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Asymmetric Synthesis of All Four Isomers of an Unusual Heterocycle-Containing Amino Acid: 2-Amino-3-furan-2-yl-pentanoic Acid

Nie, Lei[a](聂蕾) Yang, Rui[a](杨睿) Zhang, Conghai[a](张从海) Yin, Haichuan[b](尹海川)
Yan, Shengjiao[a](严胜骄) Lin, Jun*,[a](林军)

[a] *Key Laboratory of Medicinal Chemistry for Natural Resource, School of Chemical Science and Technology, Yunnan University, Kunming, Yunnan 650091, China*
[b] *The Education Department of Yunnan Province, Kunming, Yunnan 650091, China*

All four isomers of a novel β-branched unusual amino acid were designed and synthesized with high stereoselectivity (>90% *de*) and in 33%—44% overall yields by the use of 4(*R*/*S*)-5,5-dimethyl-4-phenyl-oxazolidin-2-one as the chiral auxiliary via asymmetric 1,4-Michael addition, direct or indirect azidation, hydrolysis and hydrogenation reactions.

Keywords asymmetric synthesis, unusual amino acid, oxazolidinone, chiral auxiliary, 2-amino-3-furan-2-yl-pentanoic acid

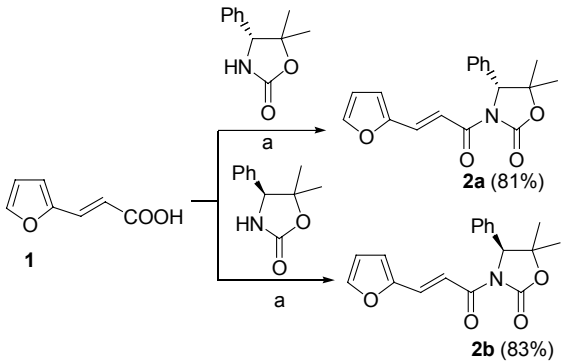
Introduction

Incorporation of conformationally constrained novel β-branched α-amino acids into bioactive peptides presents a rational approach to the design of highly potent and selective ligands.[1] Furthermore, the aromatic moieties of peptide side chain groups play an important role in the molecular recognition processes between peptide ligands and specific receptors as well as receptor subtypes. Aromatic ring-substituted amino acids can provide valuable tools in developing highly selective peptide ligands with specific structural features. In addition, they can provide a large lipophilic surface for binding to receptors and for crossing membrane barriers.[2] A general approach developed by Hruby *et al.* which can produce four pure optical isomers, has synthesized several series of specialized β-branched α-amino acids.[2-4] However, further exploration of various specialized amino acids, especially heterocycle-containing amino acids, still remain a central goal for meeting the requirements of peptide molecular design. Therefore, the design and synthesis of such unusual β-branched amino acids with lipophilic side chains have been crucial for the further development of peptides and peptide analogues.

Results and Discussion

We report herein the total asymmetric synthesis of a novel heterocycle-containing amino acid 2-amino-3-furan-2-yl-pentanoic acid. The synthesis started from the readily available starting material (*E*)-3-(furan-2-yl)-acrylic acid (**1**), which was coupled with Davies' "SuperQuats" auxiliaries (4*R*/*S*)-5,5-dimethyl-4-phenyl-oxazolidin-2-one[5] to control the diastereoselective reactions and yield the imide conjugates **2a** and **2b**[6] (Scheme 1).

Scheme 1 Preparation of **2a** and **2b**



Reagents and conditions: (a) $(CH_3)_3CCOCl$, Et_3N, *n*-BuLi, THF, N_2, −78 ℃

The chiral Michael acceptors **2a** or **2b** were reacted with EtMgBr via an asymmetric 1,4-Michael addition to produce the key intermediates **3a** or **3b**, respectively. The direct azidation of intermediates **3a** or **3b** introduced the azido group by stereoselective electrophilic azidation with trisyl azide[7] to produce α-azido derivatives **4a** or **4b**, respectively (Scheme 2).

