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Articles

Metallic Salt Promoted Radical Cyclization of β-Keto Carboxamides and Their Corresponding β-Enamino Carboxamides

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Substituted lactams and spirolactams were obtained by Mn(III)-induced radical cyclization of unsaturated β-keto carboxamides. Treatment of the corresponding tertiary enamines under similar reaction conditions and in the presence of K_2CO_3 afforded the same cyclized products but with inversion of diastereoselectivity. The oxidation of optically pure secondary enamines leads to diastereomeric spirolactams in an approximately 3:1 ratio.

Free radical cyclizations of alkenes constitute a valuable method for the synthesis of cyclic compounds.[1] The precursors for such cyclizations can vary according to the method used to generate the radical. Radical generation can be effected by reduction, isomerization, or oxidation. Oxidative methods have considerable synthetic potential, as highly functionalized products can be obtained. Among the various oxidative processes available, reactions of enolizable dicarbonyl compounds with metal salts can lead to products with high regio- and stereoselectivity.[3] Some years ago, we examined the Mn(III)-based radical cyclization of unsaturated β-keto carboxamides[4] (Scheme 1, eq 1), which affords substituted lactams and spirolactams.[5,6] In this paper, we would like to report our findings on the transformation of β-keto carboxamides and their related tertiary as well as secondary enamines into lactams and spirolactams by metallic salts (Scheme 1, eq 2).

Oxidative Radical Cyclization of β-Keto Carboxamides. β-Keto carboxamides were readily prepared by aminolysis of β-keto esters[7] or by photolysis of diazodiketones[8] in the presence of various commercially avail-

† Current adress: Pharmacor Inc. 535, bld. Cartier Ouest, Laval QC, Canada H7N 4Z9.

(1) For selected general reviews and books see: (a) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: London, 1991; Vol. 4, p 779. (b) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. (c) Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1995.

(2) For reviews see: (a) de Klein, W. J. In *Organic Synthesis by Oxidation with Metal Compounds*; Mijs, W. J., de Jonge, C. R. H., Eds.; Plenum Press: New York, 1986; p 216. (b) Melikyan, G. G. *Synthesis* **1993**, 833. (c) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519. (d) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (e) Melikyan, G. G. *Org. React.* **1997**, *49*, 427. (f) Melikyan, G. G. *Aldrichimica Acta* **1998**, *31*, 1998.

(3) (a) Curran, D. P.; Morgan, T. M.; Schwartz, C. E.; Snider, B. B.; Dombrosky, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 6607. (b) Kates, S. A.; Dombrosky, M. A.; Snider, B. B. *J. Org. Chem.* **1990**, *55*, 2427.

(4) Cossy, J.; Leblanc, C. *Tetrahedron Lett.* **1989**, *30*, 4531,

(5) (a) D'Annibale, A.; Resta, S.; Trogolo, C. *Tetrahedron Lett.* **1995**, *36*, 9039. (b) Bosman, C.; D'Annibale, A.; Resta, S.; Trogolo, C. *Tetrahedron* **1994**, *50*, 13847.

(6) (a) Snider, B. B.; Yu-Fong Wan, B.; Buckman, B. O.; Foxman, B. M. *J. Org. Chem.* **1991**, *56*, 328. (b) Zoretic, P. A.; Weng, X.; Biggers, C. K.; Biggers, M. S.; Caspar, M. L.; Davis, D. G. *Tetrahedron Lett.* **1992**, *33*, 2637. (c) Snider, B. B.; Zhang, Q. *Tetrahedron Lett.* **1992**, *33*, 5921. (d) Zhang, Q.; Mohan, R. M.; Cook, L.; Kazanis, S.; Peisach, D.; Foxman, B. M.; Snider, B. B. *J. Org. Chem.* **1993**, *58*, 7640.

(7) Cossy, J.; Belotti, D.; Bouzide, A.; Thellend, A. *Bull. Soc. Chim. Fr.* **1994**, *131*, 723.

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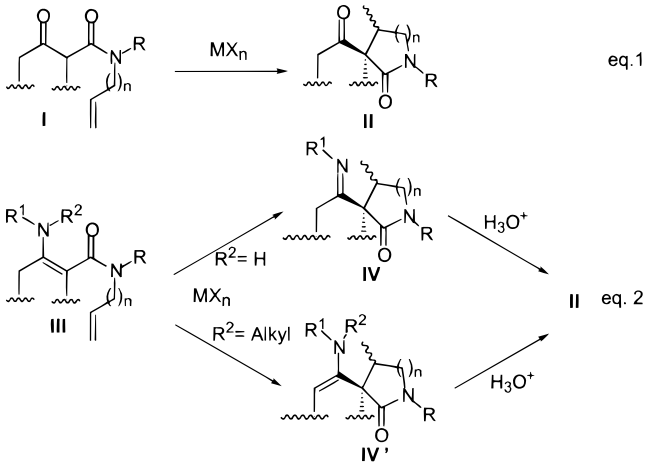
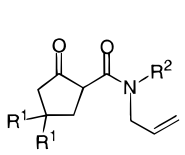
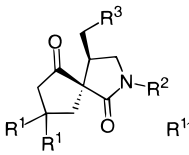
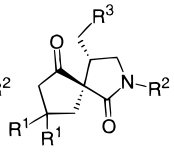
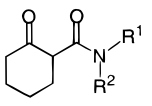
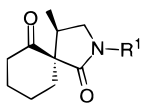
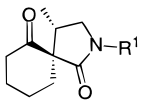
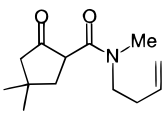
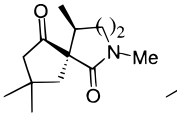
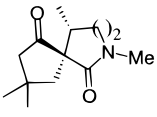
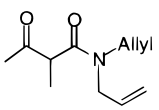
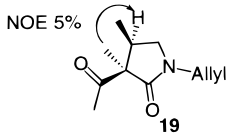
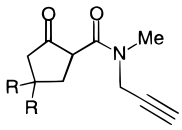
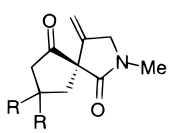
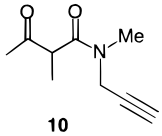
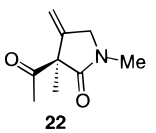
Scheme 1. Formation of Spirolactams



able amines.[9] Preliminary attempts to cyclize unsaturated β-keto carboxamides were carried out on *N*,*N*-diallyl-8,8-dimethyl-2-oxocyclopentanecarboxamide **1** (Table 1). Treatment with manganese triacetate dihydrate [Mn(OAc)$_3$·2H$_2$O] in AcOH,[10,11] afforded azaspiro[4.4]nonanes **12a/12b** as an 8:1 mixture in only 12% yield. The low yield is probably due to competitive oxidation of AcOH, which interferes with the oxidation of the β-keto carboxamides as these compounds presumably oxidize more slowly than β-keto esters.[12] When the reaction was conducted with anhydrous manganese triacetate [Mn(OAc)$_3$][13,14] in ethanol, the cyclized products **12a/12b** were obtained in 28% yield, accompanied by hydroperoxides **13a/13b**, which were isolated in 16% yield as an 8:1 mixture. When the ethanol solvent was flushed with argon for 20 min prior to use, the yield of **12a/12b** increased to 56% without affecting the reaction diastereoselectivity and no hydroperoxides were detected. The relative stereochemistry of lactams **12a** and **12b** were unambiguously established by comparison of their spectroscopic data with authentic samples previously prepared through ene reactions of enamines derived from β-keto amides.[15] The Mn(III)-based radical cyclization of

Table 1. Radical Cyclization of β-Keto Carboxamides Mediated by Mn(OAc)$_3$

Starting Material	Products		Yield % (**a**/**b**)
			
1 R^1 = Me, R^2 = Allyl	**12a** R^3 = H	**12b** R^3 = H	56 (8/1)
1 R^1 = Me, R^2 = Allyl	**13a** R^3 = OOH	**13b** R^3 = OOH	16 (8/1)
2 R^1 = H, R^2 = Allyl	**14a** R^3 = H	**14b** R^3 = H	50 (8/1)
3 R^1 = H, R^2 = Me	**15a** R^3 = H	**15b** R^3 = H	56 (7/1)
			
4 R^1 = R^2 = Allyl	**16a** R^1 = Allyl	**16b** R^1 = Allyl	42 (6/1)
5 R^1 = Me, R^2 = Allyl	**17a** R^1 = Me	**17b** R^1 = Me	45 (6/1)
			52 (5/1)
6	**18a**	**18b**	
			40
7	**19**		
			
8 R = H	**20** R = H		60
9 R = Me	**21** R = Me		55
			40
10	**22**		

unsaturated β-keto carboxamides is general as the analogues **2** and **3** afforded, respectively, **14a/14b** (50% yield, 8/1 ratio) and **15a/15b** (56% yield, 7/1 ratio). Treatment of β-keto carboxamides **4** and **5** under the same conditions provided azapiro[4.5]decanes **16a/16b** (42% yield, 6/1 ratio) and **17a/17b** (45% yield, 6/1 ratio). Azaspiro[4.5]-decanes **18a/18b** were obtained in 52% yield as a 5/1 mixture from homoallylic keto amide **6**. Interestingly, oxidation of β-keto carboxamide **7** under similar conditions afforded γ-lactam **19** (40% yield) as a single isomer. The relative stereochemistry of **19** was established by NOE experiments. Treatment of propargylic β-keto carboxamides **8**, **9**, and **10** under similar conditions provided, respectively, spirolactams **20** (60%), **21** (55%), and γ-lactam **22** (40%). The results are summarized in Table 1.

