Article

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Stereoselective Crystallization as a Key Step for the Synthesis of New Epimers of Captopril Derivatives

Aurelio Ortiz,[1]* Omar Arellano,[1] Estibaliz Sansinenea[2] and Sylvain Bernès[3]

[1] Facultad de Ciencias Químicas de la Benemérita Universidad Autónoma de Puebla.
[2] Instituto de Ciencias de la Benemérita Universidad Autónoma de Puebla, 72570, Puebla, Puebla, México.
[3] Facultad de Ciencias Químicas, Universidad Autónoma de Nuevo León, Monterrey, N. L. 64570, México.

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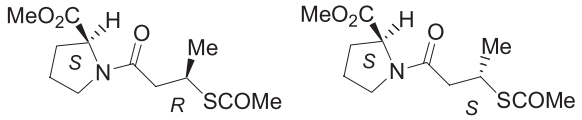
Abstract: The present work describes the synthesis of two new diastereomers of captopril derivatives. These epimers were achieved by conjugate addition of thioacetic acid and α-toluenethiol to a α,β-unsaturated system. The diastereomeric ratios obtained from this reaction were low at 0 °C and moderate at -50 °C. The importance of this synthesis, however, is that in one case, both epimers can be isolated in good yields. Their isolation was possible because of the high crystallinity showed by one epimer compared to the other one. The absolute configuration of the solid compound was established by X-ray analysis.
Key words: Captopril, ACE inhibitor, antihypertensive, conjugate addition of thiols.

Resumen: El presente trabajo describe la síntesis de dos nuevos diastereómeros derivados del captopril. Estos epímeros fueron obtenidos a través de la adición conjugada del ácido tioacético y α-toluenotiol a un sistema α, β-insaturado. Las relaciones diastereoméricas para esta reacción fueron bajas a 0 °C y moderadas a -50 °C. Sin embargo, la importancia de esta síntesis radica en que, en un caso, ambos epímeros pueden ser separados en rendimientos químicos aceptables. La separación de los epímeros fue posible debido a la alta cristalinidad que presentó un epímero en comparación del otro. La configuración absoluta del epímero cristalino fue establecida por difracción de Rayos-X.
Palabras clave: Captopril, Inhibidor ACE, antihipertensivo, adición conjugada de tioles.

Introduction

Captopril, (2*S*)-1-[(2*S*)-2-methyl-3-sulfanylpropanoyl]-pyrrolidine-2-carboxylic acid, is a widely prescribed orally active angiotensin-converting enzyme inhibitor (ACE inhibitor), used for the treatment of hypertension and some types of congestive heart failure. Captopril was the first ACE inhibitor developed in 1975 by Ondetti *et al* [1]. However, it produces some side effects like skin rashes and taste disturbances, which are attributed to the unique sulfhydryl functionality [2]. It is known that the (*S*, *R*) epimer of captopril has 100-fold lower activity than captopril itself [1]. In general captopril has been the subject of extensive researches [3]. However, only a few studies about captopril synthesis have been reported. Captopril can be prepared by coupling (2*S*)-3-acetylthio-2-methylpropanoyl chloride with L-proline under basic conditions [4]. Davies has described a highly diastereomeric asymmetric synthesis of (-)-captopril by using an iron (0)-based chiral auxiliary [5]. A highly diastereoselective Michael addition of a thiol to α-substituted α,β-unsaturated esters has been also applied to the asymmetric synthesis of a captopril derivative [6]. Analogues of captopril have been obtained by modification of its basic structure, with the aim to increase their activity and to avoid side effects [7].

We describe herein a simple procedure affording two structural isomers of captopril derivatives. Stereoselective crystallization was the key step to obtain both epimers **4a** and **5a** in a diastereomerically pure form (Figure 1).



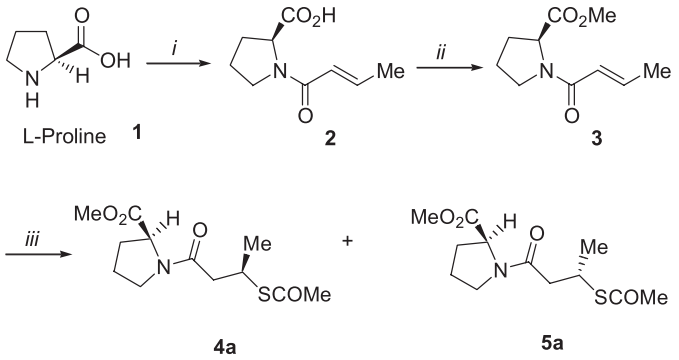
Liquid **4a** Solid **5a**

Fig. 1. Epimeric captopril derivatives.

