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Stereoselective synthesis of 1-amino-5-butyl-3-oxo-cyclohexane-1-carboxylic acid derivatives

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Butyl-substituted 1-amino-3-oxocyclohexane-1-carboxylic acid derivatives have been prepared from 5,5-tethered dienes of (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine in stereoselective synthesis. RCM reactions of the diene afforded a heterospirenone which was the substrate for the conjugated addition reaction with lithium dibutylcuprate. Hydrolysis of the adduct provided cyclic α-amino acid derivatives. The absolute configuration at the new stereocentres were established by X-ray analyses.

Key words: constrained α-amino acids, Schöllkopf's auxiliary, stereoselective synthesis, ring closing methathesis, X-ray crystal structure

INTRODUCTION

Synthetic enantiomerically pure α-amino acids with constrained geometry and their derivatives play an important role in pharmaceutical drug design and development. Incorporation of constrained α-substituted α-amino acids into peptides constitutes an efficient approach for generating structurally defined peptides as conformational probes and bioactive agents [1–4]. Constrained cyclic α-amino acids are promising candidates for stabilizing highly regular β-helical motifs excised from naturally occurring proteins. Theoretical studies showed that presence of 1-aminocyclohexane-1-carboxylic acid in flexible loops of β-helical motifs affected their conformational stability by absorbing part of overall structure fluctuations [5].

Preparation of enantiomerically pure synthetic amino acids can be achieved either by applying chromatographic resolution procedures on chiral stationary phases or by asymmetric synthesis. Chemically, asymmetric synthesis can be performed using chiral auxiliaries (chirons), reagents or catalysts [6–8]. In recent years, a methodology for asymmetric synthesis of conformationally constrained α-amino acids, which involves bisalkenylation or alkenylation-alkynylation of the Schöllkopf's bislactim ether reagent followed by a ring closing metathesis reaction (RCM) and hydrolysis of spirocyclic intermediates, has been developed [9 and references therein]. This methodology allowed partially to prepare cyclohexenone chiral intermediates whose further hydrolytic cleavage furnished new cyclic constrained oxo-substituted α-amino acids [10, 11]. When the mentioned cyclohexenone chiral substrates were treated with organocuprates, formation of substituted cyclohexanone adducts took part. Mild acid hydrolysis of the latter afforded new cyclic α-amino acid derivatives with an additional alkyl or aryl substituent which rigidifies the cyclohexane ring [11, 12]. This method was applied also for preparation of cyclic rigidified homoserine analogues [12]. Herein, we describe a study designed to yield a cyclohexanone ring containing α-amino acid derivatives with an additional alkyl substituent, in this particular case a butyl substituent.

RESULTS AND DISCUSSION

The starting substrate for the present work was chiral cyclohexenone **2**, which was prepared from the bislactim ether **1** by stepwise substitutions at C-5 in the pyrazine ring, followed by cyclization of epimeric allylic alcohols applying the Grubbs ring closing metathesis (RCM) methodology (catalyst: bis(tricyclohexylphosphine)benzylidene ruthenium dichloride) [13] and, finally, Swern oxidation of the obtained epimeric cyclohexenols as described in [12, 14, 15]. The com-

