JOC Notes

New and Expeditious Tandem Sequence Aza-Michael/Intramolecular Nucleophilic Substitution Route to Substituted γ-Lactams: Synthesis of the Tricyclic Core of (±)-Martinellines

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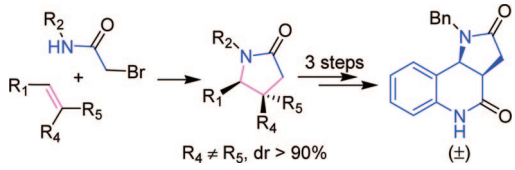

A new and highly diastereoselective tandem reaction aza-Michael/intramolecular nucleophilic substitution is presented. This unprecedented tandem reaction between *N*-substituted α-bromoacetamides and Michael acceptors proceeds with good yields and excellent diastereoselectivity to provide the corresponding trisubstituted γ-lactam systems. An application to the concise synthesis of the tricyclic core of (±)-martinelline alkaloids is also described.

Nitrogen heterocycles are of considerable interest in a number of areas, ranging from drug discovery to the polymer industry. γ-Lactams and their reduced forms, belonging to this family, are very attractive cyclic systems because they are present in wide range of natural and non-natural biologically active molecules and drug candidates.[1] Especially, functionalized chiral γ-lactams have proven to serve as crucial building blocks of numerous syntheses[2] and constitute also valuable intermediates for the synthesis of enantiopure γ-amino acids related to inhibitory neurotransmitter GABA as biologically active compounds in the CNS system of mammals.[3]

Various synthetic approaches to γ-lactam skeletons have been reported and the most frequently employed include (i) the cyclization of nitrogen radicals onto unsaturated systems from *N*-haloamides **2**,[4] (ii) the cycloaddition reaction between imines **3** and cyclic anhydrides **4**,[5] (iii) the thermal reactions of π-allyltricarbonyliron lactam complexes **5** obtained from oxazines and diiron nonacarbonyl,[6] (iv) the transition metal (Rh, Ru)-catalyzed intramolecular carbenoid C−H insertion by decomposition of α-diazocarbonyl compounds (**6**, X = N_2)[7] or Au(I)-catalyzed intramolecular addition of β-ketoamides to unactivated alkenes (**6**, X = H_2 and C=R_4 linkage as a double bond),[8] (v) the ring expansion through N_1−C_4 cleavage of 4-substituted β-lactams of type **7**[9] and the [3 + 2] annulation reactions of allylic silanes with chlorosulfonyl isocyanate or α-sulfonylacetamides with substituted (*Z*)-2-bromo-2-propenoates.[10] A plethora of other specific enantioselective and racemic methods, not presented in Scheme 1, has been outlined recently by Wang et al.[11]

To address substrate limitations of existing methods for the preparation of *N*-heterocyclic compounds, we have explored the synthetic potential of α-bromoacetamides of type **9**. We have previously demonstrated their engagement with dimethyl malonate to provide efficaciously in very good yields symmetrical and unsymmetrical spiro-bis-imides and corresponding 3-methoxycarbonyl succinimides in a one-pot procedure or two-step sequence, respectively.[12] In this paper, we explore the scope and limitations of a new and rapid tandem sequence aza-

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(1) For recent representative examples, see: (a) Roberson, C. W.; Woerpel, K. A. *J. Org. Chem.* **1999**, *64*, 1434–1435. (b) Gandon, V.; Bertus, P.; Szymoniak, J. *Synthesis* **2002**, 1115–1120. (c) Tye, H.; Whittaker, M. *Org. Biomol. Chem.* **2004**, *2*, 813–815. (d) Freifeld, I.; Armbrust, H.; Langer, P. *Synthesis* **2006**, 1807–1808. (e) Candeias, N. R.; Gois, P. M. P.; Afonso, C. A. M. *J. Org. Chem.* **2006**, *71*, 5489–5497. (f) Rhee, J. U.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 10674–10675.

(2) Ordóñez, M.; Cativiela, C. *Tetrahedron: Asymmetry* **2007**, *18*, 3–99.

(3) (a) Coppola, G. M.; Schuster, H. F. In *Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids*; John Wiley: New York, 1987. (b) Nájera, C.; Yus, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2245–2303.

