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Manganese(III)-Promoted Free Radical Cyclizations of Enamides Leading to β-Lactams

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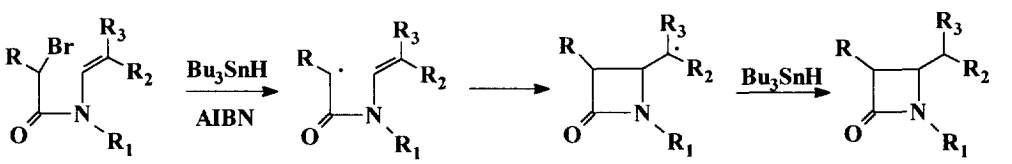
Abstract: Reaction of variously substituted enamides with $Mn(OAc)_3 \cdot 2H_2O$ afforded β-lactamic products in modest to good yields, depending mostly on the solvent and reaction conditions. The substitution pattern of the enamidic double bond was found of primary importance for the outcome of the reaction. © 1997 Published by Elsevier Science Ltd.

Recently, radical ring-closure reactions leading to four membered rings have been considerably studied; in this field a really interesting and useful approach was the 4-*exo-trig* intramolecular addition of 4-pentenyl radicals to double bonds, used either in the formation of cyclobutanes[2] or in the synthesis of β-lactams from suitable precursors.

As regards the 4-*exo-trig* cyclization to azetidinones, the pioneering work was carried out by Pattenden who studied the cyclization of N-allylcarbamoyl cobalt intermediates under heating or irradiation with a sunlamp.[3a,b] A little later, a general approach involving the generation of radicals **2** from α-bromoenamides **1** by treatment with Bu_3SnH/AIBN and their subsequent cyclization to β-lactams **4** was contemporarily reported by Belletire[4] and Ishibashi and Ikeda.[5a-e]

The effectiveness of these last reductive methods depended mostly on the nature of the substituents at the enamide olefinic carbon far away from nitrogen atom. According to the postulated reaction path, shown in Scheme 1, the best results were obtained when R_2 and R_3 were aryl or phenylthio groups, both able to stabilize the cyclic radical intermediate **3**.

Scheme 1



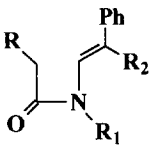
1 **R = alkyl**
R_1 = alkyl, aryl
R_2 = R_3 = aryl, PhS

2 **3** **4**

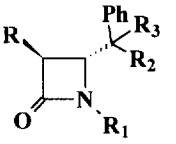
More recently, Zard reported a similar approach to β-lactams under mild reducing conditions, i.e., the Ni-mediated cyclization of N-ethenyltrichloroacetamides in acetic acid.[6]

In the last few years, our work has been concerned with Mn(III)-based oxidative radical additions to double bonds. Mn(III)-promoted reactions were known to be useful tools to carry out ring closures,[7] but, at that moment, mostly 5-*exo-trig* processes were reported in literature[8a-c] and no applications of Mn(III) to 4-*exo-trig* cyclizations had been described.

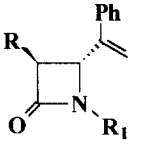
Thus, we decided to study the reactivity of suitable N-vinylamides (enamides) with $Mn(OAc)_3 \cdot 2H_2O$ and recently our preliminary results on the cyclization of α-methoxycarbonyl-N-ethenylamides **5** were reported.[9]



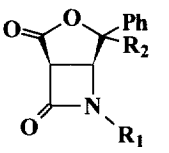
5 R = CO_2Me, R_1= alkyl, R_2= Ph
10 R = CO_2Me, R_1= alkyl, R_2= Ph
16 R = COMe, R_1=alkyl, R_2= Ph



9 R = CO_2Me, R_1= alkyl, R_2= Ph, R_3 = OAc
11 R = CO_2Me, R_1 = alkyl, R_2= Me, R_3 = OAc
15 R = CO_2Me, R_1 = alkyl, R_2= Ph, R_3 = OMe



14 R = CO_2Me, R_1= alkyl

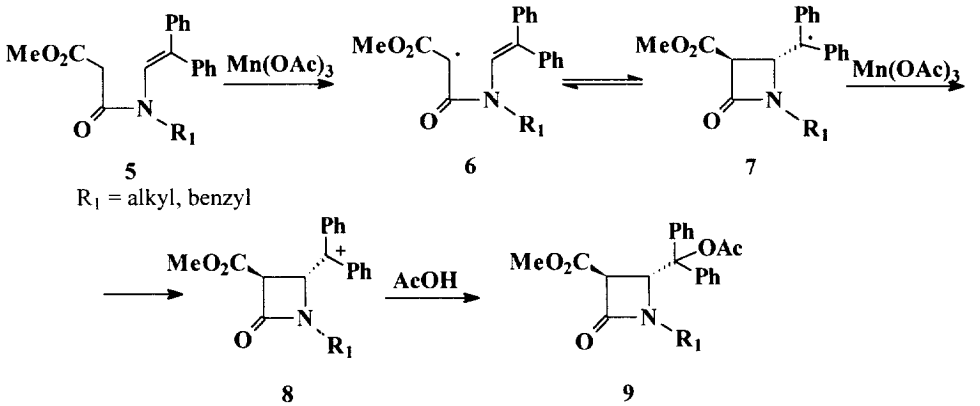


12 R_2 = Ph, R_1= alkyl
13 R_2 = Me, R_1= alkyl

Compounds **5**, easily accessible by literature methods,[10] reacted in glacial acetic acid at 70°C to afford acetoxylated β-lactams **9** in modest to good yields.