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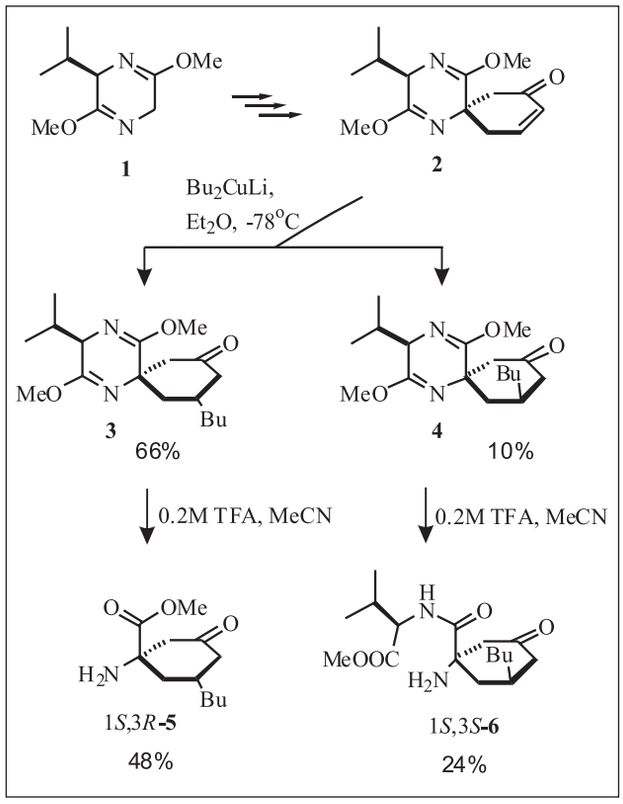
pound **2** possessed the (2*R*, 5*S*) configuration assigned by a single crystal X-ray analysis [12].

In the next step, the chiral cyclohexenone substrate **2** was subjected to the conjugate addition reaction with lithium dibutylcuprate as a reagent generated *in situ* from CuI and BuLi in dry degassed diethyl ether. The conjugate addition reaction was carried out at –78 °C to give isomeric adducts **3** and **4** in 66% and 10% yields, respectively. Both isomers were isolated epimerically pure by flash chromatography.



The molecular structure of **3** and **4** was proved by methods of NMR spectroscopy and mass spectrometry. The presence of the butyl substituent for **3** and **4** was identified by the presence of a triplet of the methyl group protons at 0.88 (*J* 7.0 Hz) and 0.89 (*J* 7.0 Hz), respectively. The mass spectra in both cases contained a peak of the molecular ion with m/z 322. In order to assess the spatial structure of butyl isomers, a single crystal X-ray analysis was performed. The minor adduct was found to have the structure **4** in which the butyl group has a *cis*-facial relationship to the 6-methoxy group in the pyrazine ring (Fig. 1). The absolute configurations at the stereogenic center 5'*S* were established relative to the known chirality (2*R*) at C2 of the pyrazine ring.

The stereoselectivity of conjugate addition with dibutylcuprate can be rationalized in terms of a difference in the shielding of the two faces of the cyclohexenone ring. Inspection of a molecular model shows that one face of the cyclohexenone ring is shielded by the overlying 6-methoxy group of the orthogonal pyrazine ring, while no serious interaction is seen at the other face of it. Hence, adduct formation would be expected to be preferentially at the unshielded face with formation of the major stereoisomer **3**.

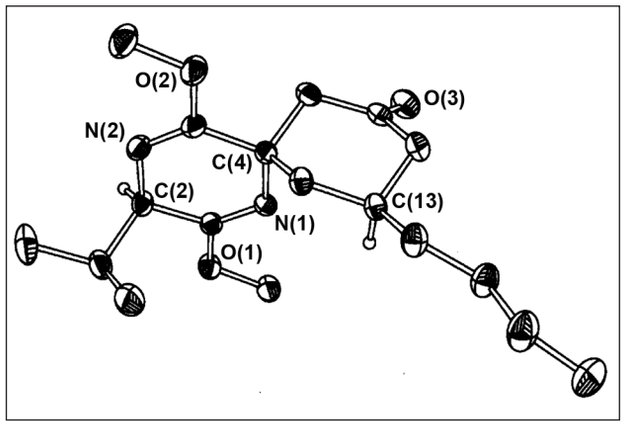


Fig. 1. ORTEP drawing of compound **4**. The thermal elipsoids are shown with 50% probability

The hydrolysis of the spirocyclic bislactim ether **3** under mild acidic conditions using 0.2 M TFA in aqueous acetonitrile furnished the desired amino acid ester **5** which was isolated after flash chromatography as a colourless oil in 48% yield. However, the hydrolytic cleavage of the spirocyclic bislactim ether **4**, carried out in analogous conditions, gave the dipeptide **6** as a major product. The structure of compound **6** was confirmed by the ^{13}C NMR spectrum which contained three signals of carbonyl carbons at 167.19, 172.1 and 200.2 ppm, respectively. The different outcome of hydrolytic cleavage of bislactim ether **4** in comparison with the hydrolysis of bislactim ether **3** can be rationalized by shielding effects at reaction centres due to different configurations of the starting substrates [12].