We note that lactam **20** can also be obtained from the allylic β-keto carboxamide **3** by treatment with 2 equiv of Mn(OAc)$_3$ and 1 equiv of Cu(OAc)$_2$, which is known to be an efficient radical oxidizing agent,[16,17] in degassed ethanol (Table 2). Other spirolactams substituted by an

(8) Cossy, J.; Belotti, D.; Thellend, A.; Pete, J. P. *Synthesis* **1988**, 720.

(9) *N*-Methyl butylamine was prepared in four steps from *N*-methylformamide.

(10) (a) Heiba, E. I.; Dessau, E. M. *J. Org. Chem.* **1974**, *39*, 3456. (b) Heiba, E. I.; Dessau, E. M.; Koehl, W. J., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 2706. (c) Heiba, E. I.; Dessau, E. M.; Koehl, W. J., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 2706.

(11) (a) Ernst, A. B.; Fristad, W.; *Tetrahedron, Lett.* **1985**, *26*, 3761. (b) Fristad, W.; Peterson, R. J. *J. Org. Chem.* **1985**, *50*, 10. (c) Fristad, W.; Peterson, R. J.; Ernst, A. B.; Urbi, R. G. *Tetrahedron* **1986**, *42*, 3429.

(12) For the radical cyclization of β-keto esters see: (a) Snider, B. B.; Mohan, R. M.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659. (b) Snider, B. B.; Dombroski, M. A. *J. Org. Chem.* **1987**, *52*, 5487. (c) Snider, B. B.; Patricia, J. J.; Kates, S. A. *J. Org. Chem.* **1988**, *53*, 2137. (d) Snider, B. B.; Patricia, J. J. *J. Org. Chem.* **1989**, *54*, 38. (e) Snider, B. B.; Buckman, B. *J. Org. Chem.* **1992**, *57*, 322. (f) Snider, B. B.; McCarthy, B. A. *J. Org. Chem.* **1993**, *58*, 6217 and other references therein.

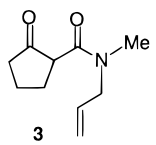
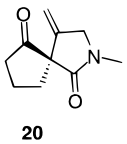
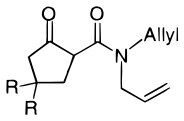
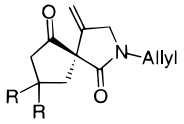
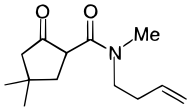
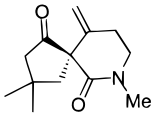
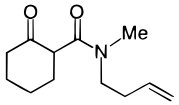
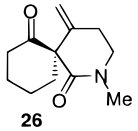
(13) (a) Chrétien, A.; Varga, G. *Bull. Soc. Chim. Fr.* **1936**, *3*, 2385. (b) Corey, E. J.; Ghoch, A. K. *Chem. Lett.* **1987**, 225.

(14) For a modified method for the preparation of anhydrous Mn(OAc)$_3$, see the Experimental Section.

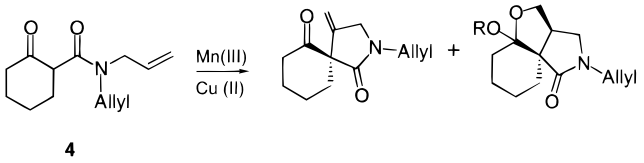
(15) Cossy, J.; Bouzide, A.; Pfau, M. *J. Org. Chem.* **1997**, *62*, 7106.

(16) For review on Cu(II) oxidation of radicals see: (a) Kochi, J. K. *Science* **1967**, *155*, 415. (b) Kochi, J. K. In *Free Radicals;* Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 1, Chapter 11. (c) Nonhebel, D. C. In *Essays on Free-Radical Chemistry*; Norman, R. O. C., Ed.; Special Publication 24; The Chemical Society: London, 1970; p 409. (d) Nigh, W. G. In *Oxidation in Organic Chemistry,* Part B; Trahanovsky, W. S., Ed.; Academic Press: New York, 1973; p 1.

Table 2. Radical Cyclization of β-Keto Carboxamides Mediated by $Mn(OAc)_3/Cu(OAc)_2$

Starting Material	Products	Yield %
 **3**	 **20**	58
 **1** R = Me **2** R = H	 **23** R = Me **24** R = H	52 65
 **6**	 **25**	55
 **11**	 **26**	40

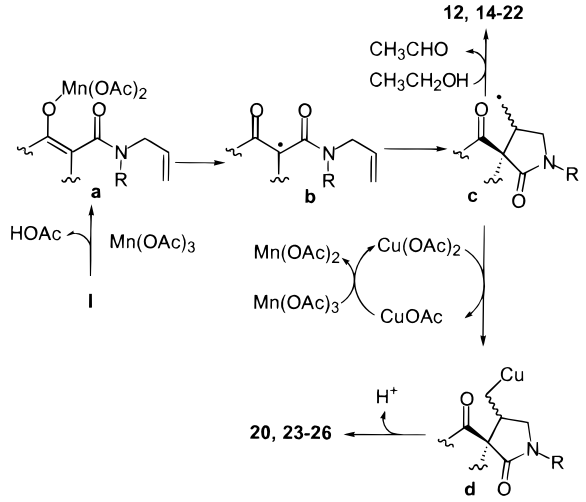
Scheme 2. Radical Cyclization of β-Keto Carboxamide 4



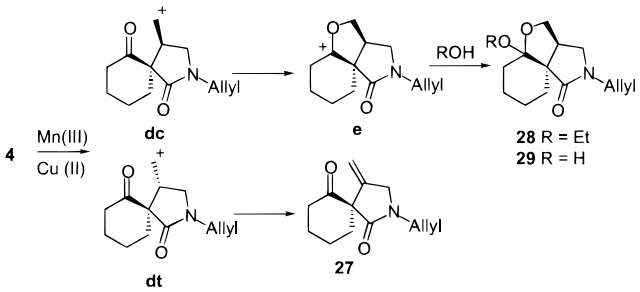
exo methylenic group such as **23**−**26** were obtained in moderate to good yields from the corresponding β-keto carboxamides **1**, **2**, **6**, and **11**.

On the other hand, treatment of β-keto carboxamides **4** under these conditions, [$(Mn(OAc)_3/Cu(OAc)_2$, 2 equiv/1 equiv)] led to a mixture of the expected product **27** (25%) along with the tricyclic acetal **28** (65%) (Scheme 2). The replacement of ethanol by wet acetonitrile furnished **27** (26%) accompanied by the hemiacetal **29** (67%).The mechanism of Mn(III)-initiated free-radical cylization of β-keto amides of type **I** starts by the loss of acetic acid to give Mn(III) enolate **a** (Scheme 3). By analogy with the metal oxidation of acetic acid[11] or β-keto esters,[12] formation of the Mn(III)-enolate is probably the rate-determining step. The next step is Mn−O bond homolysis, which results in the formation of β-keto amide radical **b**. This radical can undergo regioselective cyclization by a 5- or 6-*exo* trig process to give the cyclized radical **c**. In the presence of EtOH, which is known to be an excellent hydrogen donor, this primary radical is reduced to give the final products **12** and **14**−**22**. The hydroxyethyl radical can undergo a second oxidation by $Mn(OAc)_3$ to

Scheme 3. Mechanism for the Oxidation of β-Keto Carboxamides of Type I



Scheme 4. Formation of the Tricyclic Compounds 28 and 29



give acetaldehyde. Thus, the use of 2 equiv of $Mn(OAc)_3$ or more are essential for complete reaction. If the ethanol solution is not sufficiently degassed, radical **c** is trapped by molecular oxygen to afford the hydroperoxides **13**. On the other hand, in the presence of $Cu(OAc)_2$, primary radicals are oxidized to carbocations,[16,17] which afford, after elimination, the unsaturated cyclized products **20** and **23**−**26**.[16] The unstable monovalent species CuOAc will react with $Mn(OAc)_3$ to regenerate $Cu(OAc)_2$. Again, 2 equiv of $Mn(OAc)_3$ are necessary.

