AcOEt 8/2) 0.3; IR (neat) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20 (d, J = 7 Hz, 3H), 1.40−1.62 (m, 2H), 1.65−1.87 (m, 4H), 2.84 (q, J = 7 Hz, 1H), 3.53 (t, J = 6.5 Hz, 2H), 3.69 (s, 3H), 3.95−4.10 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 12.5, 20.2, 32.5, 33.7, 44.8, 46.6, 51.6, 65.4, 110.9, 173.7. Anal. Calcd for $C_{11}H_{19}ClO_4$: C, 52.70; H, 7.64. Found: C, 52.61; H, 7.38.

2-[2-(4-Chlorobutyl)[1,3]dioxolan-2-yl]butyric Acid Methyl Ester (10b). Compound **10b** was obtained as colorless oil following the general procedure in 86% yield: R_f (cyclohexane/AcOEt 9/1) 0.25; IR (neat) 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.50−1.82 (m, 8H), 2.63 (dd, J = 3.75 and 11.5 Hz, 1H), 3.53 (t, J = 7 Hz, 2H), 3.70 (s, 3H), 3.94−4.03 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 12.5, 20.2, 21.1, 32.7, 33.9, 45.0, 51.7, 55.4, 65.5, 110.9, 173.3. Anal. Calcd for $C_{12}H_{21}ClO_4$: C, 54.44; H, 8.00. Found: C, 54.21; H, 8.16.

2-[2-(4-Chlorobutyl)[1,3]dioxolan-2-yl]pent-4-enoic Acid Methyl Ester (10c). Compound **10c** was obtained as colorless oil in 80% yield following the general procedure: R_f (cyclohexane/AcOEt 9/1) 0.3; IR (neat) 1740, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.41−1.60 (m, 2H), 1.62−1.94 (m, 4H), 2.33−2.53 (m, 2H), 2.80 (dd, J = 3.75 and 11.5 Hz, 1H), 3.53 (t, J = 6.5 Hz, 2H), 3.67 (s, 3H), 3.95−4.05 (m, 4H), 4.94−5.09 (m, 2H), 6.42−6.81 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.0, 31.9, 32.4, 33.8, 44.7, 51.4, 52.8, 65.3, 110.4, 116.4, 135.2, 172.3. Anal. Calcd for $C_{13}H_{21}ClO_4$: C, 56.42; H, 7.65. Found: C, 56.69; H, 7.66.

2-[2-(4-Chlorobutyl)[1,3]dioxolan-2-yl]-3-phenylpropionic Acid Methyl Ester (10d). Compound **10d** was obtained as colorless oil in 80% yield following the general procedure: R_f (cyclohexane/AcOEt 9/1) 0.3; IR (neat) 1730, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43−1.61 (m, 2H), 1.73−1.97 (m, 4H), 2.88−3.04 (m, 3H), 3.52 (t, J = 6.5 Hz, 2H), 3.53 (s, 3H), 3.96−4.05 (m, 4H), 7.10−7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.1, 32.5, 33.8, 34.0, 44.9, 51.5, 55.5, 65.4, 110.6, 126.2, 128.3, 128.5, 139.2, 172.4. Anal. Calcd for $C_{17}H_{23}ClO_4$: C, 62.48; H, 7.09. Found: C, 62.47; H, 7.26.

General Procedure for the Preparation of Compounds 11. To a solution of compound **10** (6 mmol, 1 equiv) in acetonitrile (50 mL) were added NaI (6 mmol, 1 equiv), Na_2CO_3 (30 mmol, 3 equiv), tetrabutylammonium iodide (0.6 mmol, 0.1 equiv), and (*S*)-1-phenylethylamine (6 mmol, 1 equiv). The reaction mixture was refluxed for 48 h. The solvent was evaporated, and water (30 mL) was added. The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. Column chromatography on silica gel gave pure compounds **11**.

2-{2-[4-(1(*S*)-Phenylethylamino)butyl][1,3]dioxolan-2-yl)propionic Acid Methyl Ester (11a). Compound **11a** was obtained as pale yellow oil in 72% yield following the general procedure: R_f (AcOEt) 0.25; IR (neat) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18 (d, J = 7 Hz, 3H), 1.34 (d, J = 6.5 Hz, 3H), 1.35−1.50 (m, 5H), 1.60−1.80 (m, 2H), 2.33−2.55 (m, 2H), 2.82 (q, J = 7 Hz, 1H), 3.67 (s, 3H), 3.72 (q, J = 6.5 Hz, 1H), 3.90−4.00 (m, 4H), 7.20−7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.4, 20.5, 24.3, 30.2, 34.6, 46.6, 47.5, 51.6, 58.2, 65.4, 111.0, 126.4, 126.6, 128.2, 145.7, 173.6; HMRS (CI) *m*/*z* calcd for $C_{19}H_{30}NO_4$ (MH^+) 336.2175, found, 336.2164.