CONCLUSIONS

New conformationally constrained and functionalized cyclic α-amino acid derivatives with the α-carbon atom of the amino acid imbedded in the butylcyclohexanone ring have been synthesized in an efficient stereoselective manner. Absolute configurational assignments were effected by single crystal X-ray analyses.

EXPERIMENTAL

^{1}H NMR spectra were recorded with a Bruker DPX-300 instrument (300 MHz). ^{13}C NMR spectra were obtained on a Bruker DPX-300 instrument (75 MHz). Chemical shifts, expressed in ppm, were relative to tetramethylsilane (TMS). Chemical shifts are reported in ppm using residual $CHCl_3$ (7.24 ppm) and $CDCl_3$ (77 ppm) as references. The mass spectra under electron impact conditions (EI) were recorded at a 70 eV ionizing potential. The spectra are presented as *m/z* (% rel. int.). The optical rotations were measured at ambient

temperature. Dry THF and benzene were distilled from sodium and benzophenone under argon. Dry 1,2-dichloroethane was distilled from calcium hydride under argon. The solvents were degassed by bubbling argon through.

X-Ray crystallographic analysis data for the compound 4. X-ray data were collected on a Siemens SMART CCD diffractometer using graphite monochromated Mo*K*α radiation (λ = 0.71073 Å). Data collection method: ω-scan, range 0.6°, crystal to detector distance 5 cm. Data reduction and cell determination were carried out with the SAINT and XPREP programs [16]. The structure was determined and refined using the SHELXTL program package [17]. The non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen atoms were located from difference Fourier maps and refined with isotropic thermal parameters.

X-ray crystal data and structure determination for $C_{18}H_{30}N_2O_3$, 3: *M*r 322.44, orthorhombic, space group P2(1)2(1)2(1), *a* = 8.3675(7) Å, *b* = 13.3610(12) Å, *c* = 16.5487(14) Å, α = 90°, β = 90°, γ = 90°, V 1850.1(3) Å^3, Z = 4, D_{calc} = 1.158 mg mm^{-3}, absorption coefficient 0.078 mm^{-1}, F(000) = 704. Data were collected using a crystal, size 0.7 × 0.4 × 0.2 mm, on a Siemens SMART CCD diffractometer. A total of 31450 reflections (unique 5632) were collected for 4.09 < θ < 30.51° and –11 <= *h* <= 11, –19 <= *k* <= 19, –23 <= *l* <= 23. Completeness to θ = 30.51 was 99.6%. As the refinement method, full-matrix least-squares on F^2 were used, and the data / restraints / parameters were 5632 / 0 / 328. The final *R* indices were [$I > 2.00\sigma(I)$] R_1 = 0.0358, wR_2 = 0.0960, and (all data) R_1 = 0.0432, wR_2 = 0.1016. The goodness-of-fit on F^2 0.990 and the largest difference peak and hole were 0.305 and –0.162 e · Å^{-3}.

