Pergamon

Tetrahedron Letters 42 (2001) 8409–8413

TETRAHEDRON LETTERS

Cleavage of the N(1)–C(4) bond of 4-(4′-hydroxyphenyl)-azetidine-2-ones via quinone methide intermediates

Larry A. Cabell, Loren W. Hedrich and John S. McMurray*

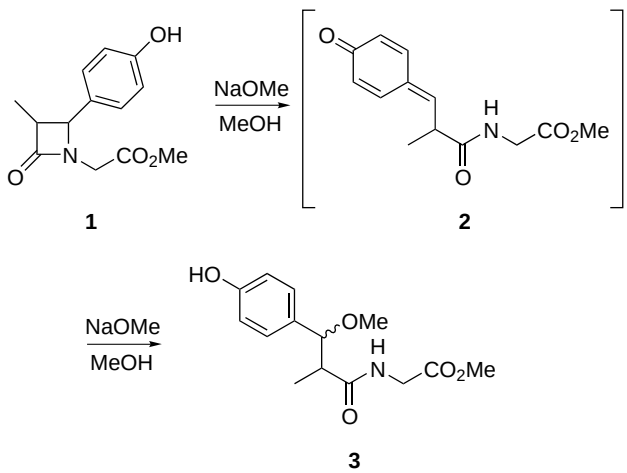
The University of Texas M. D. Anderson Cancer Center, Department of Neuro-Oncology, Box 316, 1515 Holcombe Blvd, Houston, TX 77030, USA

Received 17 July 2001; accepted 2 October 2001

Abstract—In this paper we describe a novel ring-opening reaction in which 4-(4′-hydroxyphenyl)-azetidine-2-ones, on treatment with base, rearrange to quinone methide intermediates with concomitant cleavage of the C(4)–N(1) bond. The quinone methide intermediate serves as a substrate for Michael-type 1,6 conjugate additions.

Since the discovery of penicillin, β-lactams have generated great interest in organic and medicinal chemistry. Because of the inherent ring strain, this four-membered heterocycle is susceptible to reactions that cleave one or more of its bonds. The most common is cleavage of the amide bond, or 1,2 cleavage. This is the basis of action of the β-lactam-containing antibiotics[1] as well as the recently developed inhibitors of human leukocyte elastase[2] and human cytomegalovirus protease.[3] In synthetic chemistry, 1,2-ring opening reactions of β-lactams have been used for the preparation of macrocyclic alkaloids,[4] cyclic polyamines,[5] taxoids,[6] sphingolipids,[7] and β-amino acids[8] to name a few, thus underscoring the utility of this heterocycle as a synthon for the construction of other compounds.[9] Cleavage of the C(2)–C(3)[10] and C(3)–C(4)[11] bonds are also known and these are often involved in ring expansion reactions to form heterocycles such as *N*-carboxyanhydrides,[10a–e] pyrazines and oxazines.[11c,d] Cleavage of the N(1)–C(4) bond of 4-aryl-azetidine-2-ones by hydrogenolysis is well known and has been applied in the synthesis of novel amino acids and peptidomimetics.[12] β-Lactams possessing heteroatoms attached to C(4) can undergo 1,4 cleavage under acidic,[13] basic,[14] and neutral[15] conditions, depending on the nature of the functional groups at positions 1 and 3.

We report here a unique cleavage of the N(1)–C(4) bond of monocyclic β-lactams that leads to α,β-disubstituted 4-hydroxyhydrocinnamides. For example, when 4-(4′-hydroxyphenyl)-3-methyl-1-methoxycarbonylmethyl azetidine-2-one **1**, was treated with methanolic sodium methoxide, the methyl ether, 3-methoxy-3-(4-hydroxyphenyl)-2-methylpropionyl glycine methyl ester **3**, was the major product (>90%), as judged by ESI-mass spectrometry, reverse phase HPLC, and NMR (Scheme 1).



1 **2** **3**

Scheme 1.

Keywords: β-lactam; quinone methide; 1,6 conjugate addition.

* Corresponding author. Tel.: 713-745-3763; fax: 713-745-1183; e-mail: jmcmurra@mdanderson.org

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01849-4

We hypothesize that this process is initiated by phenolate formation followed by rearrangement to an intermediate quinone methide, **2** with concomitant cleavage of the 1,4 bond. The very reactive quinone methide is quenched by methoxide anion in a Michael-type 1,6 conjugate addition at the benzylic carbon to give the methyl ether, **3**.[16]

Treatment of the corresponding 4-phenyl- and 4-(4′-benzyloxyphenyl)-azetidine-2-ones under identical conditions resulted in recovery of only starting material (Scheme 2). The lack of reactivity of these analogues underscores the necessity of the 4′-hydroxyl group in the 1,4-cleavage reaction and strongly supports the quinone methide mechanism in the cleavage of 4-(4′-hydroxyphenyl) β-lactams.

