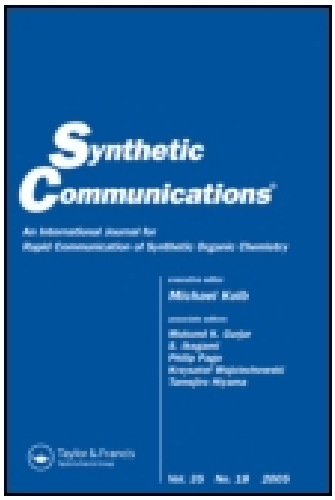

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An Efficient Synthesis of Methyl 3-Carboxy-2-oxohexahydroazepine-1-acetate

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ABSTRACT

The title compound **1** is prepared from ε-caprolactam in a five-step sequence involving *N*-alkylation of the azepine ring from a 3-(phenylselanyl)-3-(benzyloxycarbonyl) derivative **4** and the generation of the 3-carboxyazepine moiety from the resulting diester **5** by ozonolysis followed by catalytic hydrogenation.

Key Words: Methyl 3-carboxy-2-oxohexahydroazepine-1-acetate; ACE inhibitors; NEP inhibitors, ε-Caprolactam.

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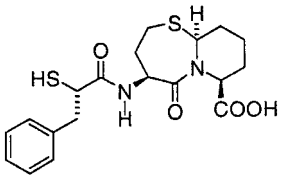
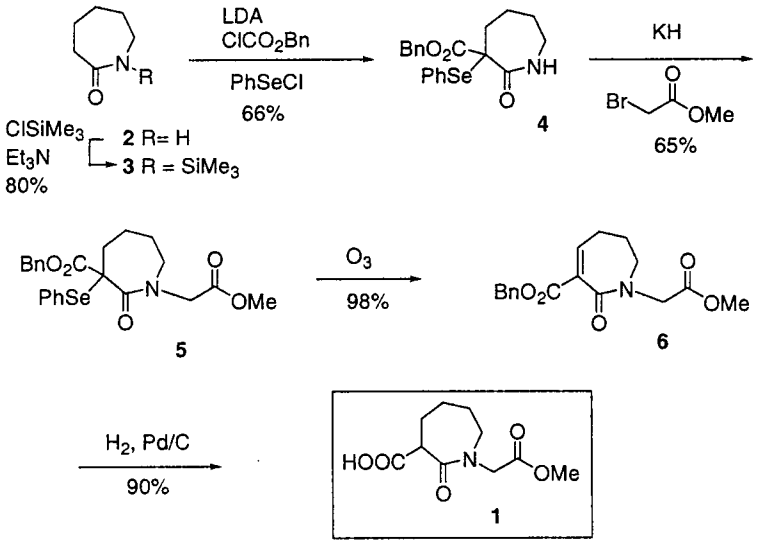
The synthesis of angiotensin-coverting enzyme (ACE) and neutral endopetidase (NEP) inhibitors has received a considerable attention during the last decade.[1–4] Many of these compounds, for instance omapatrilat,[5] incorporate a core seven-membered lactam ring. We report here a convenient and efficient preparation of 3-carboxyazepinone **1**, an interesting building block for the synthesis of new potential dual ACE/NEP inhibitors.



Omapatrilat

Starting from the commercially available ε-caprolactam, the synthesis requires the introduction of carboxy group and the acetate chain on the carbonyl α carbon and the nitrogen, respectively, of the azepinone ring. These apparently simple synthetic transformations were performed following the multistep sequence depicted in Sch. 1. A latent carboxy group, in the form of benzyl ester, was introduced at the beginning of the synthesis from an *N*-protected lactam, whereas alkylation of the nitrogen was performed from a



Scheme 1.