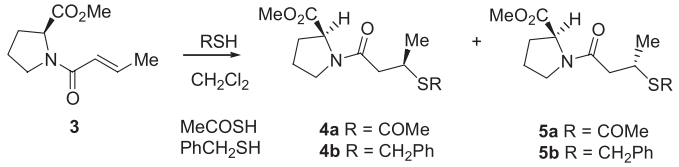
Results and discussion

Epimers **4a** and **5a** were prepared from the commercially available L-proline **1**. The first step is the reaction of the amino acid with *trans*-crotonyl chloride in aqueous NaOH (5 %) to give **2** in 45 % yield as a crystalline solid, followed by methylation with BF_3/MeOH to produce **3** in 75% yield [8]. Subsequent conjugate addition of thioacetic acid (3 equiv) to **3** at -50 °C gave a mixture of the epimeric *N*-3-thioacetyl-oxobutylproline methyl esters **4a** and **5a** in 86 % yield and with a diastereomeric ratio of 73/27, (the same reaction at -78 °C did not proceed), as shown in Scheme 1.

Conjugate addition of thiols to α,β-unsaturated carbonyl systems has been a considerable challenge in organic chemistry. This reaction allows the introduction of a new quiral center at the β-position containing a sulfur atom [9]. Therefore, conjugate addition of thiols to **3** was investigated using thioacetic



Scheme 1. *i*) aq NaOH soln 5 %, $CH_3CH{=}CHCOCl$, *ii*) BF_3·MeOH, reflux, 2h, *iii*) MeCOSH, CH_2Cl_2, -50 °C, 68 h.



Scheme 2. Conjugate addition of thioacetic acid and α-toluenethiol to compound **3**.

acid and α-toluenethiol as nucleophiles, as shown in Scheme 2 and Table 1.

When compound **3** was treated with thioacetic acid (3 equiv) in the presence of $SnCl_4$ (1.5 equiv) at 0 °C, compounds **4a** and **5a** were produced in low yields (entry 1). The possible formation of a thioacetic acid-$SnCl_4$ complex and the low nucleophilicity of thioacetic acid may account for such a low reaction yield. In the absence of $SnCl_4$ at 0 °C, this same reaction gave **4a** and **5a** as a diastereomeric mixture in better yields (entry 2). At low temperature (- 50 °C) compounds **4a** and **5a** were obtained in an 86 % yield and with a d.r. of 73/27 (entry 3). Compound **5a** showed high crystallinity and it was possible to separate it from **4a**, which is liquid, by recrystallization using a mixture of AcOEt/hexane as solvent. For **5a** the absolute configuration at the newly formed stereogenic center (C-9) is *S*, as established by single crystal X-ray analysis (Fig. 2) [10].

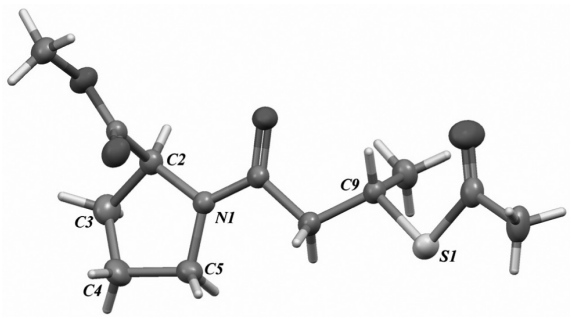


Fig. 2. Molecular structure of compound **5a**. Displacement ellipsoids for non-H atoms are shown at the 30% probability level.

The molecular structure of **5a** shows expected geometric features. The pyrrolidine heterocycle approximates an envelope conformation with C3 as flap atom, and the side chain at N1 extends without significant steric hindrance. Corresponding epimer (*S, R*)-**4a** is a liquid at room temperature, probably because of packing conflicts due to the methyl and methyl ester functional groups bonded to chiral centers, which are then oriented toward the same face of the pyrrolidine nucleus.

Finally, compound **3** was treated with α-toluenethiol (3 equiv) in the presence of $SnCl_4$ (1.5 equiv) to provide the epimeric compounds **4b** and **5b** in good yields and with a good diastereomeric ratio of 90/10 (Table 1, entry 4). In contrast with the synthesis of **4a**/**5a**, in the absence of $SnCl_4$ at 0 °C, the reaction did not produce the expected compounds **4b** and **5b** (entry 5), furthermore the major product **4b** was isolated by preparative chromatography, unlike crystallization of **4a**/**5a**. The obtainment of **4b** can be based on Cativiela's and Wu's models [8, 9c].

