A Stereoselective Synthesis of the ACE Inhibitor Trandolapril

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Abstract A conceptually novel and stereoselective synthesis of the enantiopure octahydroindole building block and its conversion into the ACE inhibitor trandolapril was achieved. Key steps include the \( \alpha \)-allylation of a protected \( \alpha \)-pyroglutamic acid derivative, a highly diastereoselective Hosomi–Sakurai reaction and a Ru-catalyzed ring-closing metathesis of a 4,5-diallylated proline. This way, the synthesis of trandolapril was efficiently achieved in 25% overall yield (12 steps).

Key words proline derivatives, ACE inhibitors, diastereoselective alkylation, Hosomi–Sakurai reaction, Ru catalysis, ring-closing metathesis

Since the discovery of captopril in 1977, inhibitors of the angiotensin-converting enzyme (ACE) have found widespread medical application, especially for the treatment of hypertension and congestive heart failure (Figure 1). A frequently prescribed member of this class of compounds is the orally active generic drug trandolapril (1). It is especially recommended for the treatment of arterial hypertension in patients after myocardial infarction with dysfunction of the left heart ventricle.

A first synthesis of trandolapril (1) was patented by Hoechst in 1981, and several alternative syntheses have been reported by others. A most difficult challenge of any trandolapril synthesis is the stereoselective preparation of the bicyclic amino acid building block 2 (trans-octahydro-1H-indole-2-carboxylic acid). Actually, as a literature search revealed, all described methods for the synthesis of this key intermediate (Scheme 1) either require long synthetic sequences, give poor yields, or result in a mixture of diastereomers. As a common feature, the known approaches towards 2 all use cyclohexane derivatives (such as compounds 3–6) as intermediates and differ in the way how the pyrrolidine ring is (more or less) stereoselectively anellated (Scheme 1).

Against this background, we reasoned that building block 2, which also can be regarded as a proline derivative, could more efficiently be synthesized starting from \( \alpha \)-proline or \( \alpha \)-pyroglutamate as well accessible (enantiopure) amino acids. We envisioned to construct the ester 2a from the diallyl-proline 8 through Ru-catalyzed ring-closing metathesis and hydrogenation/deprotection of the resulting intermediate 7 (Scheme 2).
Compound 8 in turn could be synthesized from pyroglutamic acid 10 (via intermediate 9) according to our recently developed methodology for the stereoselective synthesis of 4,5-disubstituted prolines.9 Here, we report the successful realization of this strategy and present a reliable and efficient synthesis of 2 as well as of trandolapril (1) itself.

The synthesis started with the conversion of L-pyroglutamic acid 10 into the tert-butyl-ester10 and subsequent N-Boc-protection to give the pyroglutamate 11 in 86% yield as a white crystalline solid. Following our established protocol8 the α-allylation of 11 was conducted by deprotonation with LiHMDS and subsequent treatment of the resulting lithium enolate with allyl bromide in the presence of lithium enolate with allyl bromide in the presence of tetrabutylammonium diethyl malonate.8 The crude mixture, mainly containing the monosubstituted products 9 and cis-9 (d.r. = 1:1) was readily separated by column chromatography. Recycling of the undesired cis-isomer was achieved by base-induced epimerization (TBAF in THF) and repeated chromatographic separation of the resulting trans-enriched mixture (9: cis-9 = 3:1). This way, the desired pure trans-diastereomer 9 was obtained in a satisfying overall yield of 51% starting from pyroglutamic acid 10 (Scheme 3).

According to our plan (Scheme 2), the synthesis of the key intermediate 2a proceeded with the selective reduction of lactam 9 with lithium triethylborohydride12 followed by acid-catalyzed methanolation of the crude hemiaminal to afford the 5-methoxyproline (12, d.r. = 1:1) in 81% overall yield (Scheme 4). The introduction of the second allyl side chain was then achieved with high trans-diastereoselectivity (d.r. = 17:1) by substitution of the methoxy group in 12 in a Hosomi–Sakurai-type reaction (allyl-TMS, BF₃·Et₂O).13 The observed selectivity probably results from a repulsive interaction of the allyl-TMS nucleophile with the pre-installed allyl substituent. After chromatography, the 4,5-double allylated proline derivative 8 was obtained as pure diastereomer in 74% yield.

Initially, the ring-closing metathesis of 8 was carried out in the presence of 10 mol% of Grubbs II catalyst to afford the bicyclic product 7 in only moderate yield (62%).14 However, the yield of this key step could be greatly improved to 95% by employing only 5 mol% of Grubbs II catalyst in the presence of 8 mol% of Cu according to a protocol of Lipshutz et al. (Scheme 5).15

Hydrogenation of the double bond of 7 (Pd/C in EtOH, 24 bar)16 gave rise to the octahydropindole 13 in 95% isolated yield. The cleavage of the Boc-protecting group then proceeded smoothly under established conditions (TMSOTf in CH₂Cl₂)17 to afford the envisioned trandolapril building block 2a as a white crystalline solid (m.p. 102 °C). This allowed us to unambiguously confirm the relative (and absolute) configuration of 2a by means of X-ray crystallographic analysis (Figure 2).
Having substantial amounts of the building block 2a in our hands, we decided to also probe the completion of the synthesis of trandolapril (1). For this purpose, 2a was coupled with the commercially available L-alanine derivative 14 using PyBOP\textsuperscript{18} as a coupling reagent in the presence of DIPEA as a base. The cleavage of the tert-butyl ester function of the resulting dipeptide 15 was finally achieved using TFA (20 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (0 °C, 30 min) to deliver trandolapril 1 in 92% yield over two steps (Scheme 6).