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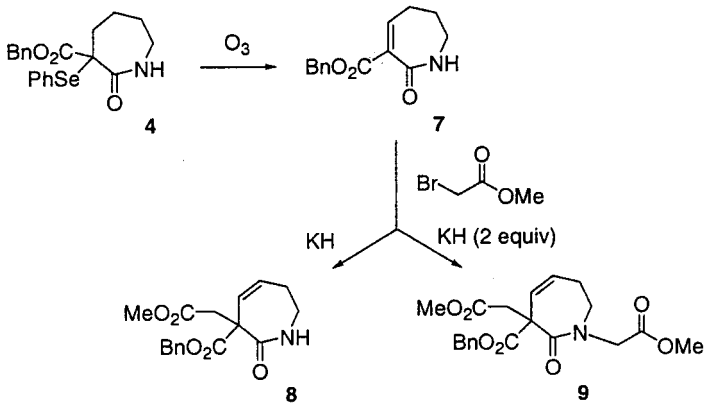
3,3-disubstituted azepinone derivative to avoid the alkylation at the α-position of the β-dicarbonyl system. We used a benzyl ester to avoid hydrolytic conditions during the deprotection step, and a phenylselanyl group to block the azepinone 3-position because this group can be easily introduced on the carbonyl α-carbon and then easily removed by ozonolysis, generating a carbon–carbon double bond.

Thus, sequential treatment of the *N*-silylated lactam **3**, prepared as reported previously,[6] with LDA (2.3 equiv), benzyl chloroformate, and phenylselanyl chloride gave the 3,3-disubstituted azepinone **4** in 66% yield. Alkylation of **4** with potassium hydride and methyl bromoacetate satisfactorily afforded (65% yield) the azepine-1-acetate **5**, which was converted by ozonolysis to the unsaturated lactam **6** in essentially quantitative yield. Finally, hydrogenation of **6** in the presence of palladium on charcoal brought about both the reduction of carbon–carbon double bond and the hydrogenolysis of the benzyl ester to give the target lactam acid **1** in 90% yield.

An alternative route to unsaturated lactam **6**, involving the alkylation of the nitrogen from unsaturated lactam **7** was not successful. Thus, although **7** could be prepared in good yield (76%) by ozonolysis of the seleno derivative **4**, all attempts to convert **7** to azepine-1-acetate **6** by alkylation with methyl bromoacetate resulted in failure. The use of LiHMDS as the base was ineffective, whereas with KH the alkylation took place at the carbonyl α carbon to give the *C*-alkylated lactam **8** (Sch. 2), a result that can be rationalized by considering the high acidity of the protons at the 5-position of the ring, which are activated by two carbonyl groups. When an excess (2 equiv) of KH



Scheme 2.

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and methyl bromoacetate was used, the *C*, *N*-dialkylated azepinone **9** was isolated in 40% yield.

EXPERIMENTAL

Melting points were determined in a capillary tube and are uncorrected. Unless otherwise indicated, NMR spectra were recorded at 200 or 300 MHz (^{1}H) and 50.3 or 75 MHz (^{13}C), and chemical shifts are reported in δ values downfield from TMS. Only noteworthy IR absorptions are listed. Thin-layer chromatography was done on SiO_2 (silica gel 60 F_{254}), and the spots were located with aqueous potassium permanganate solution. Column chromatography was carried out using the flash chromatography technique. All nonaqueous reactions were performed under inert atmosphere. Solvents for chromatography were distilled at atmospheric pressure prior to use and dried following standard procedures. Drying of the organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4 or $MgSO_4$. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses were performed by Centre d'Investigació i Desenvolupament (CSIC), Barcelona.