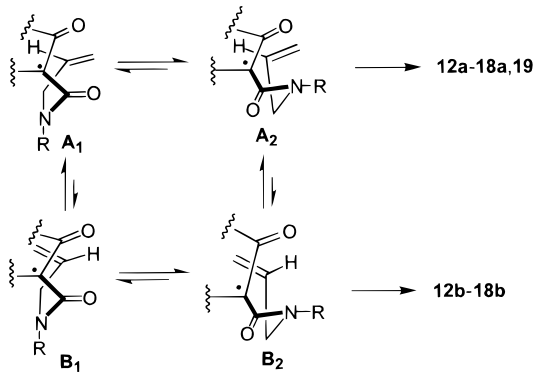
The formation of tricyclic ketal **28** or hemiacetal **29** is due to the nucleophilic attack by oxygen on the carbocation of the ketone. Inspection of molecular models shows that, in intermediate **dc**, the ketone group is close to the carbocation and a nucleophilic attack by the oxygen of the carbonyl can take place to afford the tricylic carbocation **e** (Scheme 4). This carbocation is then quenched with EtOH to give ketal **28** or with H_2O to afford the hemiacetal **29**. In intermediate **dt**, the distance between the carbocation and the ketone group does not permit bonding. The carbocation intermediate **dt** thus undergoes deprotonation to produce **27**.

To understand the diastereoselectivity of the reaction, four transition states $\mathbf{A_1}$, $\mathbf{A_2}$, $\mathbf{B_1}$, and $\mathbf{B_2}$ were taken into consideration (Scheme 5). Transition states $\mathbf{B_1}$ and $\mathbf{B_2}$ are disfavored because of the presence of an interaction between the double bond and the carbocyclic framework. Transition state $\mathbf{A_2}$ may be favored over $\mathbf{A_1}$ as, in this latter transition state, electronic repulsions between the two carbonyl groups can take place.

Oxidative Radical Cyclization of Tertiary and Secondary β-Carboxamido Enamines. We were un-

(17) (a) Kochi, J. K.; Bacha, J. D. *J. Org. Chem.* **1975**, *33*, 2746. (b) Bacha, J. D.; Kochi, J. K. *Tetrahedron* **1968**, *24*, 2215. (c) Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 843.

Scheme 5. Diastereoselectivity and Transition States for the Radical Cyclization of β-Keto Carboxamides



able to prepare enantioenriched spirolactams from β-keto carboxamides bearing a chiral auxiliary on the amide function.[18] We therefore turned our attention to the oxidation of β-carboxamido enamines containing a chiral auxiliary in the enamine function. We anticipated that the replacement of an enol double bond by an enamine double bond[19] would afford the imine or iminium cyclized product, which after hydrolysis would led to chiral spirolactams. While the addition of carbon radicals to enamines have been widely used in the past few years to generate 1-amino radicals,[20,21] the generation of radicals from enamines has received little attention.[22]

Enamines **30**−**34** were prepared according to the conventional procedure by condensing β-keto amides **2**−**5** and **9** with pyrrolidine in toluene with azeotropic removal of water (Scheme 6).[23] Initial attempts at free radical cyclization of enamine **30** under the conditions described for β-keto carboxamides were discouraging as substantial polymerization was observed and the cyclized products **14a/14b** were isolated in only 12% yield after flash chromatography on silica gel. Interestingly, the ratio of **14a/14b**, obtained from the oxidation of enamine **30** was 1:19 as opposed to 8:1 obtained in the oxidation of the corresponding β-keto carboxamide **2**. The yield of **14a/14b** was increased to 42% when 3 equiv of $Mn(OAc)_3$ were used in the presence of a base such as K_2CO_3. The reaction was very fast as the starting enamine was entirely transformed within 5 min. The NMR spectrum of the crude reaction mixture indicated the presence of the enamine intermediate **35**.[15] Several attempts at isolating **35** by chromatography on alumina were unsuccessful, and only spirolactams **14a/14b** were obtained. The reaction was generalized to other tertiary enamines such as **31**−**34**.

As a result of the high control of stereoselectivity observed in these radical cyclizations, the synthesis of enantioenriched spirolactams was envisaged from the optically active enamines. Unfortunately, the preparation of enantiomerically pure enamines by condensing β-keto carboxamide **2** with (2*R*,5*R*)-dimethylpyrrolidine,[24,25] (*S*)-2-(methoxymethyl)pyrrolidine,[26] or with bis-(*R*)-1-phenylethylamine,[27] was unfruitful. This is probably due to steric hindrance of the amines. The starting β-keto amides were recovered and were accompanied, in some cases, by transamidation products when the reaction was performed at high temperatures-.Because of this failure, we turned our attention to the radical cyclization of secondary β-carboxamido enamines. The results are summarized in Table 3. The β-carboxamido enamines **36**−**39** were prepared by condensing the corresponding β-keto carboxamides with benzylamine in toluene at room temperature. These compounds are more stable than the tertiary enamines as a result of intramolecular hydrogen bonding between the NH and the carbonyl of the amide. Some of them can be isolated after purification by flash chromatography on silica gel (e.g., **36**−**38**).

Treatment of enamine **36** with 1 equiv of $Mn(OAc)_3$ in the presence of K_2CO_3 was sufficient to effect complete reaction within 30 min. The cyclized products **42a/42b** were obtained in good yield (72%), but unfortunately the diastereoselectivity was low (54/46). The β-imino lactams **42a** and **42b** were stable and were purified by flash chromatography on silica gel. Their hydrolysis was achieved with aqueous AcOH in THF to give the corresponding β-keto lactams **14a** and **14b** in high yield (90%). This reaction is general as **37** and **38** led, respectively, to **43a/43b** (yield, 66%; ratio, 53/47) and **44** (yield: 75%). In the case of imine-enamine **39**, we were not able to isolate the intermediate β-imino lactam. Purification of the reaction mixture on silica gel led directly to β-keto lactams **16a/16b** in good yield (70%) and with moderate diastereoselectivity (67/33) (Table 3).

Treatment of enamines **36** and **37** with 2 equiv of $Mn(OAc)_3$ in the presence of 1 equiv of $Cu(OAc)_2$ led, respectively, to β-imino lactams **45** (77%) and **44** (75%) (Scheme 7). Under the same conditions imine-enamine **39** led to β-keto lactam **27** (37% yield).

The radical cyclization of tertiary and secondary enamines may involve initial coordination of the enamine nitrogen with $Mn(OAc)_3$ which results in the formation of Mn(III)-complexe **f** (Scheme 8). In the case of tertiary enamines, a single electron transfer (SET) takes place immediately to give rise to radical-cation **h**. This radical cyclizes rapidly by a 5-*exo* mode to afford the cyclized

(18) For one example of asymmetric induction of β-keto amides controlled by a chiral auxiliary on the amide functionality see: (a) Cardillo, B.; Galeazzi, R.; Mobilli, G.; Orena, M. *Synlett* **1995**, 1159. (b) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1996**, 52, 1069. (c) Cossy, J.; Sallé, L. Unpublished results.

(19) For the radical cyclization of silyl enol ethers see: (a) Snider, B. B.; Kwon, T. *J. Org. Chem*. **1992**, *57*, 2399. (b) Snider, B. B.; Kwon, T. *J. Org. Chem*. **1990**, *55*, 4786.

(20) For a review see: Renaud, P.; Giraud, L. *Synthesis* **1996**, 913 and references therein.

(21) (a) Mignani, S.; Janousek, Z.; Merenyi, R.; Viehy, H. G. *Tetrahedron Lett*. **1984**, *25*, 1571. (b) Curran, D. P.; Thoma, G. *J. Am. Chem. Soc.* **1992**, *114*, 4436. (c) Renaud, P.; Shubert, S. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 433.

(22) (a) Shono, T.; Matsumura, Y.; Hamaguchi, H.; Yochida, K. *Bull. Chem. Soc. Jpn*. **1987**, *51*, 2179. (b) Chiba, T.; Okimoto, M.; Nagai, N.; Takata, Y. *J. Org. Chem*. **1979**, *44*, 3519.

(23) (a) Sauve, G.; Rao, V. S. In *Comprehensive Organic Functional Group Transformations*; Katritsky, A. R., Otto, M.-C., Rees, C.-W., Eds. Pergamon Press: New York, 1995; p 737. (b) G. Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975. (c) Stork, G.; Brizzolara, A. *J. Am. Chem. Soc.* **1963**, *85*, 208. (d) Whitessel, J. K.; Whitessel, M. A. *Synthesis* **1983**, 517.

(24) (a) Whitessel, J. K. *Chem. Rev.* **1989**, *89*, 1581. (b) Whitessel, J. K. *Acc. Chem. Res.* **1985**, *18*, 280. (c) Whitessel, J. K.; Felman, S. W. *J. Org. Chem*. **1977**, *42*, 1663. (d) Short, R. P.; Kennedy, R. M.; Masammune, J. *J. Org. Chem*. **1989**, *54*, 1755.

(25) We thank Prof. L. Ghosez from the Université Catholique de Louvain-La−Neuve (Belgique) for providing us with (+)-(2*R*,5*R*)-dimethylpyrrolidine.

(26) (a) Enders, D.; Fey. R.; Kiphardt, H. *Org. Synthesis* **1987**, *65*, 173. (b) Enders, D.; Fey. R.; Kiphardt, H. *Org. Synth.* **1987**, *65*, 183. (c) Seebach, D.; Kalnowski, H. O.; Shmidt, H. A. *Helv. Chim. Acta* **1977**, *60*, 310.