In the present paper we describe the extension of the study of the reactivity of enamides, and in particular of the effect of their structural features on the reaction course.

Scheme 2



According to the probable reaction path, shown in Scheme 2, the key-step in the reaction of **5** could be the cyclization of the intermediate **6** to **7**, and its subsequent oxidation to **8.** Therefore, if the intramolecular addition step would be reversible, the oxidation of **7** by a second equivalent of Mn(III) could shift the equilibrium towards final products.

Then, the effect of substituents on double bond is of primary importance for the stabilization of both radical **7** and carbocation **8**. To study the possible role of **8** as a reaction intermediate, we initially changed one of the phenyl substituents on the double bond for a methyl group; in this way a cationic intermediate would have still been satisfactorily stabilized. Thus, enamides **10** (easily prepared from hydratropaldehyde) were reacted with $Mn(OAc)_3$ under the usual conditions. Results, given in Table 1, are reported in comparison with those obtained from enamides **5**.

Table 1. Reaction of Enamides **5** and **10** with $Mn(OAc)_3$ in Glacial Acetic Acid for 1.5 hrs

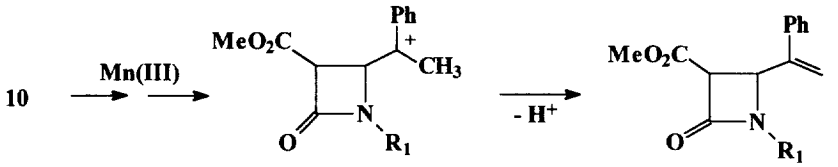
Substrate	R_1	Products (Yields %)[a]		
5a	*n*-Pr	**9a** (39)		
10a	"	**11a** (36)		**14a** (6)
5b	*i*-Pr	**9b** (50)		
10b	"	**11b** (44)		**14b** (6)
5c	*t*-Bu	**9c** (67)	**12c** (19)	
10c	"		**13c** (46)	**14c** (7)
5d	cyclopentyl	**9d** (60)		
10d	"	**11d** (50)		**14d** (15)
5e	cyclohexyl	**9e** (63)		
10e	"	**11e** (32)	**13e** (21)	**14e** (7)
5f	benzyl	**9f** (73)		
10f	"	**11f** (23)		**14f** (8)
5g	α-methylbenzyl	**9g**[b] (64)		

a) Yields are given on isolated products ; b) diastereomeric mixture

Also in this case β-lactamic products **11** were obtained from **10** in good yields. All β-lactams **9** and **11** showed a *trans* stereochemical relationship between substituents at C-3 and C-4, as demonstrated by ^{1}H-NMR

coupling constants of corresponding H-3 and H-4 protons. Enamides **10** gave always small amounts of unsaturated products **14**, whose formation was ascribed to the loss of a proton from the supposed cationic intermediate structurally analogous to **8** (Scheme 3).

Scheme 3



14

In three cases (i.e. enamides **5c** and **10c** with a *t*-butyl group on the nitrogen atom and enamide **10e**) bicyclic products **12** and **13** showing a γ-lactone system *cis*-fused with an azetidinone ring were obtained (together with the expected β-lactams). Their formation suggested the preliminary formation of the corresponding acetoxylated *cis* β-lactams, followed by an acid catalyzed intramolecular transesterification between $COOCH_3$ and OAc groups. Treatment of compounds **9c** or **11e** with Mn(III) did not effect their conversion into *cis* products **12c** and **13e** respectively. This suggested to us that the *trans* stereochemistry was established during the cyclization of intermediates **6** to **7**, and not later on.

The involvement of a cationic intermediate in our reactions (Scheme 3) was verified by reacting compounds **10** with Mn(III) in DMSO. In such a non nucleophilic solvent we expected that the carbocation intermediate would not be trapped, and so the formation of elimination products **14** would be favoured with respect to **11**. Results are reported in Table 2.