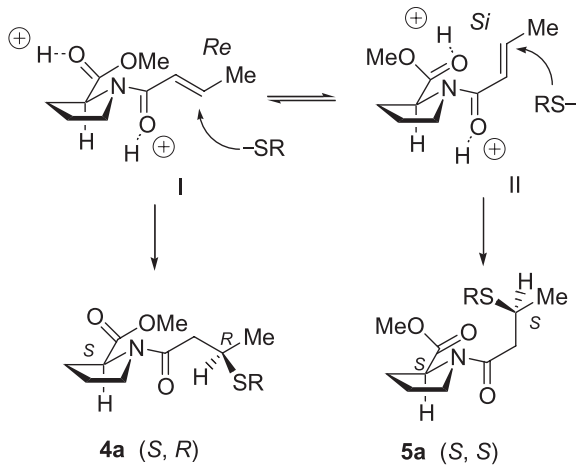
The formation of compound **4a** as major diastereomer may be rationalized via protonation of the carbonyl oxygen atoms followed by an attack of the nucleophile (RS^-) to the *Re* face of the α,β-unsaturated system **I**, as it was described by Wu [9d]. Compound **5a** should be achieved by an attack of the nucleophile (RS^-) to the *Si* face **II**, as shown in Scheme 3.

In conclusion we have described the formation of two structural isomers for derivatives of captopril. Stereoselective crystallization was the key step to obtain the two epimers **4a**/**5a** in a diastereomerically pure form. The proposed syn-

Table 1. Conjugate Addition of Thiols to compound **3**

Entry	RSH (equiv)	Lewis acid (equiv)	T(°C)/t(h)	% Yield[a]	d. r.[b] **4/5**
1	MeCOSH (3.0)	$SnCl_4$ (1.5)	0/68	8	50/50
2	MeCOSH (3.0)	none	0/68	51	53/47
3	MeCOSH (3.0)	none	-50/68	86	73/27
4	$PhCH_2SH$ (3.0)	$SnCl_4$ (1.5)	0/12	92	90/10
5	$PhCH_2SH$ (3.0)	none	0/12	0	NA

[a] Yields are for the mixture of compounds **4** and **5**. [b]diastereomeric ratios were determined by HPLC and ^1H NMR on the crude products.



Scheme 3. Possible course of the transformation of **3** to **4a** and **5a**

thetic method has the advantage to afford both compounds **4a** and **5a** as a diastereomeric mixture, when the reaction is carried out with three equivalents of thioacetic acid at 0 °C. Since compound **5a** resulted to be highly crystalline compound while **4a** is a liquid, both epimers may be easily isolated in good yields by taking advantage of their different physical properties. Thioacetic acid showed a lower nucleophility compared to α-toluenethiol. However, thioacetyl group in compounds **4a** and **5a** can be straightforwardly removed through standard procedures [13].

Experimental

***N*-Crotonyl-L-proline 2**. To a solution of L-proline **1** (1 g, 8.7 mmol) in 20 mL of 5% NaOH kept at 0 °C, *trans*-crotonyl chloride (1.36 g, 13.8 mmol) was added dropwise. The resulting solution was stirred for 3 h at room temperature. The reaction mixture was acidified with HCl (12 N), the organic layer was extracted with AcOEt (3 × 30 mL), dried over Na_2SO_4, filtered and concentrated in vacuum to give a colorless liquid. Purification by crystallization from AcOEt/hexane gave **2** as a white solid (0.71 g, 45 %), mp 156-158 °C; $[\alpha]^{25}_D$ = - 300.1 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.12 (1H, b, OH), 7.07 (1H, dq, *J* = 14.8, 6.8 Hz, $CHCH_3$), 6.15 (1H, dq, *J* = 14.8, 1.6 Hz, =CH), 4.64 (1H, dd, *J* = 7.8, 2.6 Hz, $CHCO_2H$), 3.67 (1H, m, CHN), 3.56 (1H, m, CHN), 2.43 (1H, m, CH), 2.10-1.97 (3H, m, CH, CH_2), 1.93 (3H, dd, *J* = 6.8, 1.6 Hz, CH_3CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.3 (CO_2H), 167.2 (CON), 144.8 (=$CHCH_3$), 121.1 (=CH) , 60.1($CHCO_2H$), 47.7 (CHN), 27.4 (CH_2), 24.8 (CH_2), 18.4 (CH_3); Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.03; H, 7.30; N, 7.50. IRν$_{max}$ (KBr): 2943.2, 1714.6, 1658.7, 1581.5, 1456.2, 1234.4 cm^{-1}.