To our delight, the solid product 1 could be recrystallized to unequivocally prove its structure and conformational preference by means of single-crystal X-ray analysis (Figure 3).

Noteworthy, when the deprotection of 15 to 1 was conducted under harsher conditions (TFA/CH\textsubscript{2}Cl\textsubscript{2} = 2:1; 2 h, r.t.) the crude product contained significant amounts of the diketopiperazine 16 as a byproduct, the structure of which was also proven by X-ray crystal-structure analysis (Figure 4).

In conclusion, taking the trandolapril building block 2a as a relevant target, we succeeded to demonstrate the usefulness of our previously developed protocol for the stereoselective synthesis of 4,5-dialkylated prolines.\textsuperscript{19,20} Starting from enantiopure L-pyroglutamic acid the stereochemically pure octahydroindole 2a was obtained in 27% overall yield (10 steps) exploiting a highly diastereoselective Hosomi–Sakurai allylation and a ring-closing metathesis as key steps. The conversion of 2a into the drug trandolapril (1) was then achieved in 92% yield through peptide-coupling and deprotection under mild conditions. In contrast to previous syntheses of 1 our strategy uniquely relies on the annulation of the 6-membered ring using a pyrrolidine building block from the chiral pool.

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**Supporting Information**

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**References and Notes**


(20) Detailed experimental procedures and characterization data are given in the Supporting Information.

**Synthesis of Di-tert-butyl-(2S,4R)-4,5-diallylpyrrolidine-1,2-dicarboxylate (8)**

To a solution of 0.55 g (1.61 mmol, 1.0 equiv) of methoxyproline (12) in 13 ml CDCl3, were added 0.64 ml (4.03 mmol, 2.5 equiv) of allyl-TMS at –78 °C. Afterwards, 0.85 ml (3.22 mmol, 2 equiv) of BF3·OEt2 (48%) were added dropwise over 5 min. After 2 h of stirring at –78 °C, the reaction mixture was quenched with 5 ml of a saturated solution of NaHCO3 and the aqueous layer extracted three times with 30 ml of MTBE. The organic layers were washed twice with saturated solution of sodium chloride, dried over MgSO4, filtered, and evaporated to dryness. After chromatographic separation of the diastereomeric mixture (17:1 'cis/trans') and purification on silica (EtOAc/CDHex = 1:4) 0.42 g (1.19 mmol, 74%) of the dialylated proline 8 was obtained as a colorless oil. 1H NMR (300 MHz, CDCl3, mixture of rotamers): δ = 5.76–5.50 (m, 2 H, H-10/13), 4.99–4.85 (m, 4 H, H-11/14), 4.10–3.93 (m, 1 H, H-2), 3.58–3.42 (m, 1 H, H-3). 13C NMR (75 MHz, CDCl3, mixture of rotamers): δ = 172.2 (C-10), 154.3 (C-13), 126.4, 126.1 (C-7/8), 80.8, 79.6 (C-16), 62.9 (C-2), 59.4, 58.9 (C-5), 41.3, 38.8 (C-4, 11), 79.6 (C-14), 61.0 (C-2), 60.2 (C-5). HRMS (ESI): m/z = [M + Na]+ calcd: 346.1989; found: 346.1987. The colorless oil 8 was obtained as a colorless oil. 1H NMR (300 MHz, CDCl3, mixture of rotamers): δ = 5.76–5.50 (m, 2 H, H-10/13), 4.99–4.85 (m, 4 H, H-11/14), 4.10–3.93 (m, 1 H, H-2), 3.58–3.42 (m, 1 H, H-3). 13C NMR (75 MHz, CDCl3, mixture of rotamers): δ = 172.2, 172.0 (C-6), 154.1, 153.7 (C-15), 136.4, 135.7, 135.4 (C-10/13), 116.8, 116.7 (C-11/14), 80.6 (C-7), 79.6, 79.5 (C-16), 62.9 (C-2), 59.4, 58.9 (C-5), 41.3, 40.2 (C-4), 38.8 (C-12), 38.1, 37.8 (C-9), 33.3, 32.4 (C-3), 28.3, 27.9 (C-8/17) ppm. HRMS (ESI): m/z = [M + Na]+ calcd: 374.2302; found: 374.2301.

**Synthesis of Di-tert-butyl-(2S,3aR)-3a,4,7a-hexahydro-1H-indole-1,2-dicarboxylate (7)**

To a solution of 0.40 g (1.14 mmol, 1.0 equiv) of diallylproline 8 in 35 ml CH2Cl2, was added 0.06 mmol (0.05 equiv) 4-tert-butyliodide 7 and 0.02 g (0.09 mmol, 0.08 equiv) Cul at room temperature. After stirring for 2.5 h, the solution was evaporated under reduced pressure to dryness. After chromatographic purification on silica (CyHex/EtOAc = 4:1) the hexahydroidole 7 (0.35 g, 1.08 mmol, 95%) was obtained as colorless oil. 1H NMR (300 MHz, CDCl3): δ = 5.72–5.62 (2 H, H-10/13), 4.37–4.11 (1 H, H-2), 3.25–3.04 (1 H, H-3), 1.46 (18 H, H-12/15) ppm. HRMS (ESI): m/z = [M + Na]+ calcd: 346.1989; found: 346.1987.