* E-mail: linjun@ynu.edu.cn
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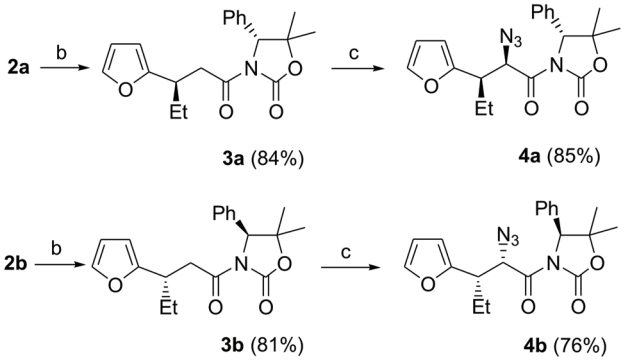
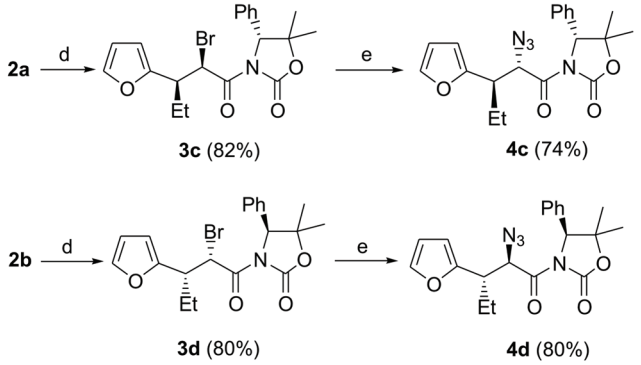
Scheme 2 Preparation of **4a** and **4b**



Reagents and conditions: (b) EtMgBr, CuBr•Me_2S, THF, N_2, −78 ℃; (c) KHMDS/NaH, Trisyl azide; HOAc, THF, N_2, −78 ℃

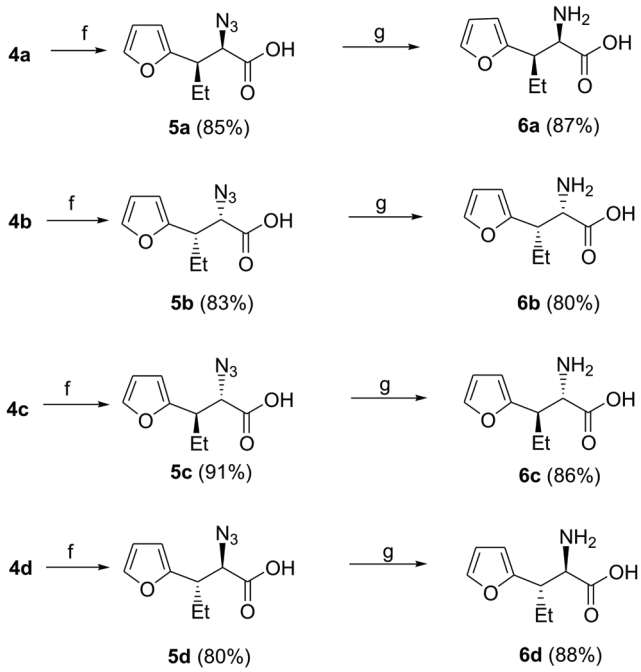
On the other hand, a one-pot tandem asymmetric 1,4-conjugate addition of organocuprates to the prochiral α,β-unsaturated intermediates **2a** or **2b**, followed by electrophilic bromination with *N*-bromosuccinimide (NBS), yielded the bromo-compounds **3c** or **3d**. Then, the bromo group of **3c** or **3d** was substituted by S_N2 displacement with NaN_3 which replaced the tetramethylguanidium azide[8] to give α-azido products with different α configurations, so that **4c** or **4d** were obtained (Scheme 3) with high chiral selectivity (>90% *de*). Via these two methodologies, we successfully synthesized all four isomers of α-azido products **4a**—**4d**. The removal of the chiral auxiliary of compounds **4a**—**4d** was performed using LiOH in the presence of hydrogen peroxide to yield azido acids **5a**—**5d** in moderate yields and the chiral auxiliary was recovered for further use at the same time.[9] The resulting azido acids **5a**—**5d** were subject to catalytic hydrogenation (10% Pd/C) at 138—207 kPa for 2 h. The crude amino acids were purified by ion-exchange chromatography to obtain the desired corresponding optically pure target α-amino acids **6a**—**6d** (Scheme 4).