Table 2. Reaction of Enamides **10** with $Mn(OAc)_3$ in DMSO for 50 hrs

Substrate	Products (Yields[a] %)
10a	**11a** (27) **14a** (8)
10b	**11b** (32) **14b** (4)
10d	**11d** (25) **14d** (10)

a) Yields are calculated on isolated products

Comparable amounts of acetoxylated and unsaturated products were obtained in DMSO although in lower yields and longer reaction times than in acetic acid. The formation of compounds **11** in DMSO was explained by the proximity of Mn(III) to the radical-bearing carbon, in such a way that the acetate ligands lost during its reduction could be trapped by a cationic intermediate analogous to **8**. However, a valuable

hypothesis involves a ligand transfer oxidation process by Mn(III). The same type of behaviour was observed in the reaction of enamides **5** with $Mn(OAc)_3 2H_2O$ in methanol (see Table 3). Also in this case a mixture of acetoxylated compounds **9** (identical to those obtained in acetic acid) and methoxylated derivatives **15** was observed. Products **9** initially present in the reaction mixture were shown to be subsequently converted into **15** within a few hours. Enamide **5c** in MeOH afforded the bicyclic product **12c**, too. This represents a further indication of the role of *t*-butyl group in promoting a *cis* stereochemistry of substituents at C-3 and C-4. This is consistent with the corresponding observation of the analogous role played by sterically hindering groups (such as *t*-Bu) on N-atom in the strictly related CAN-promoted radical cyclization of enamides in MeOH.[11]

Table 3. Reaction of Enamides **5** with $Mn(OAc)_3$ in Methanol for 20 hrs

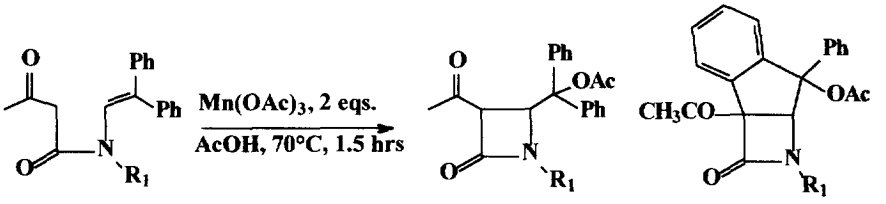
Substrates	Products (Yields[a] %)
5a	**15a** (43)
5c	**15c** (35) **12c** (16)
5d	**15d** (33)
5e	**15e** (60)

a) Yields are calculated on isolated products

As regards enamides with a still different substitution pattern at the β-carbon of the double bond (e.g. H and Ph, or two alkyl groups), they were really hard to synthesize, and in any case afforded mixtures of products containing only traces of β-lactams.

A complementary objective of our study was the evaluation of the effect that a different electron withdrawing group in α-position with respect to amidic carbonyl group of **5** would exert on the generation of radical **6**. We chose an acetyl group as R, and to this purpose, acetoacetyl enamides **16** were prepared according a new experimental procedure developed in our laboratory.[12]

Scheme 4



16b R_1 = i-Pr
16e R_1 = cyclohexyl

17b (26%)
17e (53%)

18b (28%)
18e (18%)

The introduction of an acetyl group as R made enamides **16** really reactive, probably enhancing their enolization ability (it is known that radical formation is supposed to occur from the enolized form of β-dicarbonyl compounds[7]). As a matter of fact, they were converted into products in short times even at room temperature.

In this case, the amount of Mn(III) was crucial. With the usual two equivalents of Mn(III), a mixture of acetoxylated compounds **17** and polycyclic compounds **18** was formed (see Scheme 4).

The formation of compounds **18** is certainly due to a further oxidation of the C-3 carbon of **17**, and the attack of the resulting radical to the phenyl group. This hypothesis was proved by reacting pure compound **17e** with excess Mn(III) at 70°C; the reaction was complete in three hours affording **18e** in 81% yield. This further oxidation-cyclization was not observed when the reaction between **16** and Ce(IV) was performed;[11] thus, it seems to be a peculiar feature of Mn(III) oxidant.

This Mn(III)-promoted methodology proved to be quite effective in the formation of β-lactamic products, and appreciable *trans* stereochemistry is observed in most cases. The oxidative pathway offers the possibility of a functionalization of the enamide olefinic β-carbon not directly involved in the cyclization; in this way oxygen nucleophiles can be introduced providing a handle for further modification of products. The presence of suitable activating groups at C-3 makes its subsequent oxidation-cyclization possible, leading in some cases to tricyclic β-lactams. Due to its mild conditions, the method constitutes a really simple approach to β-lactams.

The application of our methodology to the synthesis of more elaborate compounds will be presented in due course.

EXPERIMENTAL

Starting enamides were prepared according to literature procedures. Chemicals were purchased from Aldrich and used without further purifications. The progress of reactions and chromatographic separations were monitored by TLC on silica gel plates (Merck Kieselgel 60 F_{254} ϕ 0.25 mm). Column chromatography was performed on silica gel (Merck Kieselgel, 70-230 mesh). ^1H and ^{13}C-NMR spectra were recorded on a Varian XL 200 Gemini spectrometer. The following symbols were used to report the multiplicity and the shape of the signals: s (singlet), d (doublet), t (triplet), q (quartet), se (sextet), m (multiplet).

