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# Mn(III)-Promoted Sulfur-Directed 4-*Exo-Trig* Radical Cyclization of Enamides to β-Lactams

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**Abstract:**

The synthesis of β-lactams vinylated at C-4 from N-(3-phenylthio-1-alkenyl)amides was carried out by Mn(III)-promoted 4-*exo-trig* radical cyclization followed by β-fragmentative loss of phenylthiyl radical. The effects on the reaction course of different substituents both on enamidic nitrogen atom or double bond were analyzed. The overall reaction was stereoselective, leading to *trans* azetidinones. 

***Keywords:*** Azetidinones, Cyclisation, Enamides, Fragmentation Reactions, Manganese and Compounds, Radical Reactions

## Introduction

In recent times the synthesis of four membered rings, mostly β-lactamic systems, by means of radical cyclizations has attracted considerable attention;[1-4] in particular the synthesis of azetidinones by 4-*exo-trig* intramolecular addition to double bond of radicals (generated by $Bu_3SnH$) from α-bromoenamides was extensively studied.[5-9]

In the last years we have been studying Mn(III) or Ce(IV)-promoted oxidative reactions of various classes of compounds. At this purpose we recently reported the reaction of "activated" enamides **1** (bearing an enolizable EWG group adjacent to amidic carbonyl group) with $Mn(OAc)_3 \cdot 2H_2O$ in glacial acetic acid at 70°C,[10-11] or with ceric ammonium nitrate in methanol at room temperature,[12] affording azetidinones **5** in good yields (Scheme 1).

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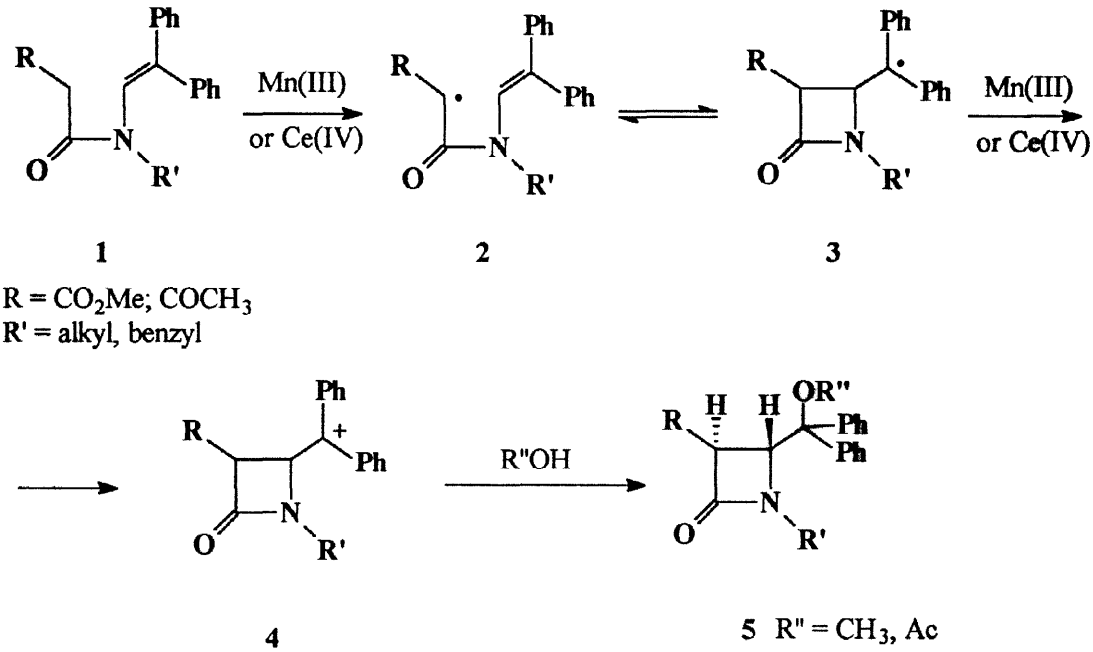
Reasonably these transformations involved the transition-metal promoted generation of α-carbamoylalkyl radicals **2**, and their subsequent 4-*exo-trig* cyclization to intermediates **3**.

Both these procedures required two equivalents of oxidant, due to the second oxidative step, converting **3** to carbocation **4**. Its trapping by solvent afforded product **5**. The stereochemistry of compounds 5 was in most cases *trans* with respect to substituents at C-3 and C-4. Nevertheless, *cis* products were in some cases formed in not negligible or even prevalent amount.