(27) Overberger, C. G.; Marullo, N. P.; Hiskey, G. G. *J. Am. Chem. Soc.* **1961**, *83*, 1374.

Scheme 6. Spirolactams from Tertiary β-Carboxamido Enamines

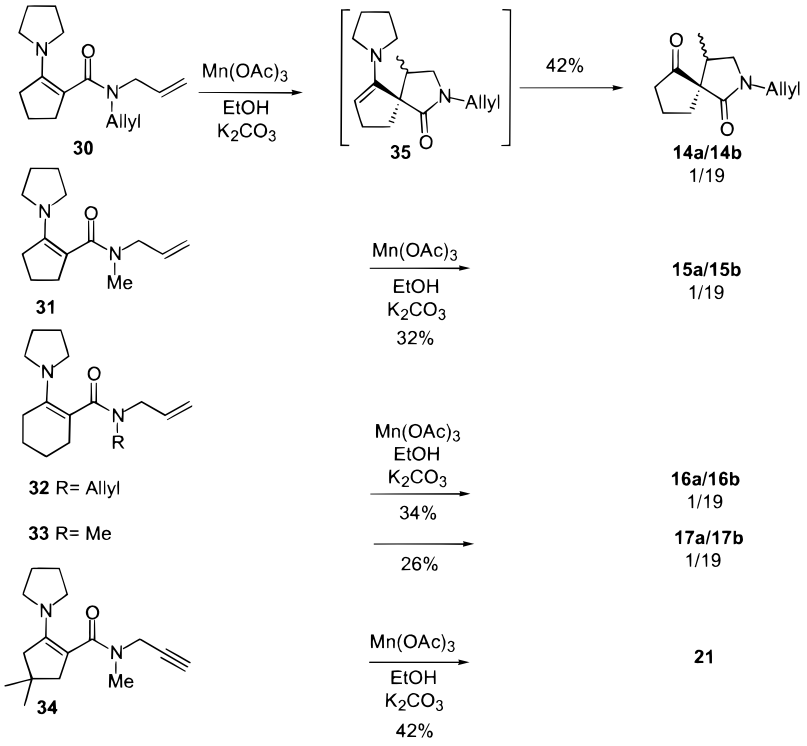
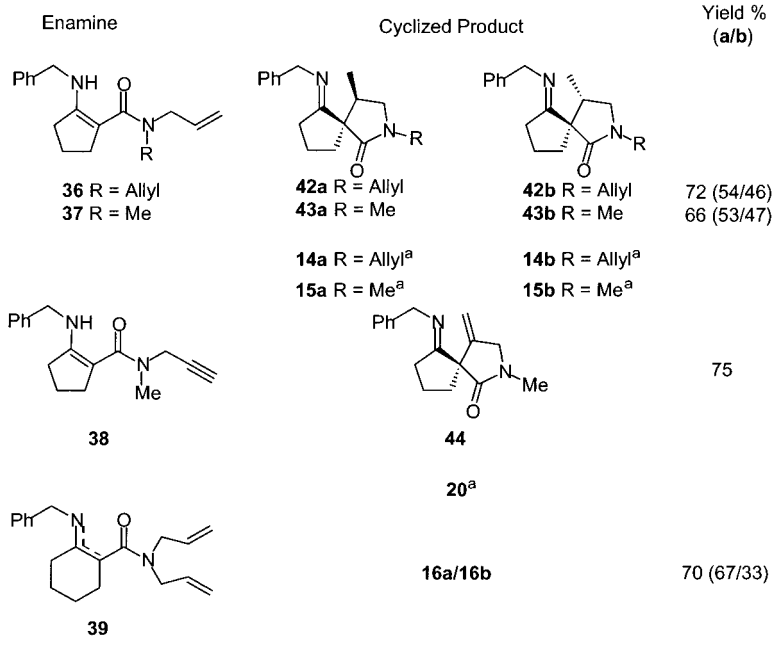


Table 3. Radical Cyclization of Secondary β-Carboxamido Enamines Mediated by $Mn(OAc)_3$

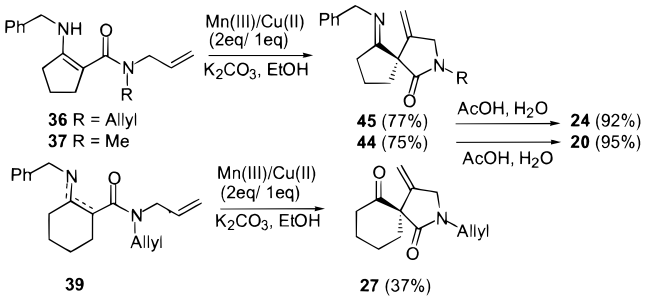


[a] After hydrolysis with aqueous acetic acid, **42a** ->**14a** (90%); **42b** ->**14b** (90%); **43a** -> **15 a** (90%); **43b** ->**15b** (90%); **44** ->**20** (92%).

iminium-radical **i**, which after deprotonation leads to the enamine-radical **j**. In the case of secondary enamines, the generation of the free radical **l** may follow an analogous pathway or it may be preceded by the loss of acetic acid through intermediate **k**. Radical **l** undergoes regioselective cyclization by a 5-*exo* process to give imine-radical **m**. As it was the case for β-keto carboxamides, the radicals **j** and **m** can be reduced by abstraction of hydrogen from EtOH or possibly from the starting secondary enamine. These radicals can also undergo a second oxidation in the presence of $Cu(OAc)_2$ and be transformed to the unsaturated spirolactams **44**, **45**, and **27**.

The high stereoselectivity of the reaction involving tertiary enamines can be attributed mainly to the interactions created by the pyrrolidine moiety, disfavoring transition states $\mathbf{C_1}$ and $\mathbf{D_1}$ where severe repulsions between the methylenic groups of the pyrrolidine ring and the alkyl group of the amide are developed (Scheme

Scheme 7. Radical Cyclization Mediated by Mn(III)/Cu(II)



9). Transition state $\mathbf{C_2}$ is also disfavored as a result of steric interactions between the pyrrolidine ring and the double bond, which is sterically more demanding than a hydrogen atom.

The lack of diastereoselectivity observed in the case of secondary enamines is probably due to the absence of steric factors as well as electronic factors that could control the approach of the double bond to the radical. Thus, all the transition states $\mathbf{E_1}$, $\mathbf{E_2}$, $\mathbf{F_1}$, and $\mathbf{F_2}$ can exist (Scheme 10).

Asymmetric Synthesis of Spirolactams. Oxidation of the (*R*)-1-phenylethylamine-derived propargylamido enamine **40** with 1 equiv of $Mn(OAc)_3$ led to the two diastereoisomeric spirolactams **46** and **47**, which were separated by flash chromatography on alumina in isolated yields of 45% and 15% (Scheme 11). The allylamido enamine **41** afforded spirolactams **46** and **47** in 65% and 25% yield, respectively, when treated with 1 equiv of $Mn(OAc)_3$ and 1 equiv of $Cu(OAc)_2$. We have to point out that we were not able to determinate the absolute configuration of the spiro center. However, one can suppose that the major isomer could be **46** in which the stereochemistry of the newly formed center is (*R*) arising from approach of the unsaturation from the less hindered side, assuming a preferred conformation of the phenylethyl auxiliary as shown.

Other Metallic Salt Promoted Radical Cylizations of *β*-Enamino Carboxamides. Electroanalytical studies have shown that *β*-enamino carboxamides have a low redox potential (<0.80 V vs. the standard calomel electrode).[29] This observation prompted us to examine other low valent metallic salts with a low redox potential such as AgOAc,[30] $Co(OAc)_2$,[31] CuCN and $Cu(OAc)_2$.[32] Treatment of tertiary as well as secondary enamines such as **30** and **36** with AgOAc, $Co(OAc)_2$, and CuCN led, respectively, to the cyclized products **14a/14b** and **42a/42b** with good chemical yields (Table 4). The diastereoselectivity remained unchanged, indicating that the metals are not involved in the cyclization process. When $Cu(OAc)_2$ is used, **30** and **36** were transformed, respectively, to **20** and **45**. The reactions with CuCN and $Cu(OAc)_2$ required heating to 80 °C.