Reaction of enamides 5 with $Mn(OAc)_3$ (in AcOH, or DMSO, or MeOH) - To a solution of 1.0 mmol of enamide **5** in 10 ml of solvent, 2.0 mmoles of $Mn(OAc)_3 \cdot 2H_2O$ (536 mg) were added. The resulting brown suspension was stirred at 70°C under an argon athmosphere for variable times (1.5, 20 and 50 hours for AcOH, MeOH and DMSO respectively). At the end of reaction the mixture was then poured into water (100 ml), and extracted with CH_2Cl_2 (4 x 20 ml). Subsequently the organic phase was washed with brine (in the case of reactions carried out in acetic acid, the organic phase was firstly washed with saturated $NaHCO_3$ solution until neutrality), and finally dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure at room temperature afforded an oily residue in most cases. This residue was chromatographed on a silica gel column eluted with light petroleum ether/Et_2O to afford pure products.

Compound 9a - ^1H NMR : 0.87 (3H, t, J = 8.7 Hz, N-C-C-CH_3), 1.56 (2H, se, J = 7.7 Hz, N-C-CH_2-C), 2.14 (3H, s, OAc), 2.81 (1H, dt, J_{AB} = 14.4 Hz, J_2 = 7.4 Hz, N-CH_A-C-C), 3.49 (1H, dt, J_{AB} = 14.3 Hz, J2 = 7.3 Hz, N-CH_B-C-C), 3.68 (1H, d, J = 1.9 Hz, H-3), 3.78 (3H, s, COOMe), 5.48 (1H, d, J = 2.3 Hz, H-4), 7.10-7.50 (10H, m, aromatic protons); ^{13}C NMR: 11.00, 20.81, 21.90, 44.28, 52.65, 57.33, 57.58, 87.42, 126.84-

128.57, 139.40, 140.16, 162.39, 167.62, 169.14. Anal. calctd for $C_{23}H_{25}NO_5$: C, 69.84; H, 6.38; N, 3.54; found: C, 69.89; H, 6.27; N, 3.47.

Compound 9b - ^{1}H NMR: 1.27 (3H, d, J = 6.6 Hz, CH_3 of i-Pr), 1.35 (3H, d, J = 6.9 Hz, CH_3 of i-Pr), 2.01 (3H, s, OAc), 3.23 (1H, m, CH of i-Pr), 3.67 (1H, d, J = 2.5 Hz, H-3), 3.74 (3H, s, COOMe), 5.41 (1H, d, J = 2.5 Hz, H-4), 7.10-7.50 (10H, m, aromatic protons); ^{13}C NMR: 20.14, 20.31, 21.87, 48.78, 52.65, 56.73, 56.88, 87.05, 126-128.61, 139.68, 140.09, 161.96, 169.12. Anal. calctd for $C_{23}H_{25}NO_5$: C, 69.84; H, 6.38; N, 3.54; found: C, 69.88; H, 6.31; N, 3.42.

Compound 9c - ^{1}H NMR: 1.22 (9H, s, t-Bu), 2.09 (3H, s, OAc), 3.70 (1H, d, J = 2.3 Hz, H-3), 3.75 (3H, s, COOMe), 5.39 (1H, d, J = 2.3 Hz, H-4), 7.00-7.50 (10H, m, aromatic protons); ^{13}C NMR: 22.26, 28.00, 52.67, 55.35, 57.95, 60.60, 87.26, 127-35-128.27, 138.64, 140.74, 162.92, 168.12, 169.03. Anal. calctd for $C_{24}H_{27}NO_5$: C, 70.38; H, 6.65; N, 3.42; found: C, 70.43; H, 6.62; N, 3.38.

Compound 9d - ^{1}H NMR: 0.85-1.95 (8H, m, cyclopentyl), 2.11 (3H, s, OAc), 3.43 (1H, m, N-CH), 3.64 (1H, d, J = 2.4 Hz, H-3), 3.77 (1H, s, COOMe), 5.39 (1H, d, J = 2.4 Hz, H-4), 7.00-7.50 (10H, m, aromatic protons); ^{13}C NMR: 21.92, 23.97 29.49, 31.64, 52.57, 56.80, 57.82, 58.10, 87.23, 127.01-128.52, 139.70, 140.14, 161.54, 167.85, 169.12. Anal. calctd for $C_{25}H_{27}NO_5$: C, 71.23; H, 6.46; N, 3.32; found: C, 71.30; H, 6.41; N, 3.27.

Compound 9e - ^{1}H NMR : 0.90-2.05 (10H, m, cyclohexyl), 2.12 (3H, s, OAc), 2.74 (1H, m, N-CH), 3.68 (1H, d, J = 2.1 Hz, H-3), 3.77 (3H, s, COOMe), 5.40 (1H, d, J = 2.1 Hz, H-4), 7.00-7.50 (10H, m, aromatic protons); ^{13}C NMR: 21.86, 25.10, 25.85, 30.46, 52.58, 56.86, 87.11, 127.00-129.00, 139.76, 140.13, 161.97, 167.82, 169.11. Anal. calctd for $C_{26}H_{29}NO_5$: C, 71.69; H, 6.72; N, 3.32; found: C, 71.74; H, 6.75; N, 3.25.