Benzyl 2-oxo-3-(phenylselanyl)hexahydro-1*H*-azepine-3-carboxylate (4). A solution of 1-(trimethylsilyl)-azepin-2-one[6] (3, 2.6 g, 13.8 mmol) in anhydrous THF (30 mL) was slowly added at −78°C to a solution of LDA (21 mL, 1.5 M in THF, 31.8 mmol), and the resulting mixture was stirred for 45 min. Then, benzyl chloroformate (2.5 mL, 15 mmol) in THF (30 mL) and, after 30 min of continuous stirring at −78°C, PhSeCl (3.4 g, 18 mmol) in THF (30 mL) were sequentially added to the solution. The resulting mixture was stirred at −78°C for 2 h and at room temperature for 1 h, and poured into water. The aqueous solution was extracted with Et_2O, and the combined organic extracts were washed with brine, dried, and concentrated. The residue was chromatographed (1 : 1 EtOAc-hexane) to give **4** (3.7 g, 66%). Mp 117–118°C. IR (KBr) 1718, 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 VMHz) δ 1.41–1.71 (m, 4H), 1.92–2.17 (m, 2H), 2.66–2.82 (m, 1H), 2.95–3.10 (m, 1H), 5.23 (s, 2H), 6.27 (brs, 1H, NH), 7.20–7.41 (m, 10H); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ 26.69 (CH_2), 28.57 (CH_2), 32.68 (CH_2), 41.83 (CH_2), 60.78 (C), 66.93 (CH_2), 128.10 (C), 128.20 (CH), 128.33 (CH), 128.47 (CH), 129.48 (CH), 135.24 (C), 138.83 (CH), 168.08 (C), 172.95 (C). Anal. Calcd for $C_{20}H_{21}NO_3Se$: C, 59.70; H, 5.26; N, 3.48. Found: C, 59.75; H, 5.52; N, 3.49.

Methyl 3-(benzyloxycarbonyl)-2-oxo-3-(phenylselanyl)hexahydro-1*H*-azepine-1-acetate (5). A solution of hexahydroazepine (**4**) (560 mg, 1.37 mmol) in THF (10 mL) was slowly added at 0°C to a suspension of KH (370 mg, 30% dispersion in mineral oil, 2.7 mmol) in THF (10 mL). After

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30 min of stirring, methyl bromoacetate (267 μL, 2.7 mmol) was added, the temperature was slowly raised to 25°C, and stirring was continued for another 2 h. Then, water (10 mL) was slowly added, and the aqueous solution was extracted with EtOAc. The combined organic extracts were dried and concentrated under reduced pressure. The resulting crude oil was chromatographed (hexane to 25 : 75 EtOAc-hexane) to give the alkylated product **5** (430 mg, 65%). IR (film) 1766, 1723, 1644 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.57–1.79 (m, 4H), 2.01–2.17 (m, 2H), 2.99–3.16 (m, 2H), 3.68 (s, 3H), 4.01 (d, $J = 16$ Hz, 1H), 4.33 (d, $J = 16$ Hz, 1H), 5.23 (s, 2H), 7.23–7.40 (m, 10H); ^{13}C-NMR ($CDCl_3$, 75.4 MHz) δ 25.91 (CH_2), 26.71 (CH_2), 32.40 (CH_2), 50.30 (CH_2), 51.89 (CH_3), 52.00 (CH_2), 61.10 (C), 66.80 (CH_2), 128.50 (C), 128.13 (CH), 128.31 (CH), 128.37 (CH), 129.36 (CH), 135.10 (C), 138.67 (CH), 167.83 (C), 169.12 (C), 170.33 (C). Anal. Calcd for $C_{23}H_{25}NO_5Se.3/4\ H_2O$: C, 56.52; H, 5.47; N, 2.87. Found: C, 56.54; H, 5.36; N, 2.64.