(4) For free radical cyclizations involving nitrogen, see: (a) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543–17594.

(5) (a) Ng, P. Y.; Masse, C. E.; Shaw, J. T. *Org. Lett.* **2006**, *8*, 3999–4002. For a recent one-pot, four-component synthesis of γ-lactams, see: (b) Wei, J.; Shaw, J. T. *Org. Lett.* **2007**, *9*, 4077–4080. (c) Masse, C. E.; Ng, P. Y.; Fukase, Y.; Sanchez-Rosello, M.; Shaw, J. T. *J. Comb. Chem.* **2006**, *8*, 293–296. (d) Piwowarczyk, K.; Zawadzka, A.; Roszkowski, P.; Szawkało, J.; Leniewski, A.; Maurin, J. K.; Kranza, D.; Czarnockia, Z. *Tetrahedron: Asymmetry* **2008**, *19*, 309–317.

(6) For uses of π-allyltricarbonyliron lactam complexes in organic synthesis, see: (a) Ley, S. V.; Cox, L. R.; Meek, G. *Chem. Rev.* **1996**, *96*, 423–442.

(7) For recent examples, see: (a) Choi, M. K.-W.; Yu, W.-Y.; Che, C.-M. *Org. Lett.* **2005**, *7*, 1081–1084. (b) Wee, A. G. H.; Duncan, S. C.; Fan, G.-J. *Tetrahedron: Asymmetry* **2006**, *17*, 297–307.

(8) Zhou, C.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2007**, *129*, 5828–5829.

(9) (a) Van Brabandt, W.; De Kimpe, N. *J. Org. Chem.* **2005**, *70*, 3369–3374. (b) Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *Org. Lett.* **2005**, *7*, 3981–3984. (c) Park, J.-H.; Ha, J.-R.; Oh, S.-J.; Kim, J.-A.; Shin, D.-S.; Won, T.-J.; Lam, Y.-F.; Ahn, C. *Tetrahedron Lett.* **2005**, *46*, 1755–1757.

(10) For examples of [3 + 2] annulations, see: (a) Roberson, C. W.; Woerpel, K. A. *J. Org. Chem.* **1999**, *64*, 1434–1435. (b) Romero, A.; Woerpel, K. A. *Org. Lett.* **2006**, *8*, 2127–2130. (c) Sun, P.-P.; Chang, M.-Y.; Chiang, M. Y.; Chang, N.-C. *Org. Lett.* **2003**, *5*, 1761–1763.

(11) Dong, C.; Mo, F.; Wang, J. *J. Org. Chem.* **2008**, *73*, 1971–1974, references therein.

(12) Allous, A.; Comesse, S.; Daïch, A. *Lett. Org. Chem.* **2008**, *5*, 73–78.

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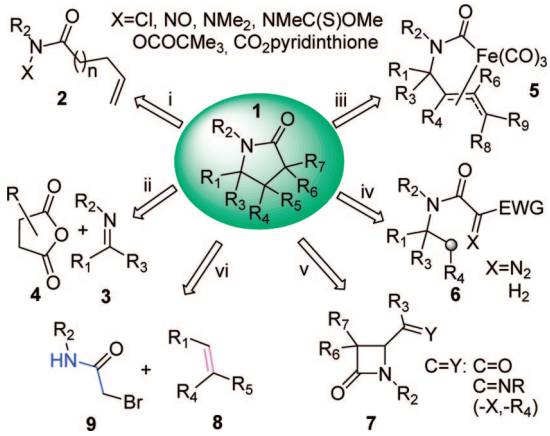
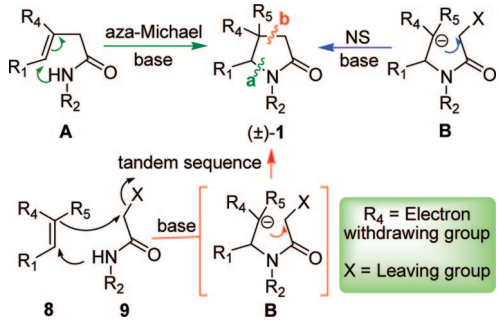
SCHEME 1. Representative Strategies Used for the Synthesis of γ-Lactam Skeletons



SCHEME 2. Mechanistic Aspect of the Tandem Sequence

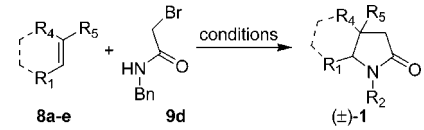


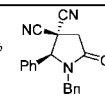
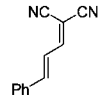
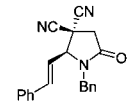
Michael/intramolecular nucleophilic substitution between *N*-substituted α-bromoacetamides **9** and various Michael acceptors. We also demonstrate its synthetic utility with the tricyclic core **13** of both (±)-martinelline and (±)-martinellic acid alkaloids.