β-Lactam **1** was a mixture of *trans* enantiomers.[17] Due to attack of the methoxide on either side of the flat quinone methide system, each enantiomer of **1** could potentially produce two diastereomers of **3**. The (3*R*,4*S*) β-lactam would give the (2*R*,3*S*) and (2*R*,3*R*) 3-methoxy propionamides, respectively. Likewise, (3*S*,4*R*) **1** would give (2*S*,3*S*) and (2*S*,3*R*) products, respectively. Because (2*R*,3*S*) **3** and (2*S*,3*R*) **3** are enantiomers as are (2*R*,3*R*) **3** and (2*S*,3*S*) **3**, the product would appear as two compounds. In fact, **3** was a mixture of two methyl ethers formed in a ratio of 3:2 as judged by reverse phase HPLC, ^{1}H NMR and MS.

Using chiral chromatography, we demonstrated the presence of all four of the 3-methoxypropionamide stereoisomers. Starting β-lactam **1** was separated by chiral HPLC into the individual enantiomers (4.6×250 mm Chiralpak AS column (Chiral Technologies, Exton, PA), 10% EtOH/hexane, 1 ml/min, multiple runs). The order of elution from the chiral column was (+)-**1** followed by (−)-**1**. The absolute configurations at C(3) and C(4) of the separated enantiomers are currently unknown. Each individual β-lactam was subjected to the NaOMe/MeOH ring-opening reaction and both produced the two methyl ethers in a ratio of 3:2 as did the racemic mixture of **1**. The diastereomers of **3** were separated by chiral HPLC an a different column (4.6× 250 mm Phenomenex 2205 column, 10% EtOH/hexane, 1 ml/min). The chromatogram of the methyl ethers produced from (+)-**1** was identical to that from (−)-**1**. The first eluting product from both chromatograms gave identical mass and NMR spectra confirming that they are enantiomers. The second eluting compounds also gave identical analytical signatures. These reactions were carried out on <10 mg each of (+)-**1** and (−)-**1** so the absolute configurations of the stereocenters of the stereoisomers of **3** are not known at this time.

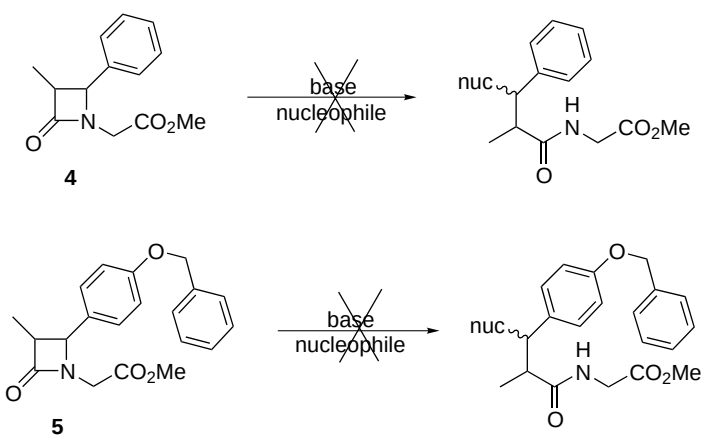
To test the influence of the size of the substituent at C(3) on stereochemical outcome, a series of β-lactams with increasing sized alkyl substituents was synthesized and treated with NaOMe/MeOH (Table 1).[17] Again two products were formed. In the series Me, Et, iPr, the product ratios increased with increasing size of the alkyl group. These results indicate that the size of the substituent at C(3) plays a significant role in the stereochemical outcome of the Michael addition at C(4).

When using nitromethane as the Michael donor in the presence of NaOMe in MeOH and **1a** as the starting material, competition between methoxide and the nitromethane anion occurred giving a mixture of products. In the aprotic solvent, DMF, with DBU as the base, the reaction proceeded smoothly at room temper-

Table 1. Product ratios of β-lactam ring-opening reaction products[18]

C(3) substituent	NaOMe/MeOH		CH_3NO_2/DBU/DMF	
	% Yield	Product ratio[a]	% Yield	Product ratio
1a, Me	94	3:2	90	2:1
1b, Et	>98	2:1	89	2.7:1
1c, iPr	95	4.9:1	99	[b]
1d, $CH_2C_6H_{11}$	96	3:1	93	4:1

[a] Product ratios were determined from integration of the amide proton resonances in the ^{1}H NMR spectra of crude products.
[b] Only one stereoisomer was detected.