Methyl 3-(benzyloxycarbonyl)-2-oxo-2,5,6,7-tetrahydro-1*H*-azepine-1-acetate (6). A stream of ozone gas was bubbled through a cooled (−78°C) solution of selenide 5 (430 mg, 0.9 mmol) in anhydrous CH_2Cl_2 (25 mL) until it turned pale blue. The solution was purged with Ar, and the temperature was slowly raised to 25°C. After 30 min of stirring, the mixture was poured into brine (20 mL), and the aqueous solution was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated under reduced pressure. The resulting crude oil was chromatographed (1 : 1 EtOAc-hexane) to give tetrahydroazepine 6 (280 mg, 98%) as an oil. IR (film) 1732, 1651, 1620 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 1.96–2.09 (ddd, $J = 6.6$, 6.6 and 13.4 Hz, 2H), 2.46–2.57 (dd, $J = 7.4$ and 14.8 Hz, 2H), 3.35–3.42 (t, $J = 6.6$ Hz, 2H), 3.74 (s, 3H), 4.30 (s, 2H), 5.25 (s, 2H), 7.32–7.40 (m, 5H); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ 23.44 (CH_2), 27.82 (CH_2), 47.61 (CH_2), 48.89 (CH_2), 52.04 (CH_3), 66.45 (CH_2), 127.69 (CH), 127.84 (CH), 128.24 (CH), 131.43 (C), 135.58 (C), 145.25 (CH), 163.56 (C), 166.31 (C), 169.54 (C). Anal. Calcd for $C_{17}H_{19}NO_5 \cdot 1/3\ H_2O$: C, 63.16; H, 5.86; N, 4.37. Found: C, 63.05; H, 5.86; N, 4.37.

1-(Methoxycarbony1methy1)-2-oxohexahydro-1*H*-azepine-3-carboxylic acid (1). A mixture of benzyl ester **6** (280 mg, 0.87 mmol) and 10% Pd-C (50 mg) in EtOAc (10 mL) was stirred under H_2 for 15 h at room temperature. The mixture was filtered through Celite, and the filtrate was evaporated to afford the acid **1** (180 mg, 90%) as an oil. IR (film) 1747, 1648 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.76–1.88 (m, 4H), 2.10–2.15 (m, 1H), 2.34–2.42 (m, 1H), 3.24–3.34 (m, 1H), 3.51–3.56 (m, 1H), 3.75–3.78 (m, 1H), 3.77 (s, 3H, OCH_3), 4.22 (s, 2H, CH_2N); ^{13}C-NMR ($CDCl_3$, 75.4 MHz) δ 26.26 (CH_2), 28.37 (CH_2), 28.90 (CH_2), 47.40 (CH_2), 50.60 (CH_2), 50.84 (CH_2), 52.28 (CH_3), 168.83 (C), 172.53 (C), 175.41 (C). Anal. Calcd for $C_{10}H_{15}NO_5 \cdot 1/2\ H_2O$: C, 50.42; H, 6.77; N, 5.88. Found: C, 50.38; H, 6.76; N, 5.83.

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Benzyl 2-oxo-2,5,6,7-tetrahydro-1*H*-azepine-3-carboxylate (7). A stream of ozone gas was bubbled through a cooled (−78°C) solution of selenide 4 (1.0 g, 2.5 mmol) in anhydrous CH_2Cl_2 (40 mL) until it turned pale blue. The solution was purged with Ar, and the temperature was slowly raised to 25°C. After 30 min of stirring, the mixture was poured into brine (20 mL), and the aqueous solution was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated under reduced pressure. The resulting crude oil was chromatographed (1 : 1 EtOAc-hexane to EtOAc) to give tetrahydroazepine 7 (463 mg, 76%) as a solid. Mp 86–87°C. IR (KBr) 3213, 1715, 1668 cm^{-1} ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 1.85-1.98 (ddd, $J = 6.6$, 6.6 and 13.6 Hz, 2H), 2.36–2.48 (dd, $J = 7.4$ and 14.2 Hz, 2H), 3.15–3.24 (dd, $J = 6.6$ and 12.6 Hz, 2H), 5.25 (s, 2H), 7.33–7.40 (m, 5H); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ 24.27 (CH_2), 28.59 (CH_2), 39.30 (CH_2), 66.80 (CH_2), 128.05 (CH), 128.11 (CH), 128.46 (CH), 131.54 (C), 135.68 (C), 145.97 (CH), 163.96 (C), 168.93 (C). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.63; H, 6.14; N, 5.78.