**Scheme 1**




**1** **2** **3**

R = $CO_2Me$; $COCH_3$
R' = alkyl, benzyl

**4**

**5** R" = $CH_3$, Ac

The presence of phenyl groups on enamidic double bond was found to be crucial for the successful outcome of the reactions, probably because of the good stabilization of both intermediates **3** or **4** by aryl groups. This is in agreement with data reported in literature about the effect of aryl or arylthio groups on similar 4-*exo-trig* reductive methods.

We tried to use enamides disubstituted with alkyl groups on the β position of double bond, which were obtained by usual methods, but yields of β-lactams were really low and formation of by-products was prevalent. Thus, such a need of aryl groups on the enamidic double bond was the main limitation of our oxidative method.

With a view to an application of these methodologies to the synthesis of more elaborated azetidinones, we were interested to study the utilization of enamides different from **1** (especially as regards substituents on double bond) in these Mn(III)-promoted reactions.

**Results and Discussion**

Indeed, in our purpose the second oxidative step, i.e. the oxidation of **3** to **4**, could be replaced by a more efficient reaction of the first cyclic intermediate arising from the 4-*exo-trig* intramolecular addition. A convenient process seemed to be the β-fragmentation of a suitably substituted intermediate. By the way, the introduction of a sulfur substituent at the allylic position of the enamide double bond, which was first reported by Zard and Quiclet-Sire in recent papers,[13-14] constituted a rather original approach. This pattern of substitution allowed the 4-*exo-trig* process to be driven to completion by the loss of a phenyl thiyl radical (this process is extremely fast, and its rate was estimated to be about $1.6 \cdot 10^7 s^{-1}$).

A β-fragmentative path was really interesting to be tested in our oxidative conditions, due to the possibility of comparison of its effectiveness with that of the oxidation of radical **3** by Mn(III). Furthermore, it would have been a widening of the applicability of our procedure.

The first step of our work was the choice of suitable N-1-propenyl-3-phenylthioenamides, bearing an activating group $R_1$ in the α-position of acyl moiety. For this purpose the early experiments were carried out employing α-methoxycarbonylenamides **6a-f**, prepared in good yields according to the literature procedures (See Experimental).[15] The same methods applied to the synthesis of α-chloro and α-cyano enamides were not as suitable as for compounds **6**, affording enamidic products in really low yields.

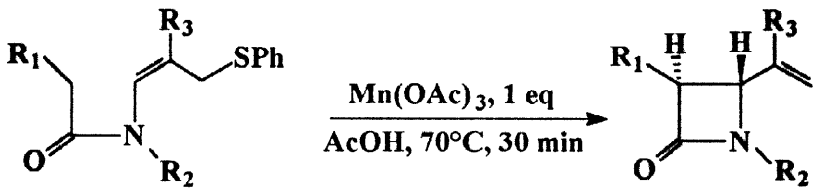
Thus, enamides **6a-f** were reacted with one equivalent of manganese(III) acetate dihydrate in glacial acetic acid at 70°C. Results are reported in Table 1.

We obtained the expected β-lactamic products **7a-f** vinylated in C-4 in modest to good yields. Their formation was in all cases stereoselective. Indeed the only lactamic products were lactams bearing the substituents at C-3 and C-4 in a *trans* relationship, as deduced by the analysis of $^1H$ NMR coupling constants between H-3 and H-4 (about 2.5 Hz).

Then, the reaction path seemed to be that shown in Scheme 2 for enamides **6a-d**, i.e. the Mn(III)-promoted generation of α-carbamoylalkyl radical radicals **8a-d**, followed by their *4-exo-trig* cyclization to **9a-d**. These cyclic intermediates underwent a β-fragmentation to give products **7a-d** and phenylthyil radicals. The involvement of such radicals was demonstrated by the formation, together with the lactamic products, of PhSSPh, their self-recombination product.

In agreement with the reaction path, a merely fragmentative fate for the cyclic radical **9** was confirmed by reacting the enamides with more that one equivalent of Mn(III). In these conditions no significant yields enhancement was observed, and only vinylated β-lactams were obtained. This fact, together with the lacking of products eventually derived from the capture of any carbocationic intermediate, seemed to suggest that further oxidation of **9** by Mn(III) was slower than the loss of phenylthyil radical.