***N*-Crotonyl-(L)-proline methyl ester 3**. BF_3·MeOH (10 mL) was added to **2** (1.00 g, 5.46 mmol). The solution was refluxed for 3 h and cooled, and 20 mL of a saturated solution of $NaHCO_3$ were added. The organic layer was extracted with CH_2Cl_2 (4 x 20 mL), dried over Na_2SO_4, filtered and concentrated in vacuum to give a dense yellow liquid. The crude was purified by chromatography column using silica gel and hexane-AcOEt (1:2) as eluent to give **3** as yellow dense liquid (0.80 g 75 %); $[\alpha]^{25}_D$ = - 96.17 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.0 (1H, dq, *J* = 15.04, 7.0 Hz, $CH_3\underline{CH}$=), 6.16 (1H, dq, *J* = 15.2, 1.2 Hz, HC=), 4.54 (1H, dd, *J* = 8.6, 4.4 Hz), 3.75 (3H, s, CO_2CH_3), 3.60 (1H, m, CHNH), 2.25-1.95 (5H, m, CHN, CH_2, CH_2), 1.90 (3H, dd, *J* = 7.0, 1.6 Hz, $\underline{CH_3}CH$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.8 (CO_2CH_3), 164.8 (CON), 142.3 ($\underline{CH}$=CH_3), 122.2 (CH=), 58.7 (CH_3O), 52.1 (CHCO), 46.7 (CHN), 29.0 (CH_2), 24.7 (CH_2), 18.04 ($\underline{CH_3}CH$=); IRν$_{max}$ (KBr): 3579.6,2952.8, 1739.7, 1662.5, 1614.3, 1450.4, 1417.6, 1139.9 cm^{-1}.

Procedure for the conjugate addition of thiols to the *N*-Crotonyl-(L)-proline methyl ester 3. To a solution of **3** (100 mg, 0.5 mmol) in dry CH_2Cl_2 thioacetic acid was added (0.19 g, 2.53 mmol) at -50 °C under argon atmosphere. Then, the solution was stirred for 68 h, poured into a saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 30 mL). The extracts were washed with aqueous NaOH solution (10 %), brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography using AcOEt/hexane (2/1) as eluent to give a mixture of products **4a** and **5a** (118 mg, 86%) as dense liquids.

The separation of epimers **4a** and **5a** was carried out by recrystallization from ETOAc/Hexane

(3*R*)-*N*-3-acetylthio-1-oxobutyl-L-proline methyl ester 4a. (80 mg); $[\alpha]^{25}_D$ = -41.6 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.50 (1H, dd, *J* = 8.4, 4.0 Hz, $\underline{CH}COCH_3$), 3.93 (1H, m, CHS), 3.72 (3H, s, CO_2CH_3), 3.65 (1H, m, CHN), 3.54 (1H, m, CHN), 2.74 (1H, dd, *J* = 15.6, 5.6 Hz, CH_AH_B), 2.54 (1H, dd, *J* = 16.0, 8.2 Hz, CH_BH_A), 2.30 (3H, s, CH_3COS), 2.23 (1H, m, CH_2), 2.06 (1H, m, CH_2), 2.00 (2H, m, CH_2), 1.40 (3H, d, *J* = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 195.4 (COS), 172.4 (CO_2CH_3), 168.8 (CON), 58.6 (CH_3O), 52.2 ($CHCO_2CH_3$), 47.1 (CH_2N), 40.7 (CHS), 36.0 (CH_2), 30.7 (CH_2), 29.2 (CH_2), 24.8 (CH_3), 20.5 (CH_3); IRν$_{max}$ (KBr): 2950.9, 2875.7, 1745.5, 1681.8, 1649.0, 1454.2 cm^{-1}; HRMS (EI) calculated for ($C_{12}H_{19}NO_4S$) *m/z* 273.1035, found *m/z* 273.1036.