As highlighted in Scheme 2, two possible disconnections **a/b** could be considered to reach these architectures. Either by an intramolecular 1,4-addition of an amide in basic medium to an α,β-unsaturated system via **A**[13] or by an intramolecular nucleophilic substitution of the stabilized anion onto the acetamide carbon bearing a good leaving group via **B**.[14] We anticipated that it would be possible to perform this sequence in a one-step fashion using a new tandem reaction from Michael acceptor **8** and *N*-substituted α-bromoacetamide **9**. The amidate anion derived from **9** in basic medium would lead to concomitant aza-Michael addition into species **B** and its spontaneous intramolecular nucleophilic substitution by displacement of the leaving group X, providing directly compound **1** in a single synthetic operation. While a recent study by Tu and co-workers[15] for the syntheses of (±)-3-demethoxyerythratidinone and (±)-erysotramidine has highlighted the use of *N*-alkyl-α-halogenoacetamides for the formation of numerous γ-lactams, no examples of this tandem reaction have been described.

In the outset, the reaction we investigated as the first step of our strategy uses *N*-benzyl-α-bromoacetamide (**9d**, R_2 = Bn and X = Br) as a model amide and different activated Michael acceptors **8a−e** in the presence of different base, and the results are shown in Table 1.[16]

TABLE 1. Reaction of *N*-Benzyl-α-bromoacetamide (9d) with Michael Acceptors 8a−e in the Presence of Base[a]



Entry	Substrate 8	Conditions	Product 1	Yield[a]
1	 **8a**	K_2CO_3, CH_3CN[b]	 **1d**	nr[d]
2	"	*t*-BuOK, THF[c]	"	23%
3	"	NaH, THF[c]	"	63%
4	"	KHMDS, THF[c]	"	24%
5	 **8b**	NaH, THF[c]	no product	-
6	 **8c**	NaH, THF[c]	no product	-
7	 **8d**	NaH, THF[c]	no product	-
8	 **8e**	NaH, THF[c]	 **1l**	35%

[a] Isolated yield. [b] 2.5 equiv of K_2CO_3 was used in refluxing CH_3CN. [c] 1.5 equiv of base was used in THF at rt. [d] No reaction.

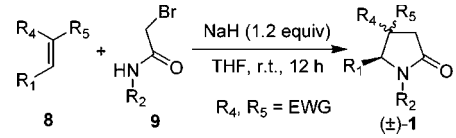
To our surprise, however, reaction of *N*-benzyl-α-bromoacetamide (**9d**) with the Knoevenagel substrate **8a** in dry acetonitrile in the presence of K_2CO_3 produced none of the desired γ-lactam **1d** (entry 1). The starting materials were recovered in all cases regardless of changes in the reaction temperature and time. Numerous other bases (entries 2−4), which have wide usages, were investigated. Most gratifyingly, good yields (63%) were obtained when the reaction was carried out with 1.5 equiv of NaH in THF at room temperature for 12 h (entry 3). Replacement of NaH with *t*-BuOK or KHMDS was also successful, albeit in low yield (23% (entry 2) or 24% (entry 4)). We hypothesized that, due to the low nucleophilicity of amides, with the optimized conditions found above no reaction would occur with α,β-unsaturated systems bearing only one electron-withdrawing group. This was tested by using different Michael acceptors, and indeed we never observed the expected product **1** (entries 5−7). When diene **8e** was used under the same conditions, the expected γ-lactam product **1l** was obtained in only 35% yield. The remaining alkene introduces also another point of the molecular diversity.