**Table 1.**
Reaction of Enamides 6 with $Mn(OAc)_3$

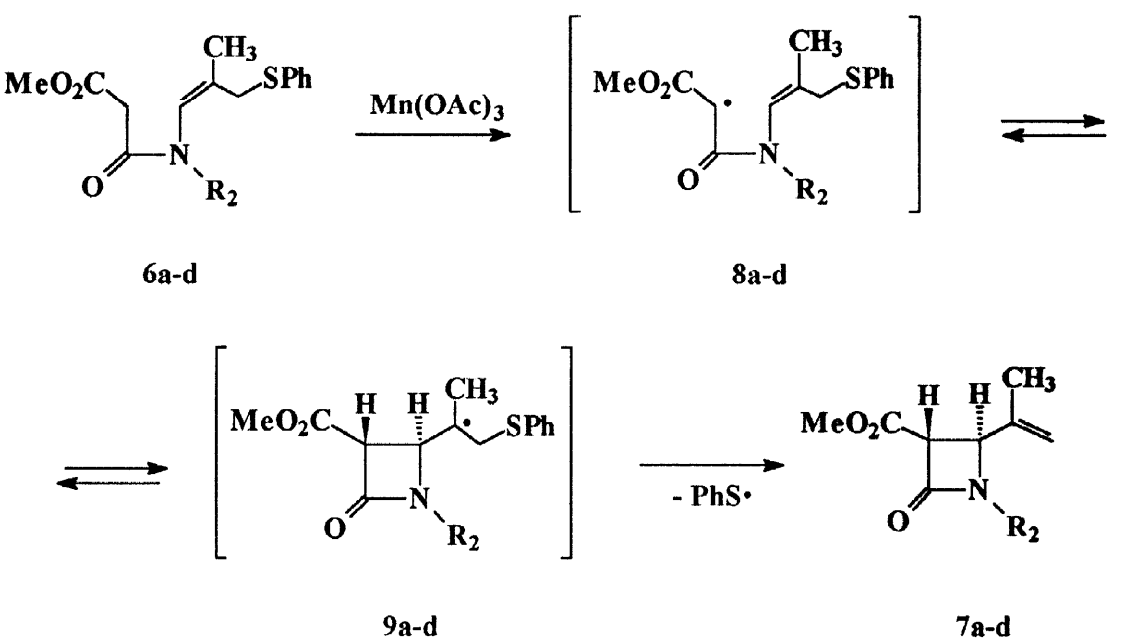



6 7

| Enamide | $R_1$ | $R_2$ | $R_3$ | Product | Yield (%)[a] |
|---|---|---|---|---|---|
| **6a** | $CO_2CH_3$ | $PhCH_2$ | $CH_3$ | **7a** | 43 |
| **6b** | $CO_2CH_3$ | Cyclohexyl | $CH_3$ | **7b** | 45 |
| **6c** | $CO_2CH_3$ | *t*-butyl | $CH_3$ | - | - |
| **6d** | $CO_2CH_3$ | $CH(CH_3)Ph$ | $CH_3$ | **7d** | 54[b] |
| **6e** | $CO_2CH_3$ | $PhCH_2$ | H | - | - |
| **6f** | $CO_2CH_3$ | $PhCH_2$ | Ph | **7f** | 58 |
| **6g** | $CO_2(CH_2)_3CH_3$ | $PhCH_2$ | $CH_3$ | **7g** | 47 |
| **6h** | $CO_2CH_2CH(CH_3)_2$ | $PhCH_2$ | $CH_3$ | **7h** | 41 |
| **6i** | $CO_2$Cyclohexyl | $PhCH_2$ | $CH_3$ | **7i** | 36 |

a)Yields refer to chromatographically isolated products; b) 1:1 mixture of diastereomers

## Scheme 2

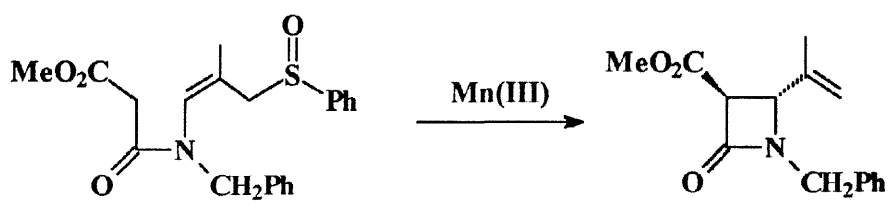



6a-d 8a-d 9a-d 7a-d

Then, we decided to modify the structure of the starting enamides **6**, in such a way to clarify the distinct effect of the substituents $R_1$, $R_2$ and $R_3$ on the reaction course.