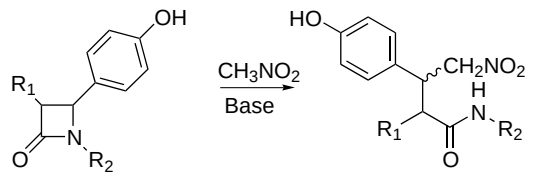
Scheme 2.

ature giving only nitromethane adducts, **6**, in good yield[19] (Scheme 3). The substituent effects at C(3) paralleled those of the NaOMe/MeOH reaction (Table 1). However, the iPr group promoted high stereoselectivity as only one stereoisomer was detectable.

Interestingly, ring-opening of a series of β-lactams with potassium *tert*-butoxide and nitromethane in DMF resulted in stereoselective Michael addition. These reactions were carried on a multigram scale[20] and produced only one set of enantiomers of **6** in excellent yields (Table 2). Again the configurations of the stereocenters is currently unknown.

When the substituent at C(3) was phenoxy (**7**), treatment with NaOMe/MeOH did not produce the corresponding 3-methoxypropionamide. Instead, the elimination product, 2-phenoxy-4-hydroxycinnamylglycine methyl ester, **9**, was formed (Scheme 4). Cinnamide formation also occurred on treatment of **7** with DBU in DMF. As before, analogues possessing either a hydrogen atom or benzyloxy group at the 4 position of the phenyl ring were subjected to treatment with NaOMe/MeOH or DBU/DMF and no cinnamide was formed in either case. Therefore, conversion of **7** to **9** does not proceed by simple β-elimination. Rather, the starting β-lactam most likely opened up to the quinone methide intermediate **8**, which rearranged to give the cinnamide.

In summary, we report a novel reaction in which 4-(4′-hydroxyphenyl) β-lactams undergo base-mediated cleavage of the N(1)–C(4) bond via formation of a quinone methide. When the substituent at C(3) is alkyl, the quinone methide can then serve as an acceptor in 1,6 conjugate addition reactions. Asymmetric induction occurs in the conjugate addition step. When KO′Bu is used with nitromethane the reaction gives highly stereoselective Michael addition products. When the substituent at C(3) is phenoxy, the quinone methide rearranges to the corresponding 4-hydroxy cinnamide.

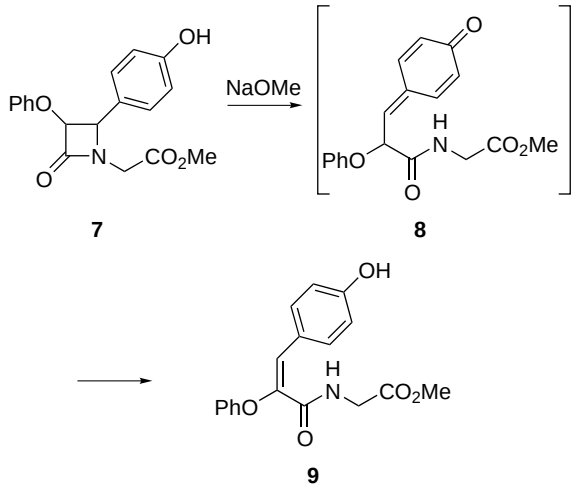


1 **6**

Scheme 3.

Table 2. Ring-opening of β-lactams with KO′Bu and CH_3NO_2

	R_1	R_2	% Yield
6a	Me	CH_2CO_2Me	70
6e	$CH_2C_6H_{11}$	Ph	75
6f	CH_2Ph	Ph	76



7 **8** **9**

Scheme 4.

Acknowledgements

We gratefully acknowledge financial support from the Physicians Referral Service of the M. D. Anderson Cancer Center (L.W.H.), the National Cancer Institute, #CA53617 (J.S.M., L.A.C.) and the Texas Higher Education Coordinating Board, #15-073 (J.S.M.). We also acknowledge the NCI Cancer Center Support Grant CA16672 for the support of our NMR and mass spectrometry facilities.