Methyl 3-(benzyloxycarbonyl)-2-oxo-2,3,6,7-tetrahydro-1*H*-azepine-3-acetate (8). A solution of tetrahydroazepine **7** (400 mg, 1.6 mmol) in THF (10 mL) was slowly added at 0°C to a suspension of KH (216 mg, 30% dispersion in mineral oil, 1.6 mmol) in THF (10 mL). After 30 min of stirring, methyl bromoacetate (156 μL, 1.6 mmol) was added, the temperature was slowly raised to 25°C, and stirring was continued for another 2 h. Then, water (5 mL) was added, and the aqueous solution was extracted with EtOAc. The combined organic extracts were dried and concentrated under reduced pressure. The resulting crude oil was chromatographed (1 : 1 EtOAc-hexane to 7 : 3 EtOAc-hexane) to give **8** (200 mg, 40%). IR (film) 3358, 1732, 1667, 1651 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 2.14–2.34 (m, 2H), 2.98–3.04 (m, 3H), 3.30–3.49 (m, 1H), 3.61 (s, 3H), 5.20 (s, 2H), 5.50 (d, $J = 10$ Hz, 1H), 5.90 (d, $J = 10$ Hz, 1H), 6.56 (brs, 1H), 7.30–7.36 (m, 5H); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ 29.47 (CH_2CH_2), 38.48 (CH_2), 42.15 (CH_2), 51.77 (CH_3), 56.67 (C), 67.66 (CH_2), 125.38 (CH), 128.20 (CH); 128.32 (CH), 128.47 (CH), 131.46 (CH), 135.18 (C), 170.29 (C), 170.96 (C), 171.85 (C). Anal. Calcd for $C_{17}H_{19}NO_5 \cdot 1/3\ H_2O$: C, 63.16; H, 6.13; N, 4.33. Found: C, 63.04; H, 6.35; N, 4.22.

Dimethyl 3-(benzyloxycarbonyl)-2-oxo-2,3,6,7-tetrahydro-1*H*-azepine-1,3-diacetate (9). A solution of tetrahydroazepine 7 (1 g, 4 mmol) in THF (50 mL) was slowly added at 0°C to a suspension of KH (1.08 g, 30% dispersion in mineral oil, 8 mmol) in THF (50 mL). After 30 min of stirring, methyl bromoacetate (780 μL, 8 mmol) was added, the temperature was slowly raised to 25°C, and stirring was continued for another 2 h. Then, water (50 mL) was slowly added, and the aqueous solution was extracted with EtOAc. The combined organic extracts were dried and concentrated under

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reduced pressure. The resulting crude oil was chromatographed (hexane to 1 : 1 EtOAc-hexane) to give the dialkylated compound 9 (620 mg, 40%). IR (film) 1732, 1651 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 2.03–2.16 (m, 1H), 2.43–2.60 (m, 1H), 2.97–3.04 (m, 2H), 2.98 (s, 2H), 3.58 (s, 3H), 3.64 (s, 3H), 3.73–3.89 (m, 1H), 4.01 (d, $J = 17.6$ Hz, 1H), 4.26 (d, $J = 17.6$ Hz, 1H), 5.19 (s, 3H), 5.51 (d, $J = 12$ Hz, 1H), 5.76 (d, $J = 12$ Hz, 1H), 7.28–7.34 (m, 5H); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ 28.08 (CH_2), 42.86 (CH_2), 46.74 (CH_2), 51.20 (CH_2), 51.75 (CH_3), 52.10 (CH_3), 56.78 (C), 67.67 (CH_2), 125.51 (CH), 128.25 (CH), 128.27 (CH), 128.42 (CH), 131.41 (CH), 135.21 (C), 169.51 (C), 169.94 (C), 170.40 (C), 170.87 (C). Anal. Calcd for $C_{20}H_{23}NO_7$: C, 61.69; H, 5.95; N, 3.60. Found: C, 61.20; H, 6.24; N, 3.46.

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