The effect of substituents $R_2$ on nitrogen atom was examined by reacting enamides **6a-d** with Mn(III). Alkyl and benzyl groups on nitrogen led to the expected products with modest to fairly good yields. Surprisingly, the presence of a *t*-butyl group resulted even in a complete inhibition of the cyclization. This result was in contrast with the positive effect on the reaction yield of such a group on the nitrogen atom, reported in our previously developed Mn(III)-promoted oxidative method.[10-12] Then, we used N-benzyl substituted enamides to study the effect of different substituents $R_3$ on the double bond. When $R_3$ was an hydrogen atom, no cyclization took place, while the best yields were obtained when $R_3$ was a phenyl group. This behaviour was in agreement with the mechanism proposed in Scheme 2, in which the cyclization step is slow and reversible, and strongly affected by the stability of the intermediate radical **9**. Indeed its stability would decrease according to following order Ph > $CH_3$ >> H. The role of bulkier alkoxy group in ester moiety was quite negligible, as enamides **6g-i** afforded β-lactams **7g-i** in yields comparable to **7a**. We also tried to change the nature of the leaving radical, using a phenyl sulfoxide instead of a sulfide group (Scheme 3). In this case, since sulphinyl radicals have been reported to be more stable[16] and more rapidly lost[17] in β-fragmentation reactions, we expected a consistent yield increase. However, this was not observed and comparable amounts of lactam **7a** were obtained from both reactions of **6a** and **6l** in the usual conditions, indirectly confirming that the cyclization was the crucial step and, due to the rate of the fragmentation step, the latter was not or little affected by the stability of the leaving radical.

**Scheme 3**

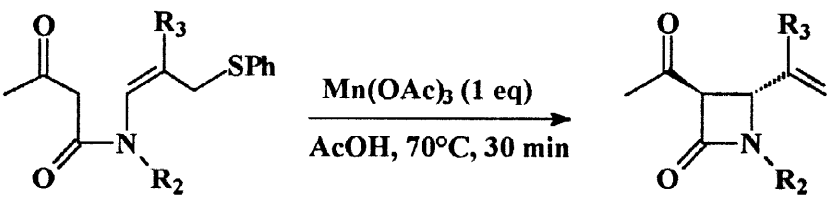



**6l** **7a (43%)**

To verify the overall stereochemistry of the transformation we used also the more easily oxidizable N-1-propenyl-3-phenylthio acetoacetamides **10**, easily prepared by a procedure developed in our laboratory.[18] In fact, since the enolizability of β-dicarbonyl compounds has been recognized as a crucial step in their oxidation by Mn(III), we chose acetyl group as the "activating" EWG substituent. Due to the great enolizability of $CH_3CO$, the corresponding β-

lactamic products **11** in our conditions could undergo further oxidation, with the possible loss of stereoselectivity. However, the obtained products were all *trans*.Yields of the azetidin-2-ones **11** obtained from compounds **10** were generally higher than from enamides **6** (see Table 2). Further experiments were carried out to evaluate the diastereoselectivity of the radical process. To this purpose we prepared enamides **10c-e**, derived from commercially available chiral amines, such as esters of α-aminoacids. Reaction of these enamides with Mn(III) gave good yields of □-lactams, but diastereomeric ratios were not as high as we expected. Just in the case of phenylglycine derived enamide **10f** diastereoselectivity in the product mixture was reasonably high (80:20 ratio).

**Table 2.**
Reaction of Enamides **10** with $Mn(OAc)_3 \cdot 2H_2O$




**10** **11**

| Enamide | $R_2$ | $R_3$ | Product | Yields (%)[a] |
|---|---|---|---|---|
| **10a** | $PhCH_2$ | $CH_3$ | **11a** | 52 |
| **10b** | cyclohexyl | $CH_3$ | **11b** | 27 |
| **10c** | $CH(CH_3)Ph$ | $CH_3$ | **11c** | 66[b] |
| **10d** | $CH(CO_2CH_2CH_3)CH_2Ph$ | $CH_3$ | **11d** | 68[c] |
| **10e** | $CH(CO_2CH_3)Ph$ | $CH_3$ | **11e** | 61[d] |

a) Yields are referred to pure, chromatographically isolated products; b) 55:45 diatereomeric mixture; c) 65:35 diastereomeric mixture; d) 80:20 diastereomeric mixture

## Conclusions

The method we report in this paper affords vinylated azetidin-2-ones in good yields starting from easily prepared precursors. The fragmentation of β-phenylthio radical intermediates involved in these reactions strongly controlled both the regiochemical (i.e. 4-*exo* vs 5-*endo-trig*) and the stereochemical outcome (formation of the only *trans*-azetidinones) of the cyclization. The reaction can be carried out with just one equivalent of oxidant, and stereoselectivity could be achieved by employing chiral substituents on the enamide nitrogen.