Since no spirolactam products were obtained when enamines **30** and **36** were treated with Lewis acids such as $EtAlCl_2$ or $ZnCl_2$,[2] an ene reaction can be ruled out.[33] Furthermore, when the reactions were performed with metallic salts in the presence $Cu(OAc)_2$ at room temperature, the oxidized products were obtained as the major products. For example, treatment of **30** and **36** with AgOAc (2 equiv) in the presence of $Cu(OAc)_2$ (1 equiv) led, respectively, to **20** (61%) and **45** (85%). As $Cu(OAc)_2$ is unable to promote the reaction at room temperature, the reaction is initiated by Ag(I) with subsequent oxidation of the radical by $Cu(OAc)_2$. Interestingly, treatment of **36** with only 1 equiv of $Cu(OAc)_2$ led directly to the oxidized product **45** in 85% yield. This is probably the result of a dismutation of Cu(I) to Cu(II) and Cu(0). The regenerated Cu(II) acts as previously noted to produce the radical cation or to oxidize the cyclized radical to the carbocation intermediate. On the other hand, 2 equiv of Cu(I) will dismutate to Cu(II) and Cu(0).[33] An arithmetical calculation shows that 1 equiv of Cu(II) can be generated from the dismutation phenomena and that the complete transformation of Cu(II) to Cu(0) follows the arithmetical serial $S_n = \Sigma_{j-1}{}^n(1/2)^j$ (j is the number of cycles to transform **36** to **45**. When n tends to infinity, S_n tends to 1).

Conclusion

An efficient synthesis of lactams and spirolactams was achieved by using Mn(III)-based radical cyclization of *β*-keto carboxamides. Reversal of diastereoselectivity was observed in the oxidative cyclization of the *β*-keto versus tertiary *β*-enamino carboxamides. The oxidative cyclization of chiral secondary enamines showed a moderate diastereoselectivity of 3−2.6:1. The diastereomeric products were readily separated by silica gel chromatography and were obtained in enantiomerically pure form, suitable for use in the synthesis of natural products having a 2-azaspiro framework.[34]

Experimental Part:

General. All experiments were run under an argon atmosphere. ^1H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ unless otherwise indicated. Mass spectra were run on a GC-MS instrument at 70 eV. Microanalysis and HRMS were performed at Paris VI University. Flash chromatography was performed on Merck silica gel 60 (230−400 mesh) or on alumina 507 C neutral (100−125 mesh).

Synthesis of *β*-Keto Carboxamides. *β*-Keto carboxamides **1**−**11** were prepared according to refs 7 and 8. Spectroscopic and physical data of **1**−**5**, **8**, and **9** are reported in the same references.

(28) When the reaction was conducted in refluxing toluene, benzene, or cyclohexane, the desired enamines were obtained in low yields because of a competitive transamidation reaction. For example the condensation of **2** with benzylamine in refluxing toluene afforded the desired enamine **39** in only 35% yield accompanied by 64% of the transamidation product. Apparently the transamidation reaction occurred first, followed by the formation of the enamine. When the enamine **39** was heated in refluxing toluene in the presence of excess $BnNH_2$, no reaction took place.

(29) Audebert, P.; Bekolo, H.; Cossy, J.; Bouzide, A. *J. Electroanal. Chem.* **1995**, *389*, 215.

(30) (a) Bhatia, B.; Punniyamurthy, T.; Iqbal, J. *J. Org. Chem.* **1993**, *58*, 5518. (b) Bhatia, S.; Punniyamurthy, T.; Bhatia, B.; Iqbal, J. *Tetrahedron* **1993**, *49*, 6101.

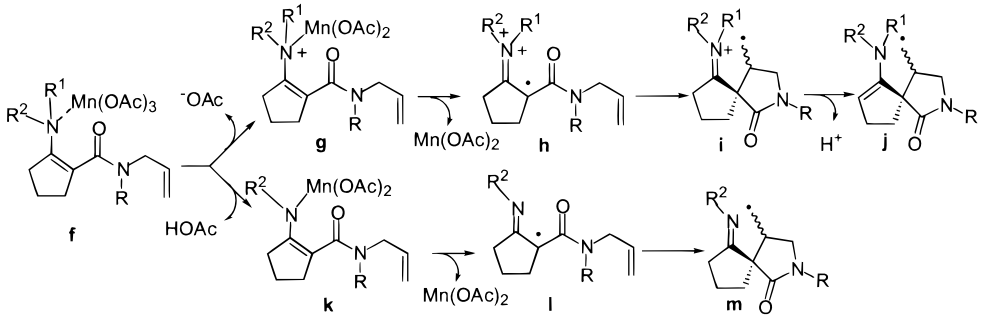
(31) (a) Chung, H. K.; Dunn, L. B., Jr. *J. Org. Chem.* **1983**, *48*, 1125. (b) Babler, J. H.; Sarussi, S. *J. Org. Chem.* **1987**, *52*, 3462. (c) Kawabata, T.; Sumi, K.; Hiyama, T. *J. Am. Chem. Soc.* **1989**, *111*, 6843.

(32) For reviews on Lewis acid catalyzed ene reactions see: (a) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021. (b) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Synlett* **1991**, 255. (c) Snider, B. B. *Acc. Chem. Res.* **1980**. (d) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Press: Oxford, 1991; Vol. 5, Chapter 1.1.

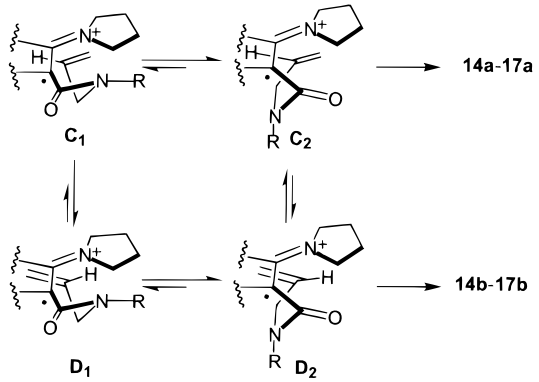
(33) A deposit of copper(0) was observed on the wall of the flask.

(34) (a) Ibragimov, A. A.; Osmanov, Z.; Tashkhodzhaev, B.; Abdullaev, M. R.; Yagudaev, N. D.; Yunusov. S. Y. *Khim. Prir. Soedin* **1981**, 623. (b) Nosgorodova, N. Y.; Maekl, S. K.; Yunusov, S. Y. *Khim. Prir. Soedin* **1973**, 196. (c) Osmanov, Z.; Ibraginov, A. A.; Yunusov, S. Y. *Khim. Prir. Soedin.* **1982**, 126. (d) Osmanov, Z.; Ibramimov, A. A.; Yunusov, S. Y. *Chem. Nat. Prod.* **1981**, 206.

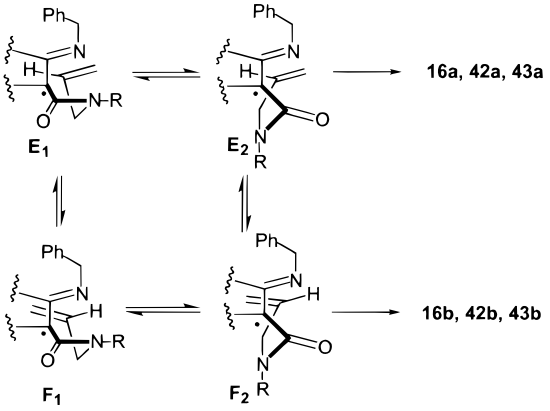
Scheme 8. Mechanism for the Formation of Spirolactams from β-Carboxamido Enamines



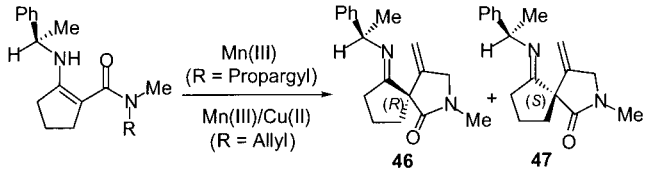
Scheme 9. Transition States in the Radical Cyclization of Tertiary β-Carboxamido Enamines



Scheme 10. Transition States in the Radical Cyclization of Secondary β-Carboxamido Enamines.



Scheme 11. Oxidation of Optically Active Secondary β-Carboxamido Enamines



40 R = Propargyl	60%	dr = 3:1
41 R = Allyl	90%	dr = 2.6:1

***N*-(But-3-enyl)-*N*-methyl-4,4-dimethyl-2-oxocyclopentanecarboxamide (6).** Colorless oil; yield 95%. IR: 1745, 1645, 1635 cm^{-1}. ^1H NMR Major rotamer: δ 1.06 (s, 3H); 1.25 (s, 3H); 3.14 (s, 3H). Minor rotamer: δ 1.04 (s, 3H); 1.23 (s, 3H); 2.96 (s, 3H). For both rotamers: δ 1.87−2.45 (m, 6H), 3.28−3.73 (m, 3H); 4.88−5.15 (m, 2H); 5.78−5.89 (m, 1H). ^{13}C NMR Major rotamer: δ 27.91 (q); 28.87 (q); 31.55 (t); 34.14 (s); 35.88 (q); 40.45 (t); 47.76 (t); 51.27 (d); 53.26 (t); 116.48 (t); 135.04 (d); 168.42 (s); 213.62 (s). Minor rotamer: δ 27.84 (q); 28.87 (q); 32.76 (t); 33.80 (q); 34.04 (s); 41.05 (t); 49.56 (t); 50.93 (d); 53.26 (t); 117.00 (t); 134.11 (d); 168.68 (s); 213.62 (s). MS: $C_{13}H_{21}NO_2$ *m/z* 223 (M^+, 100); 182 (57); 139 (42). Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.03; H, 9.48; N, 6.30.