References

1. Tipper, D. J. In *Beta-Lactam Antibiotics for Clinical Use*; Queener, R. B.; Webber, J. A.; Queener, S. W., Eds.; Marcel Dekker: New York, 1986; Chapter 2, pp. 17–48.
2. (a) Shah, K. S.; Dorn, C. P.; Finke, P. E.; Hale, J. J.; Hagmann, W. K.; Brause, K. A.; Chandler, G. O.; Kissinger, A. L.; Ashe, B. M.; Weston, H.; Knight, W. B.; Maycock, A. L.; Dellea, P. S.; Fletchet, D. S.; Hand, K. M.; Mimford, R. A.; Underwood, D. J.; Doherty, J. B. *J. Med. Chem.* **1992**, *35*, 3745–3754; (b) Macchia, B.; Gentili, D.; Macchia, M.; Mamone, F.; Martinelli, A.; Orlandini, E.; Rossello, A.; Cercignani, G.; Pierotti, R.; Allegretti, M.; Asti, C.; Caselli, G. *Eur. J. Med. Chem.* **2000**, *35*, 53–67.
3. (a) Yoakim, C.; Ogilvie, W. W.; Cameron, D. R.; Chabot, C.; Guse, I.; Hache, B.; Naud, J.; O'Meara, J. A.; Plante, R.; Deziel, R. *J. Med. Chem.* **1998**, *41*, 2882–2891; (b) Borthwick, A. D.; Weingarten, G.; Haley, T. M.; Tomaszewski, M.; Wang, W.; Hu, Z. H.; Bedard, J.; Jin, H. L.; Yuen, L.; Mansour, T. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 365–370.
4. Wasserman, H. H.; Matsuyama, H. *J. Am. Chem. Soc.* **1981**, *103*, 462–464.
5. Crombie, L.; Jones, R. C. F.; Osborne, S.; Mat-Zin, R. *J. Chem. Soc., Chem. Commun.* **1983**, 959–960.
6. (a) Boge, T. C.; Georg, G. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997; pp. 1–44; (b) Ojima, I.; Habus, I.; Zhao, M.; Georg, G. I.; Jayasinghe, L. R. *J. Org. Chem.* **1991**, *56*, 1681–1683.