The formation of an unsaturated functionality at C-4 suggests the possibility of a subsequent and selective manipulation of products; moreover the presence of an acetyl group at C-3 of lactamic products renders these compounds quite valuable intermediates, as the acetyl group could provide an entry to the hydroxyethyl side chain present in many carbapenems.

## Experimental

All reagents were purchased from Fluka and Aldrich and used without further purification. $^1H$ and $^{13}C$ NMR were recorded on a Varian XL-200 Gemini spectrometer, usind $CDCl_3$ as the solvent. Chemical shift are reported in ppm and are given in δ units. Atropaldehyde was prepared according the Crossland's procedure.[19]

**General procedure of preparation of 3-phenylthio aldehydes**: 5 mmol of α,β-unsaturated aldehyde (acrolein, methacrolein, or hydratropaldehyde) were dissolved in 20 ml of $CH_2Cl_2$ and the solution was cooled to 0°C and stirred under argon athmosphere; PhSH (5 mmol) and $Et_3N$ (0.1 mmol) were then added and stirring was continued for one hour. Removal of the solvent under reduced pressure afforded 3-phenylthio aldehydes as yellow oils in nearly quantitative yields as shown by $^1H$ NMR of the crude products.

**General procedure of preparation of imines** (modified Texier-Boullet's procedure):[20] the freshly prepared β-phenylthio aldehyde (5 mmol) and a suitable amine (5 mmol) were adsorbed on basic $Al_2O_3$ (3 g); the resulting powder was shaked and kept at room temperature for two hours; then it was eluted with $CH_2Cl_2$ and the solvent removed under reduced pressure to afford the crude imine in good yields as an oil (the imine was used without further purification).

**Preparation of enamides**: α-Methoxycarbonyl-enamides **6a-f**, were obtained by acylation of imines with methyl malonyl chloride[14]; enamides **6g-i** were obtained by DMAP-catalyzed transesterification of enamide **6a** with corresponding alcohols; acetoacetyl enamides **10a-e** were prepared refluxing imines with 2,2,6-trimethyl-1,3-dioxin-4-one.[17]

**General procedure for the radical cyclization of enamides**: 1 mmol of enamide was dissolved in glacial acetic acid (10 ml) under an argon athmosphere, then $Mn(OAc)_3 2H_2O$ (1 mmol, 268 mg) was added. The resulting mixture was heated at 70°C until its brown colour disappeared. The reaction mixture was allowed to cool at room temperature, poured into water (100 ml) and then extracted with $CH_2Cl_2$ (3 x 20 ml). The combined extracts were washed with a saturated $NaHCO_3$ solution until AcOH was removed, then with water, and finally dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was separated on a silica gel column eluted with light petroleum ether/$Et_2O$ to afford β-lactamic products as oils.

**Compound 7a** - $^1H$ NMR ($CDCl_3$, δ): 1.62 (3H, s); 3.75 (3H, s), 3.78 (1H, d, J = 2.5 Hz), 3.93 (1H, d, J = 15.0 Hz), 4.15 (1H, d, J = 2.5 Hz), 4.75 (1H, d, J = 15.0 Hz), 5.01 (2H, s), 7.20-

7.40 (5H, m). $^{13}C$ NMR ($CDCl_3$, ppm): 16.85, 45.13, 52.47, 58.73, 58.91, 116.33, 127.92, 128.41, 128.84, 134.90, 139.98, 162.11, 167.64. IR ($CHCl_3$): 2960, 1757, 1733, 1458, 1276. MS (EI) m/z (rel.int.): 166 (5), 126 (43), 125 (47), 124 (41), 110 (41), 94 (53), 90 (100), 66 (30), 64 (27). Anal. Calcd. For $C_{15}H_{17}NO_3$: C 69.48, H 6.61, N 5.40. Found C 69.50, H 6.65, N 5.35.

**Compound 7b** - $^1H$ NMR ($CDCl_3$, δ): 1.0-2.0 (13H, m), 3.30 (1H, m), 3.54 (1H, d, J = 2.4 Hz), 3.70 (3H, s), 4.32 (1H, d, J = 2.4 Hz), 5.00 (1H, s), 5.12 (1H, s); $^{13}C$ NMR ($CDCl_3$, ppm): 16.35, 24.71, 24.86, 25.01, 30.04, 30.41, 52.42, 53.24, 57.61, 58.26, 116.47, 141.40, 161.66, 167.93. IR ($CHCl_3$): 3025, 2940, 1750, 1732, 1524, 1430, 1251, 1208. MS m/z (rel.int.): 250 (3), 217 (7), 191 (6), 126 (18), 125 (100), 124 (64), 110 (57), 94 (58), 66 (43), 42 (27). Anal. Calcd. For $C_{14}H_{21}NO_3$: C 66.91, H 8.42, N 5.57; Found C 66.85, H 8.35, N 5.30.

