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Synthesis and structure determination of methyl (3*S*)- and (3*R*)-(*trans*-(3′*R*,4′*R*)-3-amino-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-2,2-dimethyl-3-ferrocenylpropanoate

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ABSTRACT

Lewis acid (ZnI_2) – promoted Mannich reaction of azetidin-2-one – tethered aldimine **3** with silylenol ether **4** in toluene at –20 °C afforded a diastereomeric mixture of β-amino acid esters **5** and **6** in ratio 65:35. Diastereomers **5** and **6** were chromatographically separated and their crystal structure determined in order to establish unambiguously both absolute and relative configurations at the stereogenic centers C11, C12, and C14. The final value of the freely refined Flack parameter of diastereomer **6**, $x = -0.003$ (3), unambiguously indicates that all three centers have *R* configuration. According to the synthetic procedure, configurations on C12 and C14 of diastereomer **5** have the same *R* orientation as of diastereomer **6**, therefore Friedel pairs for the structure of **5** were not measured. Furthermore, *S* configuration on C11 of diastereomer **5** was assigned in relation to *R* configuration at C12 and C14 stereogenic centers.

1. Introduction

The asymmetric Mannich reaction represents one of the most efficient methods for the synthesis of chiral nitrogen – containing compounds, e.g., β-amino acid esters, β-lactams, and β-amino alcohols [1–7]. It ranks also among the most potent enantioselective and diastereoselective C–C bond construction reactions that makes it an excellent choice in natural product synthesis [8]. Since Ojima et al. first described [9] the Lewis acid – promoted condensation of silylenol ethers to aldimines, this procedure has been widely used for the construction of valuable β-aminocarbonyl compounds to provide useful routes for the synthesis of β-amino acid esters that are important precursors of various β-lactams and β-amino acids [8,10–15].

Monocyclic β-lactam derivatives occupy a central place among medicinally important compounds due to their diverse and interesting antibiotic activities [16–18]. Consequently their synthesis has been of considerable interest to the synthetic community in the past few decades [19,20]. β-Lactams are also known as versatile synthons in the design of novel biologically active compounds [16–18,21,22]. Their potential is also recognized in the field of amino acid and peptide synthesis, where they provide access to non-protein α- and β-amino acids and their peptides [19,23]. The synergy of the stereoselective Mannich reaction of azetidin-2-one – tethered aldimines with silylenol ethers and post-synthetic β-lactam ring opening can provide multifunctional compounds, e.g., diamino acids and diamino alcohols. The multifunctional compounds of this type can serve as valuable precursors for exploration in the field of peptidomimetics [14,24,25], enzyme inhibition [26], and the synthesis of macrocyclic compounds [27].

In continuation of our research in the field of β-lactam chemistry [28–32], we report here Lewis acid – promoted Mannich reaction of azetidin-2-one – tethered aldimines with silylenol ethers for the synthesis of β-amino acid esters directly linked to the β-lactam ring. In this reaction, we obtained a diastereomeric mixture of β-amino acid esters **5** and **6**, which were chromatographically separated and their crystal structure determined by X-ray crystallographic analysis. The complete influence study on the diastereoselectivity of the reaction, employing the variety of substituents on the imine phenyl, Lewis acids, and solvents, will be published separately.

2. Experimental

2.1. General techniques

Melting points were determined on a Reichert Thermovar 7905 apparatus. The IR spectra were recorded by means of a FT-IR Perkin Elmer Spectrum RX I FT-IR System spectrometer (KBr pellets

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technique). The ^{1}H and ^{13}C NMR spectra (in $CDCl_3$ at room temperature) were measured on a Bruker 300 spectrometer, δ in ppm relative to tetramethylsilane as the internal reference. Microanalysis was performed on a Perkin Elmer 2400 Series II CHNS/O Analyzer. Optical rotations: Optical Activity AA-10 Automatic Polarimeter in a 1 dm cell; *c* in g/100 mL. HPLC analysis was performed on a Dr. ing. Herbert Knauer GmbH., Berlin, Germany, HPLC System supplied with UV/VIS WellChrom Diode Array Detector K-2800 using Knauer, Kromasil, 5 μm, C18 (reversed phase) 4.0 × 250 mm HPLC column operated at a room temperature and a flow rate 1 mL/min; linear gradient of water containing 9% AccQ·Tag™ Eluent A Concentrate (solvent A) and CH_3CN (solvent B); 40% A + 60% B, 0 min; 5% A + 95% B, 16 min; 40% A + 60% B, 1 min; 40% A + 60% B, 3 min. LC–MS analysis was performed on a Agilent 1200 LC–MS System equipped with binary pump, autosampler (volume injection set to 10 μL), Diode Array detector, and Agilent 6410 Triple Quadrupole Mass Spectrometer with electrospray ionization (ESI) using Agilent, Zorbax, 3.5 μm, C18 (reversed phase) 4.6 × 75 mm HPLC column operated at a room temperature and a flow rate 0.5 mL/min; isocratic gradient of water containing 0.1% formic acid (solvent A) and CH_3CN (solvent B); 30% A + 70% B, 60 min. Operating conditions of the ESI interface in positive ion mode were: source temperature 350 °C, gas (nitrogen) flow 10 L/min, fragmentor voltage 135 V, nebulizer gas (nitrogen) pressure 45 psi, capillary voltage 4000 V.