(3*S*)-*N*-3-acetylthio-1-oxobutyl-L-proline methyl ester 5a. (32 mg); mp 101-103 °C; $[\alpha]^{25}_D$ = - 94.1 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.50 (1H, dd, *J* = 8.4, 4.0 Hz, $\underline{CH}COCH_3$), 3.94 (1H, m, CHS), 3.73 (3H, s, CO_2CH_3), 3.54 (1H, m, CHN), 2.80 (1H, dd, *J* = 15.0, 4.7 Hz, CH_AH_B), 2.51 (1H, dd, *J* = 15.0, 8.8 Hz, CH_BH_A), 2.30 (3H, s, CH_3COS), 2.20 (1H, m, CH), 2.08 (1H, m, CH), 2.00 (2H, m, CH_2), 1.41 (3H, d, *J* = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 195.7 (COS), 172.4 (CO_2CH_3), 168.7 (CON), 58.6 (CH_3O), 52.3 ($CHCO_2CH_3$), 47.2 (CH_2N), 41.2 (CHS), 35.6 (CH_2), 30.7

(CH_2), 29.1 (CH_2), 25.0 (CH_3), 20.2 (CH_3); Anal. Calcd. for $C_{12}H_{19}NO_4S$: C, 52.73; H, 7.01; N, 5.12; S, 11.73. Found: C, 52.80, H 7.10, N 5.20; S, 11.21. IRν_{max} (KBr): 2976.0, 2873.7, 1743.5, 1679.9, 1647.1, 1431.1 cm^{-1}; HRMS (EI) calculated for ($C_{12}H_{19}NO_4S$) *m/z* 273.1035, found *m/z* 273.1044.

(3*R*)-*N*-3-benzylthio-1-oxobutyl-L-proline methyl ester 4b. To a solution of **3** (100 mg, 0.5 mmol) in dry CH_2Cl_2, $SnCl_4$ (0.20 g, 0.76 mmol) was added dropwise under argon atmosphere. The solution was stirred at 0 °C for 15 min. Then, α-toluenethiol (0.19 g, 1.52 mmol) was added, the solution was stirred for 12 h at 0 °C, and poured into a saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 30 mL). The extracts were washed with aqueous NaOH solution (10 %), brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography using AcOEt/ hexane (2/1) as eluent to give products **4b** and **5b** (150 mg, 92%) as a dense liquids. However the minor product **5b** was lost during its purification.

The major product **4b** was isolated by preparative chromatography using AcOEt/ hexane as eluent to give **4b** as a dense liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ : 7.38-7.20 (5H, m, Ph), 4.47 (1H, dd, *J* = 8.4, 3.7 Hz, $CHCO_2CH_3$), 3.78 (2H, d, *J* = 1.92 Hz,CH_2), 3.71 (3H, s, CH_3O), 3.65 (1H, m, CHS), 3.45 (1H, m, CHN), 3.30 (1H, m, CHN), 2.57 (1H, dd, *J* = 15.3, 6 Hz, CH_AH_B), 2.43 (1H, dd, *J* = 15.1, 8.2 Hz, CH_BH_A), 1.87-2.22 (4H, m, $2CH_2$), 1.32 (3H, d, *J* = 7.0 Hz, CH_3); RMN ^{13}C ($CDCl_3$, 75 MHz) δ : 172.7 (CO_2CH_3), 169.6 (CON), 138.5 (C*i*), 128.7 (C*m*), 128.4 (C*o*), 126.8 (C*p*), 58.6 ($CHCOCH_3$), 52.1 (CH_2S), 47.0 (CH_2N), 42.0 (CHS), 36.6 (CH_2), 29.1 (CH_2), 24.6 (CH_2), 21.3 (CH_3); HRMS (EI) calculated for ($C_{17}H_{23}NO_3S$) *m/z* 321.1399, found *m/z* 321.1402.

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10] *Crystal data for* **5a**: $C_{12}H_{19}NO_4S$, *M*=273.34, colorless prism, 0.60 0.44 0.20 mm^3, space group $P2_1$, cell parameters *a* = 6.3929 (5), *b* = 10.1935 (11), *c* = 10.8505 (10) Å, β = 91.117(7)°, *Z* = 2, D_c = 1.284 $g.cm^{-3}$. 4258 reflections were collected on a Bruker P4 diffractometer at room temp., using Mo-*K*α radiation (λ = 0.71073 Å) in the range of 2θ = 4-58°, of which 3761 were unique (R_{int} = 0.015). 166 variables refined: R_1 = 0.0370 [3174 data with $I > 2\sigma(I)$] and wR_2 = 0.0938 [all data].[11] The absolute configuration was determined by the refinement of a Flack parameter based on 1780 Friedel pairs, χ=0.03(7).[12] Complete data have been deposited with the CCDC, reference 658461. Structure factors and raw files are available on request from the authors.
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