(2*R*, 5*S*, 5'*R*)- and (2*R*, 5*S*, 5'*S*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine-5-spiro(5'-butyl-3'-cyclohexanones) 3, 4. Dry degassed diethyl ether (11 ml) was added to dry CuI (145 mg, 0.76 mmol) under argon, and the mixture was stirred at 0 °C for 5 min before etheral BuLi (1.07 ml, 1.67 mmol, 2.4 M) was added. The solution was stirred at 0 °C for 10 min, cooled to –78 °C, and a solution of (2*R*, 5*S*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine-5-spiro(4'-cyclohexen-3'-one) **2** (200 mg, 0.76 mmol) in dry diethyl ether (2 ml) was added. The reaction mixture was quenched after 45 min at –78 °C by injection of sat. NH_4Cl : aq.NH3 (conc.) (15 ml; ratio 25 : 4). The mixture was stirred until a deep blue colour developed and all the solid material dissolved. The two-phase system was separated, the aqueous layer extracted with diethyl ether (3 × 10 ml), the combined organic solutions were dried ($MgSO_4$) and evaporated. The two products were separated by flash chromatography using hexane : EtOAc 4 : 1 as an eluent. The minor isomer **4** was eluated first; yield 25 mg of a crystalline solid, melting point 61–62 °C (from hexane). $[\alpha]_D$ = –13 (c = 0.30, $CHCl_3$). ^{1}H NMR (300 MHz): d 0.76 (d, *J* 7 Hz, 3H, CH_3), 0.89 (t, *J* 7 Hz, 3H, CH_3), 1.06 (d, *J* 7 Hz, 3H, CH_3), 1.28–1.32 (m, 6H, 3 × CH_2), 1.56–1.65 (m, 1H, CH*H*), 1.85–2.56 (m, 7H 2 × CH_2, CH, CH, C*H*H), 3.63 (s, 3H, CH_3O), 3.64 (s, 3H, CH_3O), 3.94 (d, *J* 3 Hz, 1H, CH). ^{13}C NMR (75 MHz): δ 13.86 (CH_3), 17.48 (CH_3), 19.4 (CH_3), 22.60 (CH_2), 28.7 (CH_2), 31.36 (CH), 33.27 (CH), 36.64 (CH_2), 43.59 (CH_2), 45.78 (CH_2), 52.07 (CH_2), 52.26 (2 × CH_3O), 59.50 (C-5), 61.34 (C-2), 162.81 (C), 164.68 (C), 209.15 (C = O). MS (EI): 322 (29, M$^+$), 279 (100), 169 (90), 153 (48). Calculated $C_{18}H_{30}N_2O_3$: C, 67.05; H, 9.38%. Found: C, 67.36; H, 9.15%.

The major isomer **3** was the second product eluated; yield 160 mg (66%) of a crystalline solid, melting point 83–84 °C (from hexane). $[\alpha]_D$ = –7.9 (c = 0.48, $CHCl_3$). ^{1}H NMR (300 MHz): 0.68 (d, *J* 7 Hz, 3H, CH_3), 0.88 (t, *J* 7 Hz, 3H, CH_3), 1.06 (d, *J* 7 Hz, 3H, CH_3), 1.27–1.33 (m, 6H, 3 × CH_2), 1.58–1.65 (m, 1H, CH*H*), 1.97–2.51 (m, 6H, 2 × CH_2, CH, C*H*H), 2.85–2.87 (m, 1H, CH), 3.57 (s, 3H, CH_3O), 3.70 (s, 3H, CH_3O), 3.93 (d, *J* 3 Hz, 1H, CH). ^{13}C NMR (75 MHz): δ 14.0 (CH_3), 16.9 (CH_3), 19.3 (CH_3), 22.7 (CH_2), 28.7 (CH_2), 30.9 (CH), 32.7 (CH), 36.5 (CH_2), 42.4 (CH_2), 47.7 (CH_2), 51.7 (CH_2), 52.5 (CH_3O), 52.6 (CH_3O), 60.4 (C-5), 60.5 (C-2), 161.3 (C), 163.4 (C), 209.5 (C = O). MS (EI): 322 (11.0, M$^+$), 279 (100), 169 (94), 153 (55). Calculated for $C_{18}H_{30}N_2O_3$: C, 67.05; H, 9.38%. Found: C, 67.28; H, 9.50%.