Table 4. Oxidation of Enamines with Metallic Salts

enamine	metallic salt (equiv)	temp	products	yield (%) ratio (**a**/**b**)
30	$Co(OAc)_2$, (2)	rt	**14a/14b**	60 (1/19)
36	$Co(OAc)_2$, (1)	rt	**42a/42b**	65 (1.2/1)
30	AgOAc (2)	rt	**14a/14b**	51 (1/24)
36	AgOAc (1)	rt	**42a/42b**	75 (1/1.5)
30	CuCN (2)	80 °C	**14a/14b**	57 (1/16)
36	CuCN (2)	80 °C	**42a/42b**	70 (1/1.3)
30	$Cu(OAc)_2$ (2)	80 °C	**20**	61
36	$Cu(OAc)_2$ (1)	80 °C	**45**	85

***N*,*N*-Diallyl-3-methyl-2-oxobutyramide (7).** Colorless oil; yield 70%. IR: 1700; 1620 cm^{-1}. ^1H NMR: δ 1.37 (d, J = 7.0 Hz, 3H); 2.37 (s, 3H); 3.60 (q, J = 6.9 Hz, 1H); 3.81−4.17 (m, 4H); 5.10−5.27 (m, 4H); 5.70−5.87 (m, 2H). ^{13}C NMR: δ 13.92 (q); 27.01 (q); 48.13 (t); 49.30 (t); 51.52 (d); 116.81 (t); 117.43 (t); 132.62 (d); 132.74 (d); 170.37 (s); 205.05 (s). MS: $C_{11}H_{17}NO_2$ *m/z* 195 (M^+, 28); 96 (77); 56 (100). Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.44; H, 8.64; N,7.27.

***N*-Methyl-*N*-propargyl-3-methyl-2-oxobutyramide (10).** Colorless oil; yield 64% (2 rotamers in a ratio = 2/1). IR: 1725; 1645 cm^{-1}. ^1H NMR Major rotamer: δ 1.37 (d, J = 6.9 Hz, 3H); 2.17 (s, 3H); 2.29 (t, J = 2.5 Hz, 1H); 3.13 (s, 3H); 3.75 (q, J = 7.0 Hz, 1H); 4.03−4.23 (m, 2H). Minor rotamer: δ 1.39 (d, J = 7.0 Hz, 3H); 2.18 (s, 3H); 2.42 (t, J = 2.5 Hz, 1H); 3.05 (s, 3H); 3.75 (q, J = 7.0 Hz, 1H); 4.03−4.23 (m, 2H).^{13}C NMR Major rotamer: δ 13.13 (q); 26.94 (q); 34.49 (q); 36.44 (t); 51.46 (d); 71.95 (d); 78.03 (s); 169.80 (s); 204.47 (s). Minor rotamer: δ 13.36 (q); 27.08 (q); 33.56 (q); 39.51 (t); 51.46 (d); 73.13 (d); 78.03 (s); 170.06 (s); 204.47 (s). MS: $C_9H_{13}NO_2$ *m/z* 167 (M^+, 2); 58 (100). Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.37. Found: C, 64.56; H, 8.08; N, 8.45.

***N*-(But-3-enyl)-*N*-methyl-2-oxocyclohexanecarboxamide (11).** Colorless oil; yield 69%. IR: 1710, 1635 cm^{-1}. ^1H NMR Major rotamer: δ 2.90 (s, 3H). Minor rotamer: δ 2.95 (s, 3H). For both rotamers: δ 1.60−2.61 (m, 10H); 3.14−3.39 (m,1H); 3.47 (t, J = 7.5 Hz, 1H); 3.55−3.62 (m, 1H); 5.00−5.14 (m, 2H); 5.67−5.88 (m, 1H). ^{13}C NMR Major rotamer: δ 23.28 (t); 26.92 (t); 30.03 (t); 31.55 (t); 35.45 (q); 41.76 (t); 47.46 (t); 54.37 (d); 116.35 (t); 135.23 (d); 169.21 (s); 207.22 (s). Minor rotamer: δ 23.28 (t); 26.75 (t); 30.31 (t); 32.58 (t); 33.55 (q); 41.60 (t); 49.21 (t); 53.97 (d); 117.45 (t); 133.98 (d); 169.21 (s); 207.34 (s). MS: $C_{12}H_{19}NO_2$ *m/z* 210 (MH^+, 48); 209 (M^+, 4); 168 (100); 125 (71); 55. Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 69.02; H, 9.13; N, 6.67.

Synthesis of β-Enamino Carboxamides. Tertiary enamines **30**−**34** were prepared as follows. To a stirred solution of β-keto carboxamide (10 mmol) in toluene (25 mL) was added pyrrolidine (2.5 mL, 30 mmol). The mixture was stirred overnight at reflux with azeotropic removal of water. It was then concentrated at reduced pressure to give the desired

enamine in quantitative yield. For spectroscopic and physical data of **30**−**34**, see ref 15.

Secondary enamines **36**−**41** were prepared as follows. To a stirred solution of *β*-keto carboxamide (10 mmol) in toluene was added benzylamine (12 mmol) or (*R*)-phenylethylamine (12 mmol) and activated molecular sieves 3 Å. The mixture was stirred at room temperature for 2 days, then filtered and concentrated under reduced pressure to give the desired enamines. For spectroscopic and physical data of **36**−**39**, see ref 15.

(−)-*N*-Methyl-*N*-propargyl-2-[(*R*)-(1-phenylethyl)amino]cyclopent-1-enecarboxamide (40). This enamine was purified by flash chromatography using hexanes/EtOAc (70/30) as eluent. Yellow oil; yield 95%; $[\alpha]^{22}_D$ −302 (*c* 5; ethanol). IR: 3290; 1600 cm^{-1}. ^{1}H NMR: *δ* 1.80 (d, *J* = 6.9 Hz, 3H); 1.60−1.80 (m, 2H); 2.05−2.20 (m, 1H); 2.22 (t, *J* = 2.4 Hz, 1H); 2.64 (t, *J* = 7.0 Hz, 2H); 3.35 (s, 3H); 4.12 (d, *J* = 2.4 Hz, 2H); 4.54 (m, 1H); 7.20−7.35 (m, 5H); 8.60 (d, *J* = 7.3 Hz, 1H (NH)). ^{13}C NMR: *δ* 20.37 (t); 24.77 (q); 31.56 (t); 32.23 (t); 34.52 (q); 38.00 (t); 54.10 (d); 71.07 (d); 80.00 (d); 94.35 (s); 125.42 (2d); 126.72 (d); 128.40 (2d); 145.43 (s); 164.60 (s); 171.46 (s). MS: $C_{18}H_{22}ON_2$ *m*/*z* 282 (M$^+$, 5); 184 (90); 156 (100). Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.67; H, 7.80; N, 9.96.

(−)-*N*-Allyl-*N*-methyl-2-[(*R*)-(1-phenylethyl)amino]-cyclopent-1-enecarboxamide (41). This enamine was purified by flash chromatography using hexanes/EtOAc (70/30) as eluent. Yellow oil; yield 97%; $[\alpha]^{22}_D$ −375 (*c* 2; ethanol). IR: 3500; 1600; 1550 cm^{-1}. ^{1}H NMR: *δ* 1.48 (d, *J* = 6.9 Hz, 3H); 1.58−1.80 (m, 2H); 2.08−2.20 (m, 1H); 2.38−2.50 (m, 1H); 2.60 (t, *J* = 6.8 Hz, 2H); 2.93 (s, 3H); 3.95 (d, *J* = 5.2 Hz, 2H); 4.55 (q, *J* = 7.0 Hz, 1H); 5.15 (m, 2H); 5.75−5.90 (m, 1H); 7.15−7.35 (m, 5H); 8.58 (d, *J* = 7.6 Hz, 1H).^{13}C NMR: *δ* 23.27 (t); 25.78 (q); 32.43 (t); 33.31 (t); 35.43 (q); 52.22 (t); 54.96 (d); 95.75 (s); 116.93 (t); 126.29 (2d); 127.41 (d); 129.25 (2d); 135.28 (d); 146.00 (s); 164.51 (s); 172.54 (s). MS: $C_{18}H_{24}N_2O$ *m*/*z* 284 (M$^+$, 5); 184 (83); 156 (100). Anal. Calcd for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found: C, 76.12; H, 8.53; N, 9.79.

Modified Procedure for the Preparation of Anhydrous Mn(OAc)$_3$.[13] ***Caution:*** *The reaction must be run in a well-ventilated hood*. A dry, 250 mL, three-necked flask containing a magnetic stirring bar was charged with manganese(II) nitrate tetrahydrate [$Mn(NO_3)_2$·$4H_2O$] (6.0 g, 0.024 mol) and acetic anhydride. The mixture was stirred by warming gently with a heat gun until the solution became clear. The stirring was then stopped before an exothermic reaction took place. NO_2 gas was evacuated with an argon flux every 20 min over 1 h. $Mn(OAc)_3$ crystallized overnight. Anhydrous diethyl ether (20 mL) was added, and the mixture was stirred for 10 min, then allowed to settle for 20 min. The supernatant was removed by means of a syringe. The operation was repeated three times and the obtained $Mn(OAc)_3$ was dried under vacuum. Yield 95% (5.3 g).