Encouraged by the feasibility of this tandem sequence, we next examined its utility to synthesize a range of γ-lactams. In this sense, a series of *N*-substituted α-bromoacetamides was allowed to react with several Knoevenagel substrates using optimized conditions (Table 1). The results from these screen-

(13) Wakabayashi, T.; Saito, M. *Tetrahedron Lett.* **1977**, *18*, 93–97.
(14) Tarnchompoo, B.; Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron Lett.* **1987**, *28*, 6675–6678.
(15) Gao, S.; Tu, Y. Q.; Hu, X.; Wang, S.; Hua, R.; Jiang, Y.; Zhao, Y.; Fan, X.; Zhang, S. *Org. Lett.* **2006**, *8*, 2373–2376.

(16) Synthesis of all starting materials. (a) For α-bromoacetamides **9**, see: Nilsson, B. L.; Kiessling, L. L.; Raines, R. T. *Org. Lett.* **2000**, *2*, 1939–1942. (b) For Michael acceptors **8**, see: May, B. C. H.; Zorn, J. A.; Witkop, J.; Sherrill, J.; Wallace, A. C.; Legname, G.; Prusiner, S. B.; Cohen, F. E. *J. Med. Chem.* **2007**, *50*, 65–73. (c) For reagent **8k**, see ref 13.

TABLE 2. Extension of the Tandem Reaction Aza-Michael Addition/Intramolecular Nucleophilic Substitution[a]



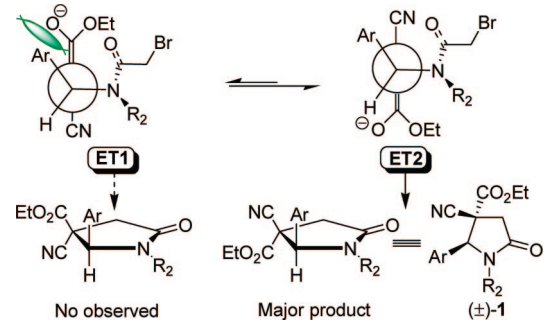
8 9 (±)-**1**

Entry	Substrate **8**	Amide R_2	Product **1a-k**	Yield(%)[a]	dr(%)[b]
1	**8a**	Bu **9a**	**1a**	54	-
2	**8a**	*i*-Pr **9b**	**1b**	50	-
3	**8a**	*t*-Bu **9c**	**1c**	nr[c]	-
4	**8a**	Bn **9d**	**1d**	63	-
5	**8a**	Ph **9e**	**1e**	49	-
6	**8f**	Bu **9a**	**1f**	53	-
7	**8g**	Bn **9d**	**1g**	52	-
8	**8h**	Bn **9d**	**1h**	60	>90
9	**8i**	Bu **9a**	**1i**	61	>90
10	**8i**	Bn **9d**	**1j**	69	>90
11	**8k**	Bn **9d**	**1k**	53[d]	-

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis. [c] No reaction occurred. [d] Harsher reaction conditions were used herein; Knoevenagel substrate **8k** (1 equiv) and α-bromoacetamide (**9d**, 2.2 equiv) were reacted with 2.4 equiv of NaH in THF for 24 h.

ings[17] are summarized in Table 2. We have shown that, as expected, the steric hindrance of the amide, which decrease the nitrogen atom nucleophilicity, plays a crucial role in the reaction. Indeed, the yields dramatically dropped from 63% when R_2 = Bn (entry 5) to 0% in the case of R_2 = *t*-Bu (entry 3). However, as may be seen in entries 6 and 7, the tandem reaction readily tolerates both the nitro substituent and the presence of a heteroaromatic ring such as a furan. Likewise, varying one electron-withdrawing substituent of the activated olefin component **8**, i.e., ester versus nitrile, seems to have no influence on the reaction profile (compare entries 4 vs 8 and 7 vs 10 vs 11). The use of harsher conditions for the less reactive olefin **8k** (compare entries 7 and 11) also has no influence on the reaction yields. Moreover the use of unsymmetrical olefins led, in all cases, to the formation of γ-lactams in good yields and excellent diastereoselectivity (95:5) determined by ^{1}H NMR spectra of the crude mixture (entries 8−10). In the latter, a *syn* relationship between the nitrile group and the aromatic ring has been established.