**Compound 7d** - $^1H$ NMR ($CDCl_3$, δ), 1:1 diastereomeric mixture: 1.51 (3H, s), 1.56 (3H, d, J = 7.2 Hz), 1.64 (3H, s), 1.76 (3H, d, J = 7.2 Hz), 3.70 (2H, m), 3.72 (3H, s), 3.75 (3H, s), 4.15 (1H, dd, J = 2.6 Hz), 4.16 (1H, d, J = 2.6 Hz), 4.45 (1H, q, J = 7.2 Hz), 4.83 (1H, q, J = 7.2 Hz), 5.00 (4H, m), 7.20-7.40 (5H, m); $^{13}C$ NMR ($CDCl_3$, ppm): 16.25, 16.46, 18.42, 19.57, 52.48, 53.26, 54.50, 57.46, 58.05, 58.44, 59.34, 116.56, 117.07, 126.79, 127.10, 127.65, 128.54, 139.57, 140.05, 140.44, 140.82, 161.60, 161.67, 167.38, 167.68. IR ($CHCl_3$): 3030, 1753, 1737, 1445, 1156, 1129. MS m/z (rel.int.) : 273 (2), 169 (15), 132 (34), 126 (20), 105 (100), 95 (21), 79 (10), 67 (13). Anal. calcd for $C_{16}H_{19}NO_3$: C 70.31, H 7.01, N 5.12; found C 70.35, H 6.95, N 5.25.

**Compound 7f** - $^1H$ NMR ($CDCl_3$, δ) : 3.75 (3H, s), 3.78 (1H, d, J = 2.2 Hz), 4.00 (1H, d, J = 15.1 Hz), 4.61 (1H, d, J = 2.2 Hz), 4.93 (1H, d, J = 15.1 Hz), 5.32 (1H, s), 7.20-7.40 (10H, m). $^{13}C$ NMR ($CDCl_3$, ppm): 45.12, 52.63, 55.91, 61.93, 115.00, 126.20-129.02, 162.49, 167.49. IR ($CHCl_3$) : 3030, 1760, 1733, 1130. MS m/z (rel.int.): 188 (20), 157 (21), 129 (100), 91 (57), 76 (10). Anal. calcd for $C_{20}H_{19}NO_3$: C 74.75, H 5.96, N 4.36; found C 74.75, H 5.90, N 4.15.

**Compound 7g** - $^1H$ NMR ($CDCl_3$, δ) : 0.95 (3H, t, J = 7.5 Hz), 1.37 (2H, se, J = 7.5 Hz), 2.18 (5H, m), 3.78 (1H, d, J = 2.6 Hz), 3.94 (1H, d, J = 15.0 Hz), 4.18 (3H, m), 4.80 (1H, d, J = 15.0 Hz), 5.03 (2H, s), 7.20-7.40 (5H, m); $^{13}C$ NMR ($CDCl_3$, ppm) : 13.66, 17.11, 30.46, 45.16, 58.82, 59.31, 65.56, 116.18, 127.78, 128.25, 128.72, 134.82, 139.90, 162.03, 167.09. IR ($CHCl_3$) : 2965, 1758, 1726, 1275, 1214, 1131. MS m/z (rel.int.): 301 (11), 169 (15), 154 (13), 132 (12), 113 (67), 112 (50), 97 (15), 96 (46), 91 (100), 67 (31), 65 (20). Anal. calcd for $C_{18}H_{23}NO_3$ : C 71.73, H 7.69, N 4.64; found C 71.05, H 7.81, N 4.54.