Procedure A. Radical Cyclization of *β*-Keto Carboxamides with Mn(OAc)$_3$. To a degassed solution of *β*-keto carboxamide (1 mmol) in ethanol (5 mL) was added a degassed solution of anhydrous $Mn(OAc)_3$ (464 mg, 2 mmol) in ethanol (5 mL). The suspension was stirred at room temperature for 6 h, then filtered over Celite and concentrated. The residue was dissolved in EtOAc and water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The products were purified by flash chromatography. Spectroscopic and physical data of **14**, **15**−**17**, **20**, and **21** were consistent with data described in ref 15. Spectroscopic and physical data of **12**, **19**, **22** are reported in a preliminary communication.[4]

2-Allyl-8,8-dimethyl-4-hydroperoxymethyl-2-azaspiro-[4.4]nonane-1,6-dione 13. This hydroperoxide was a side product when the reaction was carried out in nondegassed ethanol and was obtained in 17% yield as a colorless oil. IR: 3340; 1730; 1675 cm$^{-1.}$ MS: $C_{14}H_{21}NO_4$ *m*/*z* 268 (MH$^+$, 0.3); 267 (M$^+$, 9%); 220 (72); 137 (100). Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 63.05; H, 7.95; N, 5.13. **13a** ^{1}H NMR: *δ* 1.14 (s, 3H); 1.27 (s, 3H); 1.57−1.73 (m, 1H); 1.91−2.56 (m, 5H); 3.19−3.39 (m, 2H); 3.78−4.00 (m, 3H); 4.38 (dd, *J* = 13.8 and 4.9 Hz, 1H); 5.12−5.31 (m, 2H); 5.60−5.80 (m, 1H). ^{13}C NMR: *δ* 26.14 (s); 32.00 (q); 32.64 (q); 34.50 (t); 36.41 (d); 46.68 (t); 47.09 (t); 55.28 (t); 63.54 (s); 69.57 (t); 118.69 (t); 132.17 (d); 175.77 (s); 219.30 (s). **13b** ^{1}H NMR: *δ* 1.17 (s, 3H); 1.24 (s, 3H); 1.57−1.73 (m, 1H); 1.91−2.56 (m, 5H); 3.19−3.39 (m, 2H); 3.78−4.00 (m, 3H); 4.00−4.06 (m, 1H); 5.12−5.31 (m, 2H); 5.60−5.80 (m, 1H). ^{13}C NMR: *δ* 29.33 (t); 44.65 (d); 45.70 (t); 49.95 (t); 51.94 (t); 63.61 (s); 69.57 (t); 109.47 (t); 132.17 (d); 172.98 (s); 218.70 (s).

2,5,9,9-Tetramethyl-2-azaspiro[4.5]decane-1,7-dione 18. Colorless oil; yield 52%. IR: 1725; 1620 cm^{-1}. MS: $C_{13}H_{21}NO_2$ *m*/*z* 224 (MH$^+$, 0.3); 223 (M$^+$, 10); 140 (100); 83. Anal. Calcd for $C_{14}H_{21}NO_4$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.01; H, 9.60; N, 6.34. **18a** ^{1}H NMR: *δ* 0.94 (d, *J* = 6.7 Hz, 3H); 1.13 (s, 3H); 1.45−1.63 (m, 1H); 1.91−2.70 (m, 6H); 2.90 (s, 3H); 3.20−3.40 (m, 2H). ^{13}C NMR: *δ* 16.50 (q); 26.48 (t); 30.53 (q); 30.91 (q); 32.55 (s); 33.08 (q); 37.28 (d); 44.18 (t); 48.10 (t); 54.69 (t); 62.07 (s); 171.13 (s); 217.24 (s). **18b** ^{1}H NMR: *δ* 1.03 (d, *J* = 6.7 Hz, 3H); 1.29 (s, 3H); 1.45−1.63 (m, 1H); 1.91−2.70 (m, 6H); 2.90 (s, 3H); 3.20−3.40 (m, 2H). ^{13}C NMR: *δ* 17.06 (q); 26.17 (t); 29.97 (q); 30.13 (q); 32.76 (s); 34.88 (q) 37.55 (d); 44.35 (t); 48.73 (t); 55.47 (t); 62.00 (s); 170.98 (s); 217.12 (s).

Procedure B. Oxidative Radical Cyclization of *β*-Ketocarboxamides with Mn(OAc)$_3$/Cu(OAc)$_2$. To a degassed stirred suspension of *β*-keto carboxamide (1 mmol) and $Cu(OAc)_2$ (182 mg, 1 mmol) in ethanol (5 mL) was added dropwise a degassed solution of anhydrous $Mn(OAc)_3$ (464 mg, 2 mmol) in ethanol (5 mL). The reaction mixture was stirred at room temperature for 5 h, then filtered over Celite and concentrated. The residue was dissolved in EtOAc and water. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude was purified by chromatography on silica gel using hexanes/AcOEt as eluent to afford the cyclized products.

2-Allyl-8,8-dimethyl-4-methylene-2-azaspiro[4.4]nonane-1,6-dione 23. Colorless oil; yield 52%. IR: 1740; 1690 cm^{-1}. ^{1}H NMR: *δ* 1.18 (s, 3H); 1.27 (s, 3H); 1.87−1.96 (m, 1H); 2.22−2.42 (m, 2H); 2.53−2.60 (m, 1H); 3.27−3.35 (m, 1H); 3.37−4.08 (m, 2H); 4.16−4.26 (m, 1H); 5.06−5.30 (m, 4H); 5.68−5.82 (m, 1H). ^{13}C NMR: *δ* 28.82 (q); 29.56 (q); 33.08 (s); 45.24 (t); 45.49 (t); 51.20 (t); 53.02 (t); 65.33 (s); 107.99 (t); 117.91 (t); 131.59 (d); 144.10 (s); 171.62 (s); 211.68 (s). MS: $C_{14}H_{19}NO_2$ *m*/*z* 233 (M$^+$, 16); 150 (100). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.20; N, 6.00. Found: C, 71.90; H, 8.31; N,5.96.

2-Allyl-4-methylene-2azaspiro[4.4]nonane-1,6-dione 24. Colorless oil; yield 65%. IR: 1740; 1690 cm^{-1}. ^{1}H NMR: *δ* 1.98−2.70 (m, 6H); 3.80−4.20 (m, 4H); 5.07−5.32 (m, 4H); 5.68−5.82 (m, 1H). ^{13}C NMR: *δ* 19.98 (t); 32.42 (t); 37.65 (t); 44.90 (t); 50.84 (t); 63.11 (s); 107.89 (t); 117.87 (t); 131.41 (d); 143.44 (s); 171.63 (s); 213.55 (s). MS: $C_{12}H_{15}NO_2$ *m*/*z* 206 (MH$^+$, 7); 205 (M$^+$, 36); 150 (100). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.36; N, 6.82. Found: C, 70.35; H,7.24; N, 6.74.

2-Methyl-9,9-dimethyl-5-methylene-2-azaspiro[4.5]-decane-1,7-dione 25. Colorless oil; yield 55%. IR: 1725; 1620 cm^{-1}.^{1}H NMR: *δ* 1.12 (s, 3H); 1.27 (s, 3H); 2.02−2.75 (m, 6H); 2.96 (s, 3H); 3.24−3.42 (m, 2H); 4.09−5.05 (m, 2H). ^{13}C NMR: *δ* 29.85 (q); 29.89 (q); 30.71 (t); 33.23 (s); 35.59 (q); 47.17 (t); 49.03 (t); 53.79 (t); 64.92 (s); 110.43 (t); 143.88 (s); 169.26 (s); 213.49 (s). MS: $C_{13}H_{19}NO_2$ *m*/*z* 222 (MH$^+$, 6); 221 (M$^+$, 19); 138 (100). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.71; H, 8.63; N, 6.42.

2-Methyl-5-methylene-2-azaspiro[5.5]undecane-1,7-dione 26. Colorless oil; yield 40%. IR: 1705; 1650; 1630 cm^{-1}.^{1}H NMR: *δ* 1.83−2.22 (m, 7H); 2.38−2.49 (m, 3H); 2.98 (s, 3H); 3.18−3.42 (m, 2H); 514 (d, *J* = 2.0 Hz, 1H); 5.18 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR: *δ* 21.38 (t); 26.29 (t); 30.22 (t); 32.21 (t); 35.16 (q); 39.27 (t); 48.66 (t); 64.97 (s); 111.84 (t); 142.42 (s); 168.95 (s); 208.78 (s). MS: $C_{12}H_{17}NO_2$ *m*/*z* 208 (MH$^+$, 25); 207 (M$^+$, 59); 179 (100); 164 (62). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C,69.32; H, 8.17; N, 6.74.