SCHEME 3. Diastereoselectivity Outcome during the Process



The high degree of diastereoselectivity observed during the process could be explained by the plausible transition states presented in Scheme 3. In fact, the more stable carbanion, produced after 1,4-addition onto **8h,i** of the amides **9a,d**, is the one in which the aromatic ring and the nitrile function are adjacent leading to the major *syn* products **1h−j**. The different conformation (**ET1** and **ET2**) of the same intermediate (**ET**) displays a higher steric hindrance between the ester function or its enolate form and the aromatic system.

Having developed successfully this tandem reaction aza-Michael/intramolecular nucleophilic substitution for the generation of γ-lactam scaffolds, we sought to demonstrate its utility in a rapid and concise synthesis of the tricyclic core of (±)-martinelline alkaloids. The latter, isolated from the root bark of the tropical plant *Martinella iquitosensis* by Witherup et al.[18] at Merck, possess antibacterial activity and constitute also the first potent, naturally occurring nonpeptide bradykinin (BK) receptor antagonists to be reported.[19]

The scarcity of a partially reduced pyrrolo[3,2-*c*]quinoline skeleton as the unique structure present in these alkaloids, combined with their interesting biological profiles, has led to continued interest in total synthesis of these structures and explorations of their derivatives.[20,21] Significantly, while the importance of the impressive advances published in this area is well established, the latter strategies required in all cases many

(17) See Experimental Section for the general procedure for the preparation of γ-lactams **1**.

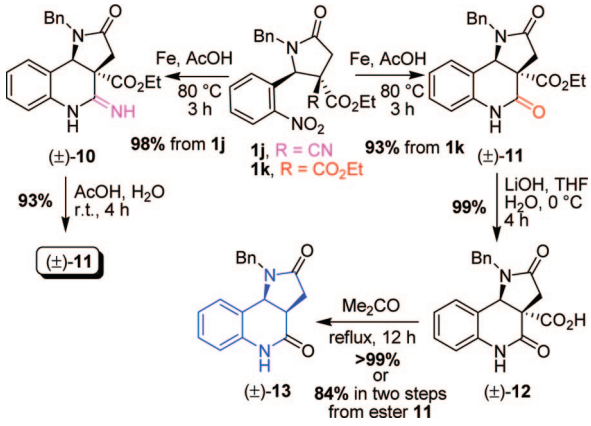
(18) Witherup, K. M.; Ransom, R. W.; Graham, A. C.; Bernard, A. M.; Salvatore, M. J.; Lumma, W. C.; Anderson, P. S.; Pitzenberger, S. M.; Varga, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6682–6685.

(19) Bock, M. G.; Longmore, J. *Curr. Opin. Chem. Biol.* **2000**, *4*, 401–406.

(20) For a recent review, see: (a) Nyerges, M. *Heterocycles* **2004**, *63*, 1685–1712.

(21) (a) For representative existing methods, see ref 5a. (b) Nieman, J. A.; Ennis, M. D. *Org. Lett.* **2000**, 2, 1395–1397. (c) He, Y.; Mahmud, H.; Moningka, R.; Lovely, C. J.; Dias, H. V. R. *Tetrahedron* **2006**, *62*, 8755–8769. (d) Miyata, O.; Shirai, A.; Yoshino, S.; Nakabayashi, T.; Takeda, Y. *Tetrahedron* **2007**, *63*, 10092–10117. For the first asymmetric total synthesis of (−)-martinelline and the second total synthesis of (−)-martinellic acid, see: (e) Ikeda, S.; Shibuya, M.; Iwabuchi, Y. *Chem. Commun.* **2007**, 504–507. (f) Badarinarayana, V.; Lovely, C. J. *Tetrahedron Lett.* **2007**, *48*, 2607–2610.