**Compound 7h** - $^1H$ NMR ($CDCl_3$, δ): 0.95 (6H, d, J = 7.0 Hz), 1.18 (3H, s), 1.95 (1H, eptuplet, J = 7.0 Hz), 3.78 (1H, d, J = 2.4 Hz), 3.94 (1H, d, $J_{gem}$ = 15.0 Hz), 3.95 (2H, d, J = 7.0 Hz), 4.15 ( 1H, d, J = 2.4 Hz), 4.81 (1H, d, $J_{gem}$ = 15.0 Hz), 5.03 (2H, s), 7.20-7.40 (5H, m); $^{13}C$

NMR ($CDCl_3$, ppm) : 17.12, 18.94, 27.61, 15.18, 58.83, 59.35, 71.61, 116.11, 127.69, 128.26, 128.73, 134.83, 139.94, 161.98, 167.02. IR ($CHCl_3$): 3075, 3030, 1759, 1727, 1130. MS m/z (rel.int.): 301 (M, 25%), 169 (11%), 113 (67%), 112 (27%), 95 (71%), 91 (100%), 67 (38%). Anal. Calcd for $C_{18}H_{23}NO_3$ : C 71.73, H 7.69, N 4.64; found C 71.47, H 7.36, N 4.70.

**Compound 7i** - $^1H$ NMR ($CDCl_3$, δ) : 1.20-2.00 (13H, m), 3.74 (1H, d, J = 1.8 Hz), 3.91 (1H, d, $J_{gem}$ = 15 Hz), 4.12 (1H, d, J = 2.2 Hz), 4.81 (1H, d, $J_{gem}$ = 15.2 Hz), 4.85 (1H, m), 5.02 (2H, s), 7.20-7.40 (5H, m); $^{13}C$ NMR ($CDCl_3$, ppm) : 17.17, 23.49, 25.25, 31.36, 45,11, 58.87, 59.72, 74.15, 115.99, 127.75, 128.22, 128.71, 134.90, 140.03, 162.18, 166.49. IR ($CHCl_3$): 3025, 2945, 1759, 1720, 1459, 1269, 1130. MS m/z (rel.int.): 327 (M, 7%), 154 (9%), 113 (100%), 95 (47%), 91 (83%), 67 (38%). Anal calcd for $C_{20}H_{25}NO_3$ : C 73.36, H 7.69, N 4.27; found C 73.10, H 7.40, N 4.20.

**Compound 11a** - $^1H$ NMR ($CDCl_3$, δ): 1.60 (3H, s), 2.28 (3H, s), 3.91 (1H, d, J = 15.4 Hz), 3.93 (1H, d, J = 2.5 Hz), 4.28 (1H, D, J = 2.5 Hz), 4.68 (1H, d, J = 15.4 Hz), 4.97 (2H, m) 7.10-7.30 (5H, m); $^{13}C$ NMR ($CDCl_3$, ppm): 17.15, 29.74, 45.18, 56.93, 67.52, 115.89, 128.01, 128.48, 128.95, 135.07, 140.30, 166.38, 196.43. IR ($CHCl_3$): 3025, 1749, 1713, 1641, 1369, 1130. MS m/z (rel.int.) : 243 (6), 202 (10), 152 (42), 111 (10), 95 (91), 91 (100), 67 (25), 43 (42). Anal. calcd for $C_{15}H_{17}NO_2$ : C 74.05, H 7.04, N 5.76; found C 74.10, H 7.05, N 5.65.

**Compound 11b** - $^1H$ NMR ($CDCl_3$, δ): 1.0-2.0 (13H, m), 2.31 (3H, s), 3.30 (1h, m), 3.84 (1H, d, J = 2.4 Hz), 4.48 (1H, d, J = 2.4 Hz), 5.00 (1H, m), 5.15 (1H, s); $^{13}C$ NMR ($CDCl_3$, ppm) : 16.84, 24.92, 25.07, 25.19, 29.93, 30.27, 30.68, 53.34, 56.37, 66.21, 115.92, 141.42, 161.513, 200.07; IR ($CHCl_3$): 3025, 2940, 1741, 1712, 1525, 1430, 1251, 1207; MS m/z (rel.int.) : 152 (24), 109 (8), 94 (100), 66 (27), 42 (63). Anal. calcd for $C_{14}H_{21}O_2N$ : C 71.44, H 9.00, N 5.95; found : C 70.95, H 8.91, N 5.78.