7. Makamura, T.; Shiozaki, M. *Tetrahedron Lett*. **1999**, *40*, 9063–9064.
8. (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Amino Acids* **1999**, *16*, 321–343; (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997; pp. 279–357.
9. Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755–1802.
10. (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Amino Acids* **1999**, *16*, 321–343; (b) Palomo, C.; Oiarbide, M.; Esnal, A.; Landa, A.; Miranda, J. I.; Linden, A. *J. Org. Chem*. **1998**, *63*, 5838–5846; (c) Palomo, C.; Aizpurua, J. M.; Cuevas, C.; Urchegui, R.; Linden, A. *J. Org. Chem*. **1996**, *61*, 4400–4404; (d) Alcaide, B.; Aly, M. F.; Sierra, M. A. *J. Org. Chem*. **1996**, *61*, 8819–8825; (e) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Carreaux, F.; Cuevas, C.; Maneiro, E.; Ontoria, J. M. *J. Org. Chem*. **1994**, *59*, 3123–3130; (f) Kita, Y.; Shibata, N.; Yoshida, N.; Kawano, N.; Matsumoto, K. *J. Org. Chem*. **1994**, *59*, 938–939; (g) Kita, Y.; Shibata, N.; Kawano, N.; Yoshida, N.; Matsumoto, K.; Takebe, Y. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2321–2329; (h) Alcaide, B.; Perez-Castells, J.; Polanco, C.; Sierra, M. A; Alcaide, B.; Miranda, M.; Perez-Castells, J.; Sierra, M. A. *J. Org. Chem*. **1993**, *58*, 297–298.
11. (a) Bertha, F.; Fetter, J.; Kajtar-Peredy, M.; Lempert, K.; Czira, G. *Tetrahedron* **1998**, *54*, 15227–15242; (b) Sapi, A.; Fetter, J.; Lempert, K.; Kajtar-Peredy, M.; Czira, G. *Tetrahedron* **1997**, *53*, 12729–12738; (c) Fetter, J.; Vasarhelyi, H.; Kajtar-Peredy, M.; Lempert, K.; Tamas, J.; Czira, G. *Tetrahedron* **1995**, *51*, 4763–4778; (d) Alcaide, B.; Martin-Cantalejo, Y.; Rodriquez-Lopez, J.; Sierra, M. A. *J. Org. Chem*. **1993**, *58*, 4767–4770; (e) Alcaide, B.; Moreno, A. M.; Rodríguez-Vicente, A.; Sierra, M. A. *Tetrahedron: Asymmetry* **1996**, *7*, 2203–2206; (f) Bose, A. K.; Kugajevsky, I. *Tetrahedron* **1967**, *23*, 957–963.
12. Examples of 1,4 ring-opening via reduction of 4-aryl β-lactams in the 'β-lactam synthon method' are reviewed in: (a) Ojima, I. *Acc. Chem. Res*. **1995**, *28*, 383–389. Other examples include (b) Banik, B. K.; Barakat, K. J.; Wagle, D. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem*. **1999**, *64*, 5746–5753; (c) Bertha, F.; Fetter, J.; Kajtá-Peredy, M.; Lempert, K. *Tetrahedron* **1999**, *55*, 5567–5580; (d) Srirajan, V.; Desmukh, A. R. A. S.; Puranik, V. G.; Bhawal, B. M. *Tetrahedron: Asymmetry* **1996**, *7*, 2733–2738.
13. (a) Opitz, G.; Kock, J. *Angew. Chem., Int. Ed*. **1962**, *2*, 152; (b) Perelman, M.; Mizak, S. *J. Am. Chem. Soc*. **1963**, *84*, 4988–4989; (c) Nisole, C.; Uriac, P.; Toupet, L.; Huet, J. *Tetrahedron* **1993**, *49*, 889–900; (d) Ref. 10f; (e) Ref. 10g.
14. (a) Alcaide, B.; Aly, M. F.; Sierra, M. A. *J. Org. Chem*. **1996**, *61*, 8819–8825; (b) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Tetrahedron: Asymmetry* **1999**, *10*, 4841–4849.
15. (a) Effenberger, F.; Gleiter, R. *Chem. Ber*. **1964**, *97*, 1576–1583; (b) Effenberger, F.; Kiefer, G. *Angew. Chem., Int. Ed*. **1967**, *6*, 951–952; (c) Effenberger, F.; Fischer, P.; Prossel, G.; Kiefer, G. *Chem. Ber*. **1971**, *104*, 1987–2001; (d) Effenberger, F.; Prossel, G.; Fischer, P. *Chem. Ber*. **1971**, *104*, 2002–2012.
16. β-Lactam ring-opening with NaOMe/MeOH. General protocol: A 25 ml flask was charged with 0.1 mmol of the desired β-lactam in 1 ml of dry MeOH. To this was added 100 μl of 1 M NaOMe/MeOH and the reaction was stirred for 24 h at room temperature. The base was quenched with 6 ml of 2% $KHSO_4$ (aq.) and total reaction volume reduced in vacuo. CH_2Cl_2 (20 ml) was added and washed with 5% aq. $NaHCO_3$ (20 ml), followed by brine (20 ml). The organic layer was dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Product purity was assessed by HPLC and diastereomer ratios were determined by integration of the amide peaks from NMR spectra in DMSO-d_6.
17. β-Lactams **1a–d**, were synthesized by the Staudinger reaction, i.e. the [2+2] cycloaddition of the ketene derived from the appropriate acid chloride and *N*-4-trityloxybenzylidene using Bu_3N in refluxing toluene (Browne, M.; Burnett, D. A.; Caplen, M. A.; Chen, L.-Y.; Clader, J. W.; Domalski, M.; Dugar, S.; Pushpavanam, P.; Sher, R.; Vaccaro, W.; Viziano, M.; Zhao, H. *Tetrahedron Lett*. **1995**, *36*, 2555–2558). The trityl group was subsequently removed with mild acid. As is typical of this synthetic method, the product was a racemic mixture of *trans* stereoisomers ($J_{3H-4H}=2.2$ Hz). All β-lactams in this study gave correct ^1H, ^{13}C NMR, and mass spectra and elemental analysis.
18. Molecular weights (M–H) of the products of Table 1 determined on a Fisons Platform II single quadrupole mass spectrometer equipped with an electrospray ionization source in negative ion (see Table 3).
19. β-Lactam ring-opening with nitromethane/DBU. General protocol: A 25 ml flask was charged with 0.1 mmol of the desired β-lactam in 1 ml of dry DMF. To this solution was added 10.8 μl (0.2 mmol) of nitromethane followed by 15 μl (0.2 mmol) of DBU and the reaction was stirred for 24 h at room temperature. The DBU was quenched with 6 ml of 2% $KHSO_4$ (aq.) and the volume was reduced in vacuo. Workup and analysis was the same as in the case of NaOMe/MeOH reactions.