SCHEME 4. Scheme Leading to Pyrroloquinoline Core 13



steps and consequently there is a need for the development of flexible strategies that will accommodate a range of structure types.[22]

In this sense, with both nitrile-ester lactam **1j** and diester lactam **1k** in hand, two different objectives were pursued: the chemical confirmation of the reaction diastereoselection observed and the synthesis of substituted pyrrolo[3,2-*c*]-quinoline **13** as the key for (±)-martinelline alkaloids (Scheme 4). So, when compound **1j** was treated with iron in glacial acetic acid at 80 °C for 3 h, only the iminoamine product **10** was isolated in nearly quantitative yield.[23] This result demonstrated the diastereoselective outcome during the tandem process, i.e., the *syn* relationship between the aromatic system and the nitrile function to the detriment of the ester group. Following the same protocol, γ-lactam **1k** provided the tricyclic lactam **11** in yield of 93%, and its structure was secured by a single X-ray analysis (see Supporting Information for CIF file and ORTEP drawing of product **11**). This product was also obtained in 93% yield from iminoamine **10** by hydrolysis in a mixture of water/acetic acid. Finally, the ester function of **11** was been removed in a two-step sequence, by classical saponification (**11** → **12**) followed by decarboxylation, providing the tricyclic system **13** already described by Shaw et al.[5a] Importantly, the same authors have converted an ester analogous of this system **13** to the complete carbon framework of martinelline alkaloids in three steps.

(22) During the preparation of this paper, an interesting strategy based on a $SnCl_4$-mediated domino reaction of 2-(cyanomethyl)-3-oxo-*N*-arylbutanamides was published. See: (a) Zhang, Z.; Zhang, Q.; Yan, Z.; Liu, Q. *J. Org. Chem.* **2007**, *72*, 9808–9810.

(23) Suzuki, M.; Kaneko, T.; Kamiyama, H.; Ohuchi, Y.; Yokomori, S. *Heterocycles* **2000**, *53*, 2471–2485.

In summary, we have developed an unprecedented and expedient synthesis of original γ-lactams via a new tandem reaction aza-Michael/intramolecular nucleophilic substitution from readily available and inexpensive reagents. Although the process has not yet been generalized to all categories of olefins (today, three levels to ensure the molecular diversity are possible), it has enabled us to synthesize successfully the tricyclic core of martinelline alkaloids with correct relative stereochemistry. Ultimately, the investigation of the applicability of this tandem reaction to synthesis of other heterocyclic compounds with promising biological profiles and its generalization to other alkenes will be the focus of future work.

Experimental Section

Typical Procedure for the Preparation of γ-Lactams 1 (Nitro-diester-γ-lactam 1k as Example). The required Knoevenagel substrate **8** (1.0 mmol) and *N*-alkyl bromo-acetamide **9** (1.1 mmol) were dissolved in freshly distilled THF (10 mL) at 0 °C. Sodium hydride (48 mg, 60% suspension in mineral oil, 1.2 mmol) was then added in one portion, and the mixture was stirred at room temperature for 12 h. The solution was cooled to 0 °C, and the reaction was quenched by careful addition of an aqueous saturated solution of NH_4Cl (10 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the organic layers were combined, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography on silica gel column to provide the desired γ-lactam **1**. (±)-Diethyl 1-benzyl-2-(2-nitrophenyl)-5-oxo-pyrrolidine-3,3-dicarboxylate (**1k**) was isolated as a white solid that melted at 101−103 °C (recrystallized from EtOAc) in 53% yield (AcOEt/cyclohexane, 30:70). IR (KBr): 2985, 1737, 1691, 1534, 1447, 1424 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, J = 7.2 Hz, 1H), 7.57 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 7.2 Hz, 1H), 7.29−7.22 (m, 4H), 7.17−7.14 (m, 2H), 6.29 (s, 1H), 4.97 (d, J = 14.6 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.85 (dq, J = 10.7 and 7.1 Hz, 1H), 3.75 (d, J = 18.0 Hz, 1H), 3.58 (dq, J = 10.7 and 7.1 Hz, 1H), 2.96 (d, J = 18.0 Hz, 1H), 1.20 (t, J = 7.0 Hz, 3H), 0.92 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 169.0, 167.0, 150.1, 135.0, 133.2, 130.7, 129.7, 128.8, 128.7, 128.6, 128.0, 125.1, 62.8, 62.5, 59.2, 59.1, 45.8, 37.6, 13.9, 13.4. Anal. Calcd for $C_{23}H_{24}N_2O_7$: C, 62.72; H, 5.49; N, 6.36. Found: C, 62.51; H, 5.86; N, 6.39.

Acknowledgment. The authors would like to thank Miss Charlotte Mazot for the preparation of starting material.

Supporting Information Available: Experimental procedures, product characterization for all new compounds synthesized and the ORTEP plot of compound **11**, as well as its CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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