**Compound 11c** - $^1H$ NMR (55:45 diastereomeric mixture) ($CDCl_3$, δ); for major isomer: 1.50 (3H, s), 2.72 (3H, d, J = 8.0 Hz), 2.28 (3H, s), 3.86 (1H, d, J = 2.6 Hz), 4.29 (1H, d, J = 2.6 Hz), 4.42 (1H, q, J = 8.0 Hz), 5.00 (2H, m), 7.20-7.40 (5H, m); for minor isomer 1.55 (3H, d, J = 8.0 Hz) 1.62 (3H, s), 2.23 (3H, s), 3.86 (1H, d, J = 2.6 Hz), 4.53 (1H, d, J = 2.6 Hz), 4.76 (1H, q, J = 8.0 Hz), 5.00 (2H, m), 7.20-7.40 (5H, m); $^{13}C$ NMR ($CDCl_3$, ppm): 16.52, 16.71, 19.34, 19.86, 24.92, 53.49, 54.34, 56.62, 57.58, 65.94, 66.48, 93.75, 116.051, 116.547, 126.00-129.00, 140.51, 141.07, 162.65, 199.66. IR ($CHCl_3$): 3070, 1745, 1713, 1641, 1402, 1360, 1286, 1117. MS m/z (rel.int.): 257 (4), 216 (4), 152 (45), 132 (27), 105 (100), 95 (56), 77 (23), 67 (13), 43 (42). Anal. calcd for $C_{16}H_{19}NO_2$ : C 74.68, H 7.44, N 5.44; found C 74.75, H 7.35, N 5.60.

**Compound 11d** - $^1H$ NMR (65:35 diastereomeric mixture) ($CDCl_3$, δ); for the major isomer: 1.26 (3H, s), 2.27 (3H, s), 3.27 (1H, dd, $J_1$ = 13.9 Hz, $J_2$ = 5.2 Hz), 3.46 (1H, dd, $J_1$ = 13.9 Hz, $J_2$ = 10.9 Hz), 3.74 (3H, s), 3.77 (1H, d, J = 2.5 Hz), 3.95 (1H, dd, $J_1$ = 10.9 Hz, $J_2$ = 5.2 Hz),

4.36 (1H, d, J = 2.5 Hz), 4.66 (1H, s), 4.78 (1H, s) 7.20-7.30 (5H, m); for the minor isomer: 1.60 (3H, s), 2.24 (3H, s), 3.10-3.30 (2H, m), 3.71 (3H, s), 3.84 (1H, d, J = 2.5 Hz), 4.03 (1H, d, J = 2.5 Hz), 4.15 (1H, dd, $J_1$ = 9.4 Hz, $J_2$ = 6.6 Hz), 4.96 (1H, s), 5.02 (1H, s), 7.10-7.30 (5H, m); $^{13}$C NMR ($CDCl_3$, ppm): 16.46, 16.83, 29.46, 29.54, 35.43, 35.56, 52.56, 52.65, 57.65, 57.81, 59.15, 59.32, 66.43, 66.83, 115.69, 116.95, 127.077, 128.60, 128.71, 128.95, 129.03, 136.97, 139.87, 164.09. IR ($CHCl_3$): 3030, 2960, 1758, 1746, 1715, 1458, 1371, 1287, 1217, 1180, 1129, 1108. MS m/z (rel.int.):315 (2), 256 (9), 230 (10), 162 (61), 111 (40), 95 (89), 91 (100), 67 (31), 43 (80). Anal. calcd for $C_{18}H_{21}NO_4$ : C 68.55, H 6.71, N 4.44; found C 68.60; H 6.65, N 4.55.

**Compound 11e** - $^1$H NMR (8:2 diastereomeric mixture) ($CDCl_3$, δ); for major isomer:1.28 (3H, s), 2.32 (3H, s), 3.73 (3H, s), 3.81 (1H, d, J = 2.5 Hz), 4.67 (1H, s), 4.80 (1H, d, J = 2.5 Hz), 4.85 (1H, s), 5.37 (1H, s), 7.20-7.40 (5H, m); for minor isomer: 1.71 (3H, s), 2.27 (3H, s), 3.71 (3H, s), 3.91 (1H, d, J = 2.5 Hz), 4.37 (1H, d, J = 2.5 Hz), 4.94 (1H, s), 5.18 (1H, s), 7.20-7.40 (5H, m); $^{13}$C NMR ($CDCl_3$, ppm): 16.15, 17.00, 29.46, 29.70, 52.76, 58.67, 59.11, 60.50, 61.69, 66.44, 66.81, 116.10, 116.19, 128.00-129.00, 130.41, 132.16, 140.16, 163.36, 169.24, 199.15. IR ($CHCl_3$): 3025, 1757, 1736, 1715, 1368, 1207, 1132. MS m/z (rel.int.): 242 (38), 200 (8), 158 (100), 152 (13) , 132 (100), 104 (15), 95 (48), 77 (20), 67 (18), 43 (37). Anal. calcd for $C_{17}H_{19}NO_4$ : C 67.76, H 6.36, N 4.65; found C 67.75, H 6.25, N 4.75.

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