Compound 9f - ^{1}H NMR: 2.07 (3H, s, OAc), 3.73 (3H, s, COOMe), 3.84 (1H, d, J = 15.7 Hz, Ph-CH_A), 3.92 (1H, d, J = 2.4 Hz, H-3), 4.87 (1H, d, J = 15.7 Hz, Ph-CH_B), 5.31 (1H, d, J = 2.4 Hz, H-4), 7.10-7.40 (15H, m, aromatic protons); ^{13}C NMR: 21.95, 46.05, 52.65, 57.27, 58.41, 86.54, 126.90-128.90, 135.49, 139.82, 140.10, 162.97, 167.52, 168.73. Anal. calctd for $C_{27}H_{25}NO_5$: C, 73.11; H, 5.69; N, 3.16; found: C, 73.18; H, 5.60; N, 3.21.

Compound 9g - inseparable mixture of two diastereomers in 1.2:1 ratio. ^{1}H NMR for the more abundant isomer: 1.64 (3H, d, J = 7.2 Hz, CH_3), 2.04 (3H, s, OAc), 3.78 (1H, d, J = 2.5 Hz, H-3), 3.82 (3H, s, COOMe), 4.14 (1H, q, J = 7.2 Hz, N-CH), 5.46 (1H, d, J = 2.5 Hz, H-4), 7.10-7.40 (15H, m, aromatic protons); for the less abundant isomer: 1.64 (3H, d, J = 7.2 Hz, CH_3), 2.11 (3H, s, OAc), 3.69 (3H, s, COOMe), 3.87 (1H, d, J = 2.6 Hz, H-3), 4.22 (1H, q, J = 7.2 Hz, N-CH), 5.12 (1H, d, J = 2.6 Hz, H-4), 7.10-7.40 (15H, m, aromatic protons). Anal. calctd for $C_{28}H_{27}NO_5$: C, 73.49; H, 5.95; N, 3.06; found: C, 73.59; H, 5.88; N, 3.12.

Compound 11a - ^{1}H-NMR: 0.83 (3H, t, J = 7.3 Hz, C-C-CH_3), 1.48 (2H, se, J = 7.3 Hz, C-CH_2-C), 1.85 (3H, s, CH_3), 2.08 (3H, s, OAc), 3.05 (1H, m, N-CH_A-C-C), 3.35 (2H, m, N-CH_B-C-C and H-3), 3.55 (3H, s, COOMe), 3.58 (1H, d, J = 2.6 Hz, H-4), 7.1-7.5 (5H, m, aromatic protons). ^{13}C-NMR: 10.98, 18.76, 20.16, 21.78, 44.02, 52.43, 55.41, 62.48, 82.73, 124.85, 128.26, 128.81, 139.93, 162.30, 167.16, 168.86. Anal. calctd for $C_{18}H_{23}NO_5$: C, 64.83; H, 6.96; N, 4.20; found: C, 64.84; H, 6.87; N, 4.16.

Compound 11b - ^{1}H NMR: 1.24 (3H, d, J = 6.8 Hz, CH_3 of i-Pr), 1.38 (3H, d, J = 6.8 Hz, CH_3 of i-Pr), 1.86 (3H, s, CH_3), 2.04 (3H, s, OAc), 3.41 (1H, d, J = 2.7 Hz, H-3), 3.47 (3H, s, COOMe), 3.57 (1H, m, CH of i-Pr), 4.19 (1H, d, J = 2.7 Hz, H-4), 7.27 (5H, m, aromatic protons). ^{13}C NMR: 17.49, 19.86, 20.24,

20.68, 21.73, 46.40, 52.23, 54.89, 61.82, 82.58, 124.67, 125.58, 128.13, 128.67, 139.78, 161.85, 166.89, 168.68. Anal. calctd for $C_{18}H_{23}NO_5$: C, 64.83; H, 6.96; N, 4.20; found: C, 64.91; H, 6.89; N, 4.13.

Compound 11d - ^{1}H NMR: 1.30-1.90 (8H, m, cyclopentyl), 2.06 (3H, s, OAc), 2.25 (1H, m, N-CH), 3.42 (1H, d, J = 2.5 Hz, H-3), 3.50 (3H, s, COOMe), 4.15 (1H, d, J = 2.5 Hz, H-4), 7.10-7.50 (5H, m, aromatic protons); ^{13}C NMR: 17.92, 21.74, 22.28, 23.48, 29.48, 30.49, 52.26, 54.91, 56.87, 62.52, 82.68, 124.70, 128.21, 128.46, 129.07, 139.83, 161.57, 167.06, 168.75. Anal. calctd for $C_{20}H_{25}NO_5$: C, 66.82; H, 7.01; N, 3.90; found: C, 66.77; H, 6.93; N, 3.98.

