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TETRAHEDRON: *ASYMMETRY*

Determination of the absolute configuration of fasidotril, a potent dual ACE/NEP inhibitor

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Abstract—The absolute configuration of fasidotril has been established by a chemical correlation leading to the stereochemical assignment of the intermediate (*S*)-3-acetylsulfanyl-2-(benzo[1,3]dioxol-5-ylmethyl)propanoic acid.

Angiotensin I converting enzyme (ACE, EC 3.4.25.1) and neprilysin (NEP, EC 3.4.24.11, also named neutral endopeptidase, enkephalinase or atriopeptidase) are two ectoenzymes that play a major role in regulating cardiovascular and renal functions such as angiotensin II, bradykinin and natriuretic peptides. Whereas ACE inhibitors are largely used drugs in the treatment of hypertension, congestive heart failure or renal insufficiency, the potential interest of achieving NEP inhibition in such diseases was only recently proposed.[1–3] Fasidotril **1** was the first drug proposed to combine in a single molecule equal inhibitory potency towards NEP and ACE, hence resulting in protection of natriuretic peptides and bradykinin to prevent angiotensin II formation.[4,5] Fasidotril is in phase II clinical trials, whereas similar compounds (e.g. omapatrilat) are undergoing larger scale clinical trials and are often designated 'vasopeptidase inhibitors' (Fig. 1).[6]

Fasidotril contains two stereogenic centers, one of which stems from natural alanine. The other one was given the (*S*)-configuration based on structure activity relationships.

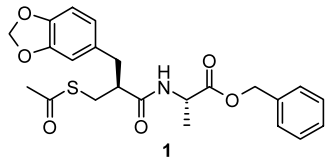

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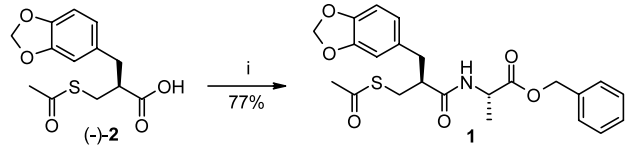
Figure 1.

Among the routes leading to fasidotril,[7] one involves the separation of the enantiomers of the acid **2** by successive recrystallizations of its α-phenethylamine or ephedrine salt.[8] The levorotatory acid can be converted to biologically active fasidotril† by condensation with (*S*)-alanine benzyl ester[8] as depicted in Scheme 1.



Scheme 1. *Reagents and conditions*: (i) Et_3N (1.0 equiv.), (*S*)-AlaOBn, CH_3SO_3H (1.0 equiv.), DCCI (1 equiv.), HOBT (1 equiv.), THF, 0°C→rt, 6 h.

Analogous condensation of the dextrorotatory acid with alanine gives a compound far less active as an ACE inhibitor. The NMR signal of the alanine methyl

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† Mp = 104°C; ^{1}H NMR (250 MHz, $CDCl_3$): 7.25 (s, 5H), 6.6 (s, 3H), 6.0 (d, 1H, J = 7.5 Hz), 5.85 (s, 2H), 5.0 (s, 2H), 4.5 (quint., 1H, J = 7.5 Hz), 3.05 (d, 2H, J = 6.1 Hz), 3.0–2.4 (m, 3H), 2.25 (s, 3H), 1.3 (d, 3H, J = 7.5 Hz). Anal. calcd for $C_{23}H_{25}NO_6S$: C, 62.30; H, 5.64; N, 3.16. Found: C, 62.2; H, 5.30; N, 3.20. $[\alpha]_D^{20} = -50.6$ (*c* 1.3, CH_3OH).

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group in this compound appears as a doublet at 1.1 ppm instead of 1.3 ppm for fasidotril. These chemical shifts are constant within a whole series of aromatic derivatives, including the unsubstituted one,[9] which is of known configuration. These results indicate that the absolute configuration of fasidotril is (*S*,*S*). This absolute configuration is now demonstrated by a chemical correlation leading to **3**. This product can be obtained from (−)-**2** by a modification of the Curtius rearrangement using diphenylphosphorylazide[10] (DPPA) in 67% yield (Fig. 2 and Scheme 2).‡

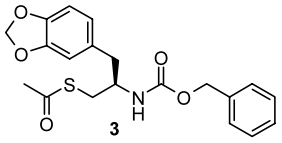

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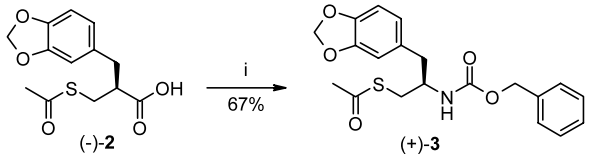
Figure 2.



Scheme 2. *Reagents and conditions*: (i) 1. DPPA (1.05 equiv.), Et_3N (1.05 equiv.), toluene, 80°C, 15 min, 2. $C_6H_5CH_2OH$ (1.2 equiv.), 80°C, 17 h.