trans-3-Amino-β-lactam **1** was prepared according to the literature [31,33].

2.1.1. (3R,4R)-3-Ferrocenylmethylidenamino-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidine (**3**)

A mixture of *trans*-(3*R*,4*R*)-3-amino-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidine **1** (68.2 mg, 0.254 mmol) and ferrocenecarboxaldehyde **2** (59.9 mg, 0.280 mmol) was dissolved in anhydrous ethanol (5.0 mL), heated under reflux for 12 h and followed by cooling to room temperature. The reaction mixture was then evaporated to dryness, redissolved in dichloromethane (5.0 mL) and dried over anhydrous sodium sulfate. Sodium sulfate was filtered off, washed with dichloromethane (3 × 5.0 mL) and filtrate evaporated to dryness. The crude **3** was purified by recrystallization from petroleum ether (b.p. 40–70 °C) to yield 91.7 mg (78%); R_f = 0.25 in dichloromethane; m.p. 167–168 °C; $[\alpha]_D$ = +314.25 (*c* = 1.00 g/100 mL, dichloromethane). IR (KBr) ν_{max}/cm^{-1}: 2928, 1736, 1702, 1458, 1347, 1253, 828; ^{1}H NMR ($CDCl_3$) δ/ppm: 3.74 (s, 3H, OCH_3), 4.23 (s, 5H, Fc), 4.28 (s, 1H, Fc), 4.41–4.45 (m, 2H, Fc), 4.49 (bs, 1H, C4, β-lactam), 4.59–4.64 (m, 1H, Fc), 4.74–4.80 (m, 1H, Fc), 5.14 (d, 1H, *J* = 1.41 Hz, C3, β-lactam), 6.79 (d, 2H, *J* = 9.06 Hz, C3 and C5, PMP), 7.28 (d, 2H, *J* = 9.06 Hz, C2 and C6, PMP), 7.38–7.40 (m, 5H, Ph), 8.26 (s, 1H, CH═N); ^{13}C NMR ($CDCl_3$) δ/ppm: 55.37 (OCH_3), 63.49 (C4, β-lactam), 68.16, 69.56, 71.09, 71.30 and 73.15 (Fc), 79.08 (C1, Fc), 83.88 (C3, β-lactam), 114.25 (C3 and C5, PMP), 118.68 (C2 and C6, PMP), 126.15 (C2 and C6, Ph), 128.55 (C4, Ph), 129.13 (C3 and C5, Ph), 130.92 (C1, Ph), 136.84 (C1, PMP), 156.11 (C4, PMP), 163.44 (CO, β-lactam), 165.46 (CH═N).

Anal. Calcd. for $C_{27}H_{24}N_2O_2Fe$ (M_r = 464.35): C 69.84, H 5.21, N 6.03%; found: C 69.65, H 5.13, N 6.21%.

2.1.2. Methyl (3S/3R)-(trans-(3′R,4′R)-3-amino-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-2,2-dimethyl-3-ferrocenylpropanoate (**5**/**6**)

To a suspension of ZnI_2 (2.10 mg, 0.0065 mmol) in anhydrous toluene (1.0 mL) a solution of imine **3** (15.0 mg, 0.032 mmol) in anhydrous toluene (4.0 mL) was added dropwise and stirred for 15 min at −20 °C. To the reaction mixture silylenol ether **4** (7.2 μL, 0.036 mmol) was added, the mixture was stirred for 6 h at −20 °C, and then overnight at room temperature. The reaction mixture was poured into ethyl acetate (20.0 mL) containing saturated solution of sodium bicarbonate (10.0 mL) and the product was further extracted with ethyl acetate (2 × 20.0 mL). The combined extracts (60.0 mL) were dried over anhydrous sodium sulfate, filtered and the filtrate evaporated to dryness. The product (14.3 mg, 78%) was obtained as a mixture of diastereomers **5**/**6**; R_f = 0.21 (**5**) and R_f 0.15 (**6**) (a mixture of ethyl acetate and petroleum ether in ratio 1:5 as eluent). RP-HPLC analysis of diastereomeric mixture showed ratio of **5** and **6** – 65:35% (**5**, 16.42 min and **6**, 17.43 min). LC–MS for $C_{32}H_{34}N_2O_4Fe$ **5**/**6** (M_r = 566.4832): calcd. *m/z* $[M]^+$ 566.19; found 566.30 (**6**, 33.74 min) and 566.30 (**5**, 46.25 min).