2-{2-[4-(1(*S*)-Phenylethylamino)butyl][1,3]dioxolan-2-yl)butyric Acid Methyl Ester (11b). Compound **11b** was obtained as pale yellow oil in 77% yield following the general procedure: R_f (AcOEt) 0.2; IR (neat) 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7 Hz, 3H), 1.33 (d, J = 6.5 Hz, 3H), 1.29−1.80 (m, 9H), 2.27−2.52 (m, 2H), 2.61 (dd, J = 3.75 and 11.5 Hz, 1H), 3.67 (s, 3H),

3.74 (q, J = 6.5 Hz, 1H), 3.88−4.01 (m, 4H), 7.20−7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.4, 20.4, 20.9, 24.3, 30.1, 34.7, 47.6, 51.5, 55.3, 58.2, 65.3, 111.1, 126.5, 126.7, 128.3, 145.6, 173.2; HMRS (CI) m/z calcd for $C_{20}H_{32}NO_4$ (MH^+) 350.2331, found 350.2336.

2-{2-[4-(1(*S*)-Phenylethylamino)butyl][1,3]dioxolan-2-yl)pent-4-enoic Acid Methyl Ester (11c). Compound **11c** was obtained as pale yellow oil in 76% yield following the general procedure: R_f (AcOEt) 0.2; IR (neat) 1735, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (d, J = 6.5 Hz, 3H), 1.19−1.52 (m, 5H), 1.56−1.89 (m, 2H), 2.26−2.54 (m, 4H), 2.79 (dd, J = 3.5 and 12 Hz, 1H), 3.62 (s, 3H), 3.71 (q, J = 6.5 Hz, 1H), 3.85−4.02 (m, 4H), 4.93−5.07 (m, 2H), 5.61−5.82 (m, 1H), 7.15−7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.4, 24.3, 30.1, 31.9, 34.9, 47.6, 51.5, 52.9, 58.3, 65.4, 110.7, 116.5, 126.4, 126.7, 128.3, 135.4, 145.7, 172.5; HMRS (CI) m/z calcd for $C_{21}H_{32}NO_4$ (MH^+), 362.2331, found 362.2337.

3-Phenyl-2-{2-[4-(1(*S*)-phenylethylamino)butyl][1,3]dioxolan-2-yl)propionic Acid Methyl Ester (11d). Compound **11d** was obtained as pale yellow oil in 70% yield following the general procedure: R_f (AcOEt) 0.2; IR (neat) 1730, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (d, J = 6.75 Hz, 3H), 1.22−1.57 (m, 5H), 1.62−1.91 (m, 2H), 2.37−2.58 (m, 2H), 2.85−3.07 (m, 3H), 3.52 (s, 3H), 3.75 (q, J = 6.75 Hz, 1H), 3.90−4.06 (m, 4H), 7.32−7.11 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 20.5, 24.2, 30.1, 33.8, 34.9, 47.5, 51.5, 55.5, 58.3, 65.5, 110.8, 126.3, 126.5, 126.9, 128.4, 128.6, 139.4, 145.5, 172.5; HMRS (CI) m/z calcd for $C_{25}H_{34}NO_4$ (MH^+) 412.2488, found 412.2480.

General Procedure for the Preparation of Compounds 6. To a solution of compound **11** (2 mmol, 1 equiv) in CH_2Cl_2 (20 mL) was added dropwise BF_3•Et_2O (20 mmol, 10 equiv). The reaction mixture was stirred at rt for 12 h. An aqueous saturated solution of $NaHCO_3$ (15 mL) was slowly added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Column chromatography on silica gel gave pure compounds **6**.