Compound 11e - ^{1}H NMR: 1.00-2.00 (10H, m, cyclohexyl), 2.10 (3H, s, OAc), 3.15 (1H, m, N-CH) 3.43 (1H, d, J = 2.6 Hz, H-3), 3.52 (3H, s, COOMe), 4.22 (1H, d, J = 2.6 Hz, H-4), 7.10-7.50 (aromatic protons); ^{13}C NMR: 17.87, 21.89, 25.08. 25.22, 25.42, 30.32, 31.03, 52.36, 54.82, 54.89, 55.02, 61.92, 82.83, 124.87, 128.27, 128.80, 140.00, 161.92, 168.77. Anal. calctd for $C_{21}H_{27}NO_5$: C, 67.53; H, 7.29; N, 3.75; found: C, 67.63; H, 7.22; N, 3.69.

Compound 11f - ^{1}H NMR (diastereomeric mixture): 1.78, 1.83, 1.90 (3H, s, CH_3), 2.02. 2.05, 2.08 (3H, s, OAc), 3.61, 3.70, 3.77 (3H, s, COOMe), 3.70-4.10 (2H, m, CH_2-Ph), 4.15 (1H, m, H-3), 4.60-5.23 (1H, m, H-4), 7.10-7.50 (10H, m, aromatic protons). Anal. calctd for $C_{22}H_{23}NO_5$: C, 69.26; H, 6.08; N, 3.67; found: C, 69.31; H, 6.13; N, 3.70.

Compound 12 - ^{1}H NMR: 0.90 (9H, s, *t*-Bu), 3.95 (1H, d, J = 4.0 Hz, H-3), 4.98 (1H, d, J = 4.8 Hz, H-4), 7.10-7.80 (10H, m, aromatic protons); ^{13}C NMR: 27.17, 55.38, 55.62, 59.15, 89.74, 126.93-129.12, 138.23, 139.93, 161.49, 168.42. Anal. calctd for $C_{21}H_{21}NO_3$: C, 75.19; H, 6.31; N, 4.18; found: C, 75.24; H, 6.26; N, 4.12.

Compound 13c - ^{1}H NMR: 1.45 (9H, s, *t*-Bu), 1.84 (3H, s, CH_3), 3.86 (1H, d J = 4.5Hz, H-3), 4.37 (1H, d, J = 4.5 Hz, H-4), 7.35 (5H, m, aromatic protons); ^{13}C NMR: 25.43, 28.04, 54.94, 55.06, 60.06, 87.22, 124.34, 128.55, 129.21, 142.77, 161.14, 168.65. Anal. calctd for $C_{16}H_{19}NO_3$: C, 70.29; H, 7.01; N, 5.13; found: C, 70.30; H, 6.95; N, 5.20.

Compound 13e - ^{1}H NMR: 1.00-2.50 (10H, m, cyclohexyl), 3.24 (1H, m, N-CH), 3.85 (1H, d, J = 4.1 Hz, H-3), 4.28 (1H, d, J = 4.1 Hz, H-4), 7.10-7.50 (5H, m, aromatic protons); ^{13}C NMR: 23.68, 24.93, 24.97, 25.37. 55.59, 55.82, 59.81, 87.10, 124.45, 128.62, 129.25, 137.65, 157.32, 160.18. Anal. calctd for $C_{18}H_{21}NO_3$: C, 72.20; H, 7.07; N, 4.68; found: C, 72.25; H, 7.11; N, 4.71.

Compound 14a - ^{1}H NMR: 0.94 (3H, t, J = 7.3 Hz, N-C-C-CH_3), 1.65 (2H, se, J = 7.3 Hz, N-C-CH_2-C), 2.95 (1H, m, N-CH_A-C-C), 3.55 (1H, m, N-CH_B-C-C), 3.73 (1H, d, J = 2.3 Hz, H-3), 3.77 (3H, s, COOMe), 4.78 (1H, d, J = 2.3 Hz, H-4), 5.33 (1H, s, olefinic proton), 5.57 (1H, s, olefinic proton), 7.10-7.50 (5H, m, aromatic protons); ^{13}C NMR: 11.19, 20.65, 22.30, 42.80, 52.68, 55.97, 61.80, 114.54, 126.11, 128.59, 128.90, 137.91, 144.23, 162.47, 167.75. Anal. calctd for $C_{16}H_{19}NO_3$: C, 70.92; H, 7.01; N, 5.13; found: C, 70.93; H, 7.05; N, 5.09.

Compound 14b - ^{1}H NMR: 1.23 (3H, d, J = 6.6 Hz, CH_3 of i-Pr), 1.40 (3H, d, J = 6.6 Hz, CH_3 of i-Pr), 3.60-3.85 (1H, m, CH of i-Pr overlapped with H-3), 3.66 (1H, d, J = 1.8 Hz, H-3), 3.76 (3H, s, COOMe), 4.77 (1H, d, J = 1.8 Hz, H-4), 5.44 (1H, s, olefinic proton), 5.57 (1H, s, olefinic proton), 7.10-7.50 (5H, m, aromatic protons); ^{13}C NMR: 20.21, 20.64, 40.36, 52.61, 55.33, 61.35, 114.92, 126.15, 128.53, 128.87, 138.12, 145.45, 162.27, 167.75. Anal. calctd for $C_{16}H_{19}NO_3$: C, 70.92; H, 7.01; N, 5.13; found: C, 70.88; H, 7.10; N, 5.11.