Table 3.

Substituent at C(3)		NaOMe/MeOH			CH_3NO_2/DBU	
		Calcd	Found		Calcd	Found
Me	**3a**	281.13	280.4	**6a**	310.12	309.2
Et	**3b**	295.14	294.3	**6b**	324.13	323.2
iPr	**3c**	309.16	310.1[a]	**6c**	338.15	336.9
$CH_2C_6H_{11}$	**3d**	363.20	362.2	**6d**	392.19	391.3

[a] Spectrum was run in positive ion mode and is reported as (M+H).

20. Representative procedure for ring opening with nitromethane and KO^{t}Bu: synthesis of 3-nitromethyl-3-(4-hydroxyphenyl)-2-methylpropionyl glycine methyl ester **6a**. Compound **1** (2 g, 8.0 mmol) and 869 μl (16.1 mmol) of nitromethane were dissolved in 8.0 ml of dry DMF. 8 ml (8.0 mmol) of 1 M KO^{t}Bu (THF) was added and the solution stirred for 36 h. The solvents were removed in vacuo. The residue was taken up in EtOAc washed with 2% $KHSO_4$ (aq.) and brine. After drying (Na_2SO_4) and evaporation ^{1}H NMR indicated the presence of only one stereoisomer. The product was isolated by silica gel chromatography (EtOAc/hexane) to give 1.74 g of product (70% yield). Mp 132.6–132.9°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (s, 1H), 7.92 (m, 1H), 7.10 (d, $J=8.0$ Hz, 2H), 6.77 (d, $J=8.0$ Hz, 2H), 4.94 (dd, $J=12$ Hz, $J_2=4$ Hz, 1H), 4.77 (t, $J=12$ Hz, 1H), 3.94 (dq, $J=18$ Hz, $J_2=6$ Hz, 2H), 3.64 (s, 3H), 3.51 (m, 1H), 2.77 (m, 1H), 0.92 (d, $J=7$ Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.14, 171.14, 157.71, 130.11, 129.53, 116.37, 79.95, 52.35, 47.95, 44.32, 41.64, 16.89, Anal. calcd: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.63; H, 5.84; N, 8.75. *N*-Phenyl 3-nitromethyl-3-(4-hydroxyphenyl)-2-benzylpropionamide **6b** 75% yield. Mp 231.7–231.9°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.11 (s, 1H), 8.63 (s, 1H), 7.47 (d, $J=8.0$ Hz, 2H), 7.15 (m, 10H), 6.88 (d, $J=8.0$ Hz, 2H), 4.97 (d, $J=8.0$ Hz, 2H), 3.79 (q, $J=8.0$ Hz, 1H), 3.14 (m, 1H), 2.95 (t, $J=12$ Hz, 1H), 2.66 (dd, $J=12.0$ Hz, $J_2=4.0$ Hz, 1H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.16, 157.93, 140.04, 139.16, 130.15, 129.80, 129.67, 129.43, 129.13, 127.15, 124.79, 120.92, 116.57, 79.56, 54.31, 47.23, 38.16. Anal. calcd: C, 70.75; H, 5.68; N, 7.17. Found: C, 70.58; H, 5.63; N, 7.03. *N*-Phenyl 3-nitromethyl-3-(4-hydroxyphenyl)-2-cyclohexylmethylpropionamide **6c** 76% yield. Mp 213.6–213.8°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.01 (s, 1H), 9.40 (s, 1H), 7.59 (d, $J=8.0$ Hz, 2H), 7.32 (t, $J=8.0$ Hz, 2H), 7.01 (m, 3H), 6.72 (d, $J=8.0$ Hz, 2H), 4.74 (d, $J=8.0$ Hz, 2H), 3.34 (m, 1H), 2.80 (t, $J=8$ Hz, 1H), 1.78 (d, $J=12$ Hz, 1H), 1.47 (m, 4H), 0.82 (m, 8H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.26, 157.73, 139.53, 130.08, 129.60, 124.84, 121.09, 116.36, 79.80, 49.54, 47.80, 39.77, 36.34, 34.89, 33.12, 27.12, 26.90, 26.79. Anal. calcd: C, 69.67; H, 7.12; N, 7.07. Found: C, 70.08; H, 7.15; N, 6.71.