The diastereomeric mixture of **5**/**6** was separated by a silica gel column chromatography and thus obtained fractions of **5** and **6** were further purified by a preparative thin layer chromatography using a mixture of ethyl acetate and petroleum ether in ratio 1:5 as eluent.

2.1.2.1. Methyl (3S)-(trans-(3′R,4′R)-3-amino-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)-2,2-dimethyl-3-ferrocenylpropanoate (**5**).

Yield: 9.9 mg (54%); R_f = 0.21; m.p. 113–114 °C; $[\alpha]_D$ = +76.19 (*c* = 0.05 g/100 mL, dichloromethane); IR (KBr)) ν_{max}/cm^{-1}: 3678, 3652, 1752, 1561, 1512, 1458, 1389, 1297, 1241, 1142, 1033, 834, 762, 705, 511; ^{1}H NMR ($CDCl_3$) δ/ppm: 0.97 (s, 3H, $(C\underline{H}_3)_2CCH(Fc)NH$), 0.99 (s, 3H, $(C\underline{H}_3)_2CCH(Fc)NH$), 2.27 (bs, 1H, NH), 3.57 (s, 3H, $COOCH_3$), 3.74 (s, 3H, OCH_3, PMP), 3.78 (s, 1H, $C\underline{H}(Fc)NH$), 3.97 (s, 1H, Fc), 4.03 (s, 5H, Fc), 4.13 (s, 2H, Fc), 4.18 (s, 1H, Fc), 4.60 (d, 1H, *J* = 1.38 Hz, C4, β-lactam), 4.72 (d, 1H, *J* = 1.26 Hz, C3, β-lactam), 6.79 (d, 2H, *J* = 8.97 Hz, C3 and C5, PMP), 7.26 (d, 2H, *J* = 8.94 Hz, C2 and C6, PMP), 7.32–7.45 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ/ppm: 21.00 ($(\underline{C}H_3)_2CCH(Fc)NH$), 22.48 ($(\underline{C}H_3)_2CCH(Fc)NH$), 48.74 ($(CH_3)_2\underline{C}CH(Fc)NH$), 51.63 ($COO\underline{C}H_3$), 55.39 ($OCH_3$, PMP), 63.12 (C4, β-lactam), 65.89 (C3, β-lactam),

Table 1
Crystallographic data collection and structure refinement details for diastereomers **5** and **6**.

Diastereomer	**5**	**6**
Empirical formula	$C_{32}H_{34}N_2O_4Fe$	$C_{32}H_{34}N_2O_4Fe$
Formula wt. (g mol^{-1})	566.48	566.48
Crystal dimensions (mm)	0.27 × 0.23 × 0.15	0.37 × 0.30 × 0.23
Space group	$P2_1$	$P2_12_12_1$
a (Å)	11.2795 (2)	10.0191 (1)
b (Å)	10.9003 (2)	10.1560 (1)
c (Å)	11.4275 (3)	27.9553 (2)
α (°)	90	90
β (°)	91.789 (2)	90
γ (°)	90	90
Z	2	4
V (Å^3)	1404.33 (5)	2844.56 (4)
D_{calc} (g cm^{-3})	1.340	1.323
μ (mm^{-1})	4.623	4.565
Θ range (°)	3.87–76.54	4.63–76.10
T (K)	293 (2)	293 (2)
Diffractometer type	Xcalibur Nova	Xcalibur Nova
Range of *h*, *k*, *l*	−11 < *h* < 14; −13 < *k* < 13; −14 < *l* < 14	−11 < *h* < 12; 12 < *k* < 12; −34 < *l* < 34
Reflections collected	13038	13836
Independent reflections	5025	5407
Observed reflections ($I \geqslant 2\sigma$)	4684	4993
Absorption correction	Multi-scan	Multi-scan
R_{int}	0.0481	0.0276
R (*F*)	0.0388	0.0327
R_w (F^2)	0.1164	0.0921
Goodness of fit	1.086	1.061
H atom treatment	Constrained	Constrained
No. of parameters	352	352
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.345; −0.320	0.378; −0.325
Flack parameter	0.006 (4)	−0.003 (3)