Compound 14c - ^{1}H NMR: 1.38 (9H, s, *t*-Bu), 3.65 (2H, d, J = 2.2 Hz, H-3), 3.75 (3H, s, COOMe), 4.77 (1H, d, J = 2.2 Hz, H-4), 5.45 (2H, overlapped s, olefinic protons), 7.10-7.50 (5H, m, aromatic protons);

^{13}C NMR: 27.70, 52.61, 55.14, 55.29, 61.42, 114.92, 126.15, 128.48, 128.85, 138.44, 147.06, 162.53, 167.84. Anal. calctd for $C_{17}H_{21}NO_3$: C, 71.04; H, 7.37; N, 4.88; found: C, 71.12; H, 7.31; N, 4.79.

Compound 14d - ^{1}H NMR: 1.39-2.30 (8H, m, cyclopentyl), 3.63 (1H, d, J = 2.3 Hz, H-3), 3.7-3.9 (1H, m, N-CH overlapped with COOMe), 3.76 (3H, s, COOMe), 4.72 (1H, d, J = 2.3 Hz, H-4), 5.41 (1H, s, olefinic protons), 5.56 (1H, s, olefinic protons), 7.33 (5H, m, aromatic protons); ^{13}C NMR: 23.46, 23.54, 29.98, 30.43, 52.62, 55.58, 56.16, 61.21, 114.86, 126.14, 128.54, 128.68, 145.20, 162.12, 167.72. Anal. calctd for $C_{18}H_{21}NO_3$: C, 72.20; H, 7.07; N, 4.68; found: C, 72.27; H, 7.03; N, 4.71.

Compound 14e - ^{1}H NMR: 1.00-2.30 (10H, m, cyclohexyl), 3.35 (1H, m, N-CH), 3.65 (1H, d, J = 2.1 Hz, H-3), 3.76 (3H, s, COOMe), 4.78 (1H, d, J = 2.1 Hz, H-4), 5.44 (1H, s, olefinic proton), 5.57 (1H, s, olefinic proton), 7.35 (5H, m, aromatic protons); ^{13}C NMR: 24.71, 24.96, 25.09, 30.35, 30.74, 32.40, 52.61, 53.97, 55.21, 61.35, 114.95, 124.70, 126.14, 128.52, 128.87, 145.39, 162.21, 167.80. Anal. calctd for $C_{19}H_{23}NO_3$: C, 72.80; H, 7.40; N, 4.47; found: C, 72.83; H, 7.36; N, 4.49.

Compound 14f - ^{1}H NMR: 3.75 (3H, s, COOMe), 3.78 (1H, d, J = 2.1 Hz, H-3), 4.05 (1H, d, J = 15.1 Hz, CH_APh), 4.63 (1H, d, J = 2.1 Hz, H-4), 4.95 (1H, d, J = 15.1 Hz, CH_BPh), 5.32 (1H, s, olefinic proton), 5.58 (1H, s, olefinic proton), 7.28 (10H, m, aromatic protons); ^{13}C NMR: 45.12, 52.63, 55.91, 61.93, 115.00, 126.20-129.02, 162.49, 167.49. Anal. calctd for $C_{20}H_{19}NO_3$: C, 74.73; H, 5.96; N, 4.36; found: C, 74.76; H, 5.89; N, 4.31.

Compound 15a - ^{1}H NMR: 0.89 (3H, t, J = 8.2 Hz, N-C-C-CH_3), 1.60 (2H, m, N-C-CH_2-C), 2.78 (1H, m, N-CH_A), 3.05 (3H, s, OMe), 3.40 (1H, m, N-CH_B), 3.66 (1H, d, J = 2.2 Hz, H-3), 3.75 (3H, s, COOMe), 4.92 (1H, d, J = 2.2 Hz, H-4), 7.00-7.50 (10H, m, aromatic protons); ^{13}C NMR: 11.00, 20.81, 21.90, 44.28, 52.65, 57.33, 57.58, 87.42, 126.84-128.76, 139.40, 140.16, 162.39, 167.62, 169.14. Anal. calctd for $C_{22}H_{25}NO_4$: C, 71.90; H, 6.86; N, 3.81; found: C, 71.96; H, 6.76; N, 3.85.

Compound 15c - ^{1}H NMR: 1.22 (9H, s, *t*-Bu), 2.95 (3H, s, OCH_3), 3.50 (1H, d, J = 2.4 Hz, H-3), 3.68 (3H, s, COOMe), 4.88 (1H, d, J = 2.4 Hz, H-4), 7.10-7.50 (10H, m, aromatic protons); ^{13}C NMR: 28.10, 52.31, 52.45, 55.36, 57.03, 61.73, 85.10, 129.08-129.11, 138.15, 138.96, 162.89, 168.22. Anal. calctd for $C_{23}H_{27}NO_4$: C, 72.40; H, 7.14; N, 3.67; found: C, 72.45; H, 7.20; N, 3.61.