The protected aminothiol **3** can also be prepared starting from a material of known absolute configuration as depicted in Scheme 3. Aminoacid (*R*)-**5** derived from piperonal was prepared using the reported procedure.[11] Esterification with ethanol and thionyl chloride leads to aminoester **6**, which is reduced with lithium aluminum hydride to aminoalcohol **7**. Selective protection of the amino group is achieved under conventional two phase system conditions. Conversion of the alcohol into the thioacetate by a Mitsunobu[12] reaction gives (*R*)-**3**.§

The measurement of the rotatory power at five different wavelengths (Na and Hg) is within the confidence margin for the two samples (+)-**3** and (*R*)-**3**. As the Curtius rearrangement is known to occur with retention of configuration,¶ the absolute stereochemistry of levorotatory acid **2** is (*S*). Conversion of this latter with alanine benzyl ester gives the biologically active diastereomer. The absolute configuration of fasidotril is thus to be assigned as (*S*,*S*) (Fig. 3).

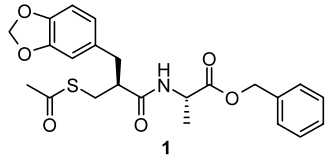


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Figure 3.

Acknowledgements

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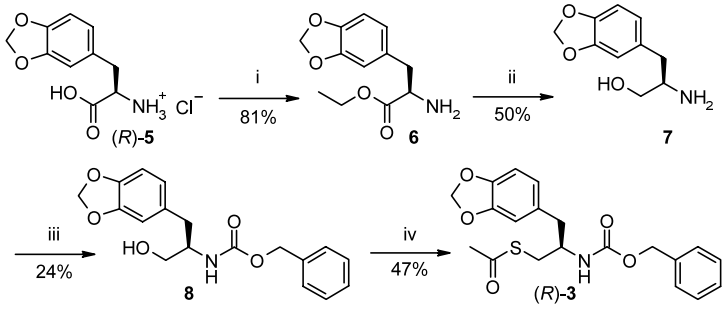

Scheme 3. *Reagents and conditions*: (i) $SOCl_2$, EtOH, reflux, 3 h (ii) $LiAlH_4$ (1.15 equiv.), Et_2O, rt, 24 h; (iii) $C_6H_5CH_2OCOCl$ (1 equiv.), K_2CO_3 (2 equiv.), AcOEt/H_2O 60/40, rt, 24 h; (iv) 1. PPh_3 (2 equiv.), DEAD (2 equiv.), THF, 0°C, 40 min, 2. AcSH (2 equiv.), THF, 0°C, 2 h then rt, 20 h.

‡ To a solution of 0.44 g (1.56 mmol) of (−)-**2** in toluene (2 mL) was added dropwise 353 μL (1.64 mmol) of DPPA and 228 μL (1.64 mmol) of triethylamine. The reaction mixture was heated at 80°C until gas evolution ceased (20 min) then 194 μL (1.87 mmol) of benzyl alcohol was added. The mixture was further heated for 17 h at 80°C, then solvent was evaporated and replaced with 15 mL of ethyl acetate. Washing successively with water, saturated $NaHCO_3$ solution and water, drying over $MgSO_4$ and concentrating afforded an off-white solid. Purification by column chromatography (heptane/AcOEt 7:3; ∅ 3 cm; 50 g SiO_2), trituration in heptane and drying over P_2O_5 gave 0.4 g (67%) of **3** as a white solid melting at 142.8°C. ^{1}H NMR (250 MHz, $CDCl_3$): 7.45–7.20 (m, 5H), 6.80–6.50 (m, 3H), 5.95 (s, 2H), 5.10 (s, 2H), 4.85 (d, 1H, J=7.7 Hz), 4.00 (m, 1H), 3.15–2.60 (m, 4H), 2.35 (s, 3H). Anal. calcd for $C_{20}H_{21}NO_5S$: C 62.00; H, 5.46; N, 3.62; S, 8.28. Found: C, 62.30; H, 5.45; N, 3.43; S, 7.98. $[\alpha]_D^{20}$=+7.6 (*c* 1.0, $CHCl_3$), $[\alpha]_{365}^{20}$=+19.7 $[\alpha]_{436}^{20}$=+14.0 $[\alpha]_{546}^{20}$=+8.8 $[\alpha]_{578}^{20}$=+7.7.

§ ^{1}H NMR (250 MHz, $CDCl_3$): 7.45–7.20 (m, 5H), 6.80–6.50 (m, 3H), 5.95 (s, 2H), 5.10 (s, 2H), 4.85 (d, 1H, J=7.7 Hz), 4.00 (m, 1H), 3.20–2.60 (m, 4H), 2.35 (s,3H). Anal. calcd for $C_{20}H_{21}NO_5S$: C, 62.00; H, 5.46; N, 3.62; S, 8.28. Found: C, 61.53; H, 5.38; N, 3.52; S, 8.26. $[\alpha]_D^{20}$=+7.4 (*c* 1.0, $CHCl_3$), $[\alpha]_{365}^{20}$=+18.3 $[\alpha]_{436}^{20}$=+12.9 $[\alpha]_{546}^{20}$=+8.2 $[\alpha]_{578}^{20}$=+7.0.

¶ (*S*)-**2** gives (*R*)-**3** as the result of the priority order change when applying the Cahn–Ingold–Prelog rules.

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