2-Methyl-3-oxo-7-(1(*S*)-phenylethylamino)heptanoic Acid Methyl Ester (6a). Compound **6a** was obtained from **11a** as pale yellow oil in 70% yield following the general procedure: R_f (AcOEt) 0.1; IR (neat) 3320, 1740, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (d, J = 7.25 Hz, 3H), 1.36 (d, J = 6.5 Hz, 3H), 1.23−1.60 (m, 4H), 2.36−2.63 (m, 4H), 2.80 (br s, 1H), 3.51 (q, J = 7 Hz, 1H), 3.69 (s, 3H), 3.81 (q, J = 6.5 Hz, 1H), 7.21−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.8, 20.9, 23.7, 28.9, 41.0, 47.1, 52.3, 52.5, 58.5, 126.6, 127.2, 128.5, 144.3, 170.9, 205.7; HRMS (CI) calcd for $C_{17}H_{26}NO_3$ (MH^+), 292.1913, found 292.1907.

2-Ethyl-3-oxo-7-(1(*S*)-phenylethylamino)heptanoic Acid Methyl Ester (6b). Compound **6b** was obtained from **11b** as pale yellow oil in 77% yield following the general procedure: R_f (AcOEt) 0.1; IR (neat) 1710, 1740, 3325 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 3H), 1.35 (d, J = 6.75 Hz, 3H), 1.43−1.69 (m, 5H), 1.82 (q, J = 7.5 Hz, 2H), 2.23−2.67 (m, 4H), 3.34 (t, J = 7.5 Hz, 1H), 3.70 (s, 3H), 3.74 (q, J = 6.75 Hz, 1H), 7.23−7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 11.9, 21.0, 21.6, 24.0, 29.2, 41.6, 47.1, 52.1, 58.3, 60.4, 126.6, 127.0, 128.4, 145.0, 170.2, 205.1; HRMS (CI) m/z calcd for $C_{18}H_{28}NO_3$ (MH^+) 306.2069, found 306.2075.

2-Allyl-3-oxo-7-(1(*S*)-phenylethylamino)heptanoic Acid Methyl Ester (6c). Compound **6c** was obtained from **11c** as pale yellow oil in 73% yield following the general procedure: R_f (AcOEt) 0.1; IR (neat) 1620, 1695, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (d, J = 6.5 Hz, 3H), 1.41−1.76 (m, 5H), 2.31−2.62 (m, 6H), 3.52 (t, J = 7.5 Hz, 1H), 3.68 (s, 3H), 3.70 (q, J = 6.5 Hz, 1H), 4.97−5.14 (m, 2H), 5.61−5.79 (m, 1H), 7.21−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.0, 24.3, 29.5, 32.2, 42.0, 47.3, 52.3, 58.2, 58.3, 117.5, 126.5, 126.8, 128.4, 134.2, 145.6, 169.6, 204.3; HRMS (CI) m/z calcd for $C_{19}H_{28}NO_3$ (MH^+) 318.2069, found 318.2066.

2-Benzyl-3-oxo-7-(1(*S*)-phenylethylamino)heptanoic Acid Methyl Ester (6d). The general procedure was followed but the reaction was conducted using 30 equiv of boron trifluoride etherate to give compound **6d** from **11d** as pale yellow oil in 74% yield: R_f (AcOEt) 0.1; IR (neat) 1710, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (d, J = 7 Hz, 3H), 1.35−1.55 (m, 4H), 1.85 (br s, 1H), 2.20−2.54 (m, 4H), 3.13 (d, J = 7.75 Hz, 2H), 3.66 (s, 3H), 3.64−3.80 (m, 2H), 7.12−7.35 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 20.9, 24.3, 29.3, 34.1, 42.7, 47.2, 52.4, 58.3, 60.2, 126.5, 126.7, 126.9, 128.4, 128.6, 128.8, 138.1, 145.6, 169.5, 204.5; HRMS (CI) m/z calcd for $C_{23}H_{30}NO_3$ (MH^+) 368.2226, found 368.2233.

General Procedure for the Preparation of Compounds 2 from Compounds 6. To a solution of compound **6** (1 mmol, 1 equiv) in 7 N methanolic solution of ammonia (15 mL) was added Na_2SO_4 (1 g). The reaction mixture was stirred at reflux temperature for 3 h and concentrated in vacuo. The residue was dissolved in dry THF (10 mL) and dropwise cannulated under argon atmosphere over a suspension of NaH (1.5 mmol, 1.5 equiv) in dry THF (8 mL). After 15 min of stirring, the reaction mixture was filtered, the solid residue was thoroughly washed with THF, and the organic layer was concentrated in vacuo to give crude compound **2.** Bulb-to-bulb distillation (180 °C, 0.1 mmHg) or column chromatography yielded pure compounds **2** as colorless oils.