Compound 15d - ^{1}H NMR: 1.30-2.30 (8H, m, cyclopentyl), 3.07 (3H, s, OMe), 3.40-3.65 (2H, m, H-3 overlapped with N-CH), 3.78 (3H, s, COOMe), 4.87 (1H, d, J = 2.2 Hz, H-4), 7.10-7.50 (10H, m, aromatic protons); ^{13}C NMR: 24.10, 24.18, 29.36, 31.98, 51.79, 52.54, 56.41, 57.58, 58.27, 84.80, 127.97-128.92, 139.12, 139.48, 161.93, 168.34. Anal. calctd for $C_{24}H_{27}NO_4$: C, 73.25; H, 6.92; N, 3.56; found: C, 73.29; H, 6.86; N, 3.49.

Compound 15e - ^{1}H NMR: 1.00-2.30 (10H, m, cyclohexyl), 2.80-2.95 (1H, m, N-CH), 3.05 (3H, s, OMe), 3.63 (1H, d, J = 2.2 Hz, H-3), 3.74 (3H, s, COOMe), 4.87 (1H, d, J = 2.2 Hz, H-4); 7.10-7.50 (10H, m, aromatic protons); ^{13}C NMR: 25.03, 25.18, 25.77, 30.39, 30.71, 51.84, 52.53, 56.24, 56.31, 57.38, 84.69, 127.00-128.91, 139.23, 139.39, 161.96, 168.33. Anal. calctd for $C_{25}H_{29}NO_4$: C, 73.67; H, 7.18; N, 3.44; found: C, 73.71; H, 7.21; N, 3.40.

Compound 17b - ^{1}H NMR: 1.16 (3H, d, J = 6.6 Hz, CH_3 of i-Pr), 1.31 (3H, d, J = 6.6 Hz, CH_3 of i-Pr), 2.12 (3H, s OAc), 2.19 (3H, s, CH_3CO), 3.14 (1H, he, J = 6.6 Hz, CH of i-Pr), 3.97 (1H, d, J = 2.4 Hz, H-3), 5.45 (1H, d, J = 2.4 Hz, H-4), 7.10-7.50 (10H, m, aromatic protons). Anal. calctd for $C_{23}H_{25}NO_4$: C, 72.79; H, 6.64; N, 3.69; found: C, 72.85; H, 6.59; N, 3.62.

Compound 17e - ^{1}H NMR: 0.80-2.00 (10H, m, cyclohexyl), 2.12 (3H, s, OAc), 2.18 (3H, s, CH_3CO), 2.54 (1H, m, N-CH), 4.00 (1H, d, J = 1.6 Hz, H-3), 5.45 (1H, d, J = 1.6 Hz, H-4), 7.10-7.50 (10H, m, aromatic protons); ^{13}C NMR: 22.14, 25.27, 25.97, 29.96, 30.66, 30.79, 55.74, 56.66, 65.71, 86.95, 126.69-129.30, 140.03, 140.64, 162.89, 168.83, 199.96. Anal. calctd for $C_{26}H_{29}NO_4$: C, 74.43; H, 6.97; N, 3.34; found C, 74.48; H, 6.91; N, 3.38.

Compound 18b - ^{1}H NMR: 1.37 (3H, d, J = 6.7 Hz, CH_3 of i-Pr), 1.41 (3H, d, J = 6.7 Hz, CH_3 of i-Pr), 2.20 (3H, s, OAc), 2.39 (3H, s, CH_3CO), 3.59 (1H, he, J = 6.7 Hz, CH of i-Pr), 4.95 (1H, s, H-4), 7.10-7.50 (9H, m, aromatic protons); ^{13}C NMR: 20.56, 20.82, 28.59, 48.44, 65.67, 79.80, 80.61, 124.42-129.96, 135.31, 142.75, 142.94, 165.64, 170.02, 200.26. Anal. calctd for $C_{23}H_{23}NO_4$: C, 73.18; H, 6.15; N, 3.71; found: C, 73.25; H, 6.06; N, 3.66.

Compound 18e - ^{1}H NMR: 1.10-2.00 (10H, m, cyclohexyl), 2.21 (3H, s, OAc), 2.40 (3H, s, CH_3CO), 3.21 (1H, m, N-CH), 4.95 (1H, s, H-4), 7.00-7.80 (9H, m, aromatic protons); ^{13}C NMR: 21.96, 25.25, 25.32, 25.71, 28.65, 30.95, 30.99, 56.47, 65.79, 79.60, 88.78, 124.37-129.80, 135.36, 142.55, 142.77, 165.28, 169.60, 199.57. Anal. calctd for $C_{26}H_{27}NO_4$: C, 74.79; H, 6.52; N, 3.36; found: C, 74.83; H, 6.47; N, 3.32.

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