Methyl (1*S*, 5*R*)-1-amino-3-oxo-5-butylcyclohexane-1-carboxylate 5. (2*R*, 5*S*, 5'*R*)-2,5-Dihydro-2-isopropyl-3,6-dimethoxypyrazine-5-spiro(5'-butyl-3'-oxocyclohexane) **3** (58 mg, 0.18 mmol) was stirred with trifluoroacetic acid (10 ml, 1.9 mmol, 0.2 M) and acetonitrile (10 ml) at ambient temperature for 4 days. The solution was evaporated almost to dryness, water (15 ml) and dichloromethane (25 ml) were added, the aqueous layer was brought to pH 10 by addition of conc. ammonia, the mixture was extracted with dichloromethane (5 × 10 ml), the combined organic layers were dried ($MgSO_4$), evaporated, and the product was isolated after flash chromatography using 2% methanol in dichloromethane; yield 20 mg (48%) of a colourless oil. $[\alpha]_D$ = +5.8 (c = 0.174, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85–1.41 (m, 11 H, CH_3, NH_2, 3 × CH_2), 2.07–2.76 (m, 6H, 3 × CH_2), 3.66–3.79 (m, 1H, CH), 3.92 (s, 3 H, OMe). Calculated for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31%. Found: C, 63.58; H, 9.47%.

Methyl (*R*)-*N*-[(1*S*, 5*S*)-1-amino-5-butyl-3-oxocyclohexane-1-carbonyl]valinate 6. (2*R*, 5*S*, 5'*S*)-2,5-Dihydro-2-isopropyl-3,6-dimethoxypyrazine-5-spiro(5'-butyl-3'-oxocyclohexane) **4** (120 mg, 0.37 mmol) was stirred with trifluoroacetic acid (20 ml, 4.09 mmol, 0.2 M) and acetonitrile (20 ml) at ambient temperature for 4 days. The solution was evaporated almost to dryness, water (15 ml) and dichloromethane (25 ml) were added, the aqueous layer brought to pH 10 by addition of conc. ammonia, the mixture was extracted with dichloromethane (5 × 10 ml), the combined organic layers were dried ($MgSO_4$), evaporated, and the pro-

duct was isolated by flash chromatography using 3% methanol in dichloromethane; yield 21 mg (24%) of a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89–0.98 (m, 9H, 3 × CH_3), 1.35–1.42 (m, 9H, NH_2, CH, 3 × CH_2), 2.11–2.84 (m, 7H, CH, 3 × CH_2), 3.80 (s, 3 H, OMe), 4.61–4.65 (m, 1H, CH), 6.38 (d, *J* 2.2 Hz, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (CH_3), 17.8 (CH_3), 19.0 (CH_3), 22.7, 28.6, 31.4, 31.7, 34.8, 35.3, 44.2, 52.6, 57.3, 128.8, 153.2, 167.19 (CO), 172.1 (CO), 200.2 (CO). Calculated for $C_{17}H_{30}N_2O_4$: C, 62.55; H, 9.26%. Found: C, 62,72; H, 9,38%.

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STEREOSELEKTYVI 1-AMINO-5-BUTIL-3-OKSOCIKLOHEKSAN-1-KARBOKSIRŪGŠTIES DARINIŲ SINTEZĖ

S a n t r a u k a

Panaudojus stereoselektyvios sintezės metodus susintetinti nauji suvaržytos konformacijos α-aminorūgščių dariniai. Žiedo uždarymo metatezės reakcijos pagalba iš žinomos konfigūracijos 5,5-dialkilenbislaktiminio eterio buvo gautas chiralinis substratas – cikloheksenonas, kurį paveikus dibutilkupratu susidarė atitinkami epimeriniai konjuguoto prijungimo produktai. Įvykdžius šių aduktų rūgštinę hidrolizę, buvo atitinkamai išskirti optiškai aktyvūs 1-amino-5-butil-3-oksocikloheksan-1-karboksirūgšties dariniai: metilesteris ir dipeptidas. Junginių absoliučioji konfigūracija nustatyta, pritaikius rentgeno spindulių analizės metodus.