2-Allyl-4-methylene-2-azaspiro[4.5]decane-1,6-dione 27. Colorless oil; yield 25% in ethanol; 26% in wet acetonitrile; R_f 0.40 (PE/AcOEt, 50/50). IR: 1700; 1650 cm^{-1}. ^{1}H NMR: *δ* 1.22−1.42 (m, 1H); 1.60−2.15 (m, 4H); 2.20−2.60 (m, 2H); 2.70−2.90 (m, 1H); 3.80−4.05 (m, 4H); 5.10−5.30 (m, 4H);

5.65−5.80 (m, 1H). ^{13}C NMR: δ 21.00 (t); 26.00 (t); 35.79 (t); 39.54 (t); 45.03 (t); 50.45 (t); 63.41 (s); 110.32 (t); 118.03 (t); 131.56 (d); 143.07 (s); 171.25 (s); 206.40 (s); MS: $C_{13}H_{17}NO_2$ *m*/*z* 219 (M^+, 80); 191 (90); 190 (100); 163 (85). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.39. Found: C, 71.24; H, 7.83; N, 6.42.

Compound 28. Colorless oil; yield 65%; R_f 0.50 (hexanes/AcOEt, 50/50). IR: 1685; 1475 cm^{-1}. ^{1}H NMR: δ 1.10 (t, *J* = 7.2 Hz, 3H); 1.24−1.41 (m, 2H); 1.47−1.59 (m, 1H); 1.63−1.80 (m, 2H); 1.90−2.12 (m, 2H); 2.20−2.32 (m, 1H); 2.60−2.72 (m, 1H); 3.20 (dd, *J* = 7.4 and 1.5 Hz, 1H); 3.35 (dd, *J* = 9.20 and 9.20 Hz, 1H); 3.47 (dq, *J* = 7.2 and 0.2 Hz, 1H); 3.53 (dq, *J* = 7.2 and 0.2 Hz, 1H); 73.62−3.80 (m, 2H); 3.92−4.08 (m, 1H); 4.20 (dd, *J* = 8.6 and 8.6 Hz, 1H); 5.13−5.30 (m, 2H); 5.67−5.82 (m, 1H). ^{13}C NMR: δ 15.32 (q); 21.85 (t); 22.02 (t); 29.00 (t); 34.08 (t); 45.10 (t); 45.22 (d); 52.08 (t); 54.54 (t); 57.81 (s); 70.53 (t); 106.32 (s); 117.30 (t); 132.43 (d); 174.11 (s); MS: $C_{15}H_{23}NO_3$ *m*/*z* 265 (M^+, 5); 220 (87); 219 (100); 191 (77). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.89; H, 8.76; N, 5.29.

Compound 29. Colorless oil; yield 67%; R_f 0.25 hexanes-(PE/AcOEt, 50/50). IR: 3300; 1660 cm^{-1}. ^{1}H NMR: δ 1.20−1.40 (m, 1H); 1.45−1.90 (m, 7H); 2.70−2.80 (m, 1H); 3.15 (m, dd, *J* = 10.3 and 1.0 Hz, 1H); 3.52 (dd, *J* = 10.1 and 5.9 Hz, 1H); 3.71 (dd, *J* = 10.0 and 4.6 Hz, 1H); 3.80 (m, 2H); 4.10 (t, *J* = 9.2 Hz, 1H); 5.20 (m, 2H); 5.60−5.70 (m, 1H); 6.14 (d, *J* = 1.7 Hz, 1H). ^{13}C NMR: δ 21.67 (t); 22.37 (t); 27.29 (t); 32.96 (t); 38.60 (d); 45.16 (t); 50.65 (t); 54.24 (s); 70.00 (t); 105.11 (s); 118.47 (t); 131.61 (d); 177.08 (s). MS: $C_{13}H_{19}NO_3$ *m*/*z* 237 (M^+, 65); 205 (100); 178 (78); 151 (90). Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.80. Found: C, 66.02; H, 8.01; N, 5.83.

Procedure C. Radical Cyclization of Tertiary Enamines with Metallic Salts. To a degassed suspension of enamine (1 mmol) and K_2CO_3 (138 mg, 1 mmol) in ethanol (10 mL) was added portionwise the metallic salt (2 mmol). The reaction mixture was stirred at room temperature until complete consumption of starting material (within 5−15 min). The reaction mixture was concentrated and diluted with EtOAc. HCl (10%) was then added until pH 5−6. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel using hexanes/EtOAc as eluent to afford respectively spirolactams **12**, **15**−**17**, and **21** with the yields indicated in Tables 3 and 5.

Procedure D. Radical Cyclization of Secondary Enamines 36−41 with Metallic Salts. As in Procedure C, except that the reaction was run with only 1 equiv of metallic salt and the solution was stirred for 30 to 60 min. The spectroscopic and physical data of the cyclized products **42**−**44** and **16** are consistent with those described in ref 15.

2-Allyl-6-benzylimino-4-methylene-2-azaspiro[4.4]-nonan-1-one 45. Colorles oil; yield 77%. ^{1}H NMR: δ 1.90−2.50 (m, 5H); 2.55−2.70 (m, 1H); 3.70−4.20 (m, 4H); 4.50 (s, 2H); 5.00 (t, *J* = 2.2 Hz, 1H); 5.06 (t, *J* = 1.9 Hz, 1H); 5.10−5.22 (m, 2H); 5.60−5.80 (m, 1H); 7.10−7.30 (m, 5H). ^{13}C NMR: δ 22.47 (t); 28.00 (t); 33.99 (t); 45.07 (t); 51.99 (t); 57.13 (t); 63.44 (s); 107.87 (t); 117.08 (t); 126.19 (d); 127.39 (2d); 128.04 (2d); 131.96 (d); 139.82 (s); 143.68 (s); 175.32 (s); 181.21 (s). MS: $C_{19}H_{22}N_2O$ *m*/*z* 294 (M^+, 15); 203 (78); 200 (100). Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.51. Found: C, 77.70; H, 7.63; N, 9.55.

(+)-(5*R*)-2-Methyl-4-methylene-6-[(*R*)-(1-phenylethyl)-imino]-2-azaspiro[4.4]nonan-1-one 46. R_f 0.25 (hexanes/EtOAc, 90/10); $[\alpha]^{22}_D$ +22.7 (*c* 1.5, EtOH). IR: 1730; 1650 cm^{-1}. ^{1}H NMR: δ 1.36 (d, *J* = 6.60 Hz, 3H); 1.75−1.95 (m, 2H); 2.12−2.50 (m, 4H); 2.95 (s, 3H); 3.85 (dt, *J* = 13.0 and 1.7 Hz, 1H); 4.23 (dt, *J* = 13.0 and 2.4 Hz, 1H); 4.40 (q, *J* = 6.6 Hz, 1H); 4.87 (t, *J* = 2.2 Hz, 1H); 5.00 (t, *J* = 1.8 Hz, 1H); 7.10−7.20 (m, 5H). ^{13}C NMR: δ 22.71 (t); 24.76 (q); 29.00 (t); 29.61 (q); 34.17 (t); 54.01 (t); 60.85 (s); 61.67 (d); 106.32 (t); 126.24 (2d); 126.31 (d); 128.15 (2d); 146.11 (s); 147.22 (s); 175.45 (s); 178.11 (s). MS: $C_{18}H_{22}N_2O$ *m*/*z* 282 (M^+, 5); 177 (70); 104 (100). Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.62; H, 7.83; N, 9.97.

(−)-(5*R*)-2-Methyl-4-methylene-6-[(*S*)−(1-phenylethyl)-imino]-2-azaspiro[4.4]nonan-1-one 47. R_f 0.30 (hexanes/EtOAc, 90/10); $[\alpha]^{22}_D$ −99.0 (*c* 0.7, EtOH). IR: 1730; 1655; 1490 cm^{-1}. ^{1}H NMR: δ 1.33 (d, *J* = 6.6 Hz, 3H); 1.85−2.00 (m, 2H); 2.10−2.50 (m, 4H); 2.94 (s, 3H); 3.85 (dt, *J* = 13.0 and 1.7 Hz, 1H); 4.23 (dt, *J* = 13.0 and 2.4 Hz, 1H); 4.40 (q, *J* = 6.6 Hz, 1H); 4.95 (t, *J* = 2.2 Hz,1H); 5.03 (t, *J* = 2.2 Hz, 1H); 7.10−7.20 (m, 5H). ^{13}C NMR: δ 22.79 (t); 24.23 (q); 28.75 (t); 29.56 (q); 33.34 (t); 54.00 (t); 60.90 (s); 61.24 (d); 105.86 (t); 126.24 (2d); 126.31 (d); 128.17 (2d); 145.47 (s); 147.60 (s); 175.27 (s); 177.94 (s). MS: $C_{18}H_{22}N_2O$ *m*/*z* 282 (M^+, 5); 178 (70); 104 (100). Anal. Calcd. for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.70; H, 7.88; N, 10.01.

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