2-[1-(1(*S*)-Phenylethyl)piperidin-2-ylidene]propionic Acid Methyl Ester (2a). Compound **2a** was obtained as colorless oil in 89% from **5** and in 71% yield from **6a** following the general procedure after purification by bulb-to-bulb distillation: $[\alpha]^{25}_D$ − 33.5 (c 1.03, $CHCl_3$); IR (neat) 1660, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (d, J = 6. 5 Hz, 3H), 1.42−1.57 (m, 4H), 1.72 (s, 3H), 2.17 (t, J = 7.25 Hz, 2H), 2.35−2.57 (m, 2H), 3.66 (s, 3H), 3.73 (q, J = 6.5 Hz, 1H), 7.23−7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 11.9, 24.1, 25.3, 29.7, 33.9, 47.1, 50.2, 58.2, 87.7, 126.4, 126.7, 128.2, 145.4, 160.3, 171.1; HRMS (CI) calcd for $C_{17}H_{24}NO_2$ (MH^+) 274.1807, found 274.1808.

2-[1-(1(*S*)-Phenylethyl)piperidin-2-ylidene]butyric Acid Methyl Ester (2b). Compound **2b** was obtained from **6b** as colorless oil in 75% yield following the general procedure after purification by bulb-to-bulb distillation: $[\alpha]^{25}_D$ −31.8 (c 1.19, $CHCl_3$); IR (neat) 1600, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J = 7.25 Hz, 3H), 1.34 (d, J = 6.5 Hz, 3H), 1.19−1.56 (m, 4H), 2.08−2.22 (m, 4H), 2.29−2.60 (m, 2H), 3.66 (s, 3H), 3.62−3.78 (m, 1H), 7.20−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.5, 19.8, 24.2, 26.1, 29.9, 33.1, 47.2, 50.2, 58.3, 95.2, 126.4, 126.7, 128.3, 145.6, 160.2, 171.2; HRMS (CI) calcd for $C_{18}H_{26}NO_2$ (MH^+) 288.1964, found 288.1951.

2-[1-(1(*S*)-Phenylethyl)piperidin-2-ylidene]pent-4-enoic Acid Methyl Ester (2c). Compound **2c** was obtained from **6c** as colorless oil in 77% yield following the general procedure after purification by bulb-to-bulb distillation: $[\alpha]^{23}_D$ −34.6 (c 1.16, $CHCl_3$); IR (neat) 1605, 1635, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (d, J = 6.5 Hz, 3H), 1.43−1.56 (m, 4H), 2.16 (t, J = 7.5 Hz, 2H), 2.30−2.61 (m, 2H), 2.92 (dt, J = 1.7 and 5.7 Hz, 2H), 3.64 (s, 3H), 3.65−3.77 (m, 1H), 4.83−5.14 (m, 2H), 5.72−5.90 (m, 1H), 7.19−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.3, 25.9, 29.9, 30.7, 33.3, 47.3, 50.5, 58.4, 90.7, 113.1, 126.5, 126.9, 128.4, 138.6, 145.7, 161.5, 171.1; HRMS (CI) calcd for $C_{19}H_{29}N_2O_2$ (MNH_4^+) 317.2229, found 317.2237.

3-Phenyl-2-[1-(1(*S*)-phenylethyl)piperidin-2-ylidene]propanoic Acid Methyl Ester (2d). Compound **2d** was obtained from **6d** as colorless oil in 79% yield following the general procedure after silica gel column chromatography: R_f (AcOEt) 0.2; $[\alpha]^{20}_D$ − 25.1 (c 1.05, $CHCl_3$); IR (neat) 1600, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (d, J = 6.5 Hz, 3H), 1.40−1.55 (m, 4H), 2.15 (t, J = 7.5 Hz, 2H), 2.30−2.45 (m, 2H), 3.595 (s, 2H), 3.61 (s, 3H), 3.68 (q, J = 6.5 Hz, 1H), 7.10−7.32 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 24.2, 25.5, 29.7, 31.9, 33.4, 47.0, 50.4, 58.2, 91.3, 125.3, 126.4, 126.8, 127.5, 128.0, 128.3, 142.7, 145.6, 162.0, 171.2; HRMS (CI) calcd for $C_{23}H_{31}N_2O_2$ (MNH_4^+) 367.2386, found 367.2382.

Supporting Information Available: Experimental procedures for the isomerization of (*E*)-**5** and the preparations of **7a** and **2a** from **5**. ^{1}H and ^{13}C NMR spectra of compounds **7a**, **11a**−**d**, **6a**−**d**, and **2a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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