Scheme 3 Preparation of **4c** and **4d**



Reagents and conditions: (d) NBS, N_2, THF, −78 ℃; (e) NaN_3, DMF, 30—40 ℃

Scheme 4 Preparation of **6a**—**6d**



Reagents and conditions: (f) LiOH/H_2O_2, THF/H_2O, 0 ℃; (g) 138—207 kPa, hydrogen (H_2), 10% Pd/C, MeOH/EtOH, 6 mol•L^{-1} HCl, ion exchange resin/column

Experimental

All reagents were commercially available and used without further purification. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker AM-300 or AM-500 spectrometer in $CDCl_3$ solution with TMS as the internal standard. Mass spectra were registered on an Agilent LC/MSD TOF spectrometer (ESI mode, 70 eV). Optical rotations were measured on a Perkin Elmer Model 341 Auto Polarimeter. The infrared (IR) spectra were recorded on a Shimadzu-450s infrared spectrophotometer with a KBr pellet. All melting points were determined on an XT4A melting point apparatus and were uncorrected. Diastereomeric excesses (*de*) were determined on a Bruker AM-500 spectrometer. THF and ether were freshly distilled from Na before use. The chiral auxiliary 4(*R*/*S*)-5,5-dimethyl-4-phenyl-oxazolidin-2-one was prepared following the Davies method.[5]

General procedure for the synthesis of compound 2

To a pre-cooled solution of **1** (5 g, 36 mmol) in dry THF (100 mL) stirred at −78 ℃, triethylamine (5 mL) was added via a syringe, followed by the addition of trimethylacetyl chloride (4.5 mL). The resulting white suspension was stirred at −78 ℃ for 15 min, 0 ℃ for 1 h, and then at −78 ℃ for another 15 min before transferring a stirred slurry of lithiated (4*R*/*S*)-5,5-dimethyl-4-phenyl-oxazolidin-2-one respectively into it via a cannula. The lithiated (4*R*)- or (4*S*)-5,5-dimethyl-4-phenyl-oxazolidin-2-one was prepared 15 min in advance at −78 ℃ by addition of *n*-butyllithium (22 mL) into the solution of (4*R*)- or (4*S*)-5,5-dimethyl-4-phenyl-oxazolidin-2-one (5.75 g, 30 mmol) in THF (80 mL) at −78 ℃. The resulting slurry was stirred at

−78 ℃ for 1 h and then at room temperature for 2 h. The reaction was always protected under a nitrogen atmosphere. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (70 mL). The organic phase was separated and the aqueous layer was extracted by ethyl acetate (75 mL×2). The combined organic phase was washed with saturated bicarbonate (80 mL×2), brine (80 mL) and water (80 mL), dried over anhydrous sodium sulfate and then rotary evaporated. The crude product was further purified by recrystallization from ethyl acetate and hexanes to give the pure product.

(*R*,*E*)-3-(3-(Furan-2-yl)acryloyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (**2a**): Yield 81%; m.p. 137—138 ℃; $[\alpha]_D^{20}$ +83.1 (*c* 1.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 7.86—6.45 (m, 10H, Ar and CH=CH), 5.18 (s, 1H, PhCH), 1.61 (s, 3H, CH_3), 1.00 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 165.4, 153.6, 151.8, 145.6, 136.8, 132.8, 129.3, 129, 126.8, 116.4, 115.1, 112.9, 82.7, 67.7, 29.4, 24.2; IR (KBr) *v*: 3506, 3339, 3112, 3029, 2987, 2935, 2866, 2644, 2359, 2143, 1886, 1765, 1679, 1614, 1551, 1467, 1395, 1331, 1246, 1159, 1108, 1036, 976, 935, 868, 830, 750, 686, 591, 524, 484, 421 cm^{-1}; ESI-MS *m/z* (%): 311 (M^+, 100); HR-MS (TOF ES^+) calcd for $C_{18}H_{17}NO_4$ $[M+Na]^+$ 334.1057, found 334.1050.

(*S*,*E*)-3-(3-(Furan-2-yl)acryloyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (**2b**): Yield 83%; m.p. 136—137 ℃; $[\alpha]_D^{20}$ −81.2 (*c* 1.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 7.86—6.46 (m, 10H, Ar and CH=CH), 5.18 (s, 1H, PhCH), 1.62 (s, 3H, CH_3), 1.01 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 165.4, 153.6, 151.8, 145.6, 136.8, 132.8, 129.3, 127.3, 126.8, 116.4, 115.2, 112.9, 82.8, 67.7, 29.4, 24.2; IR (KBr) *v*: 3512, 3347, 3031, 3101, 2987, 2939, 2870, 2643, 2554, 2486, 2144, 1956, 1887, 1769, 1679, 1615, 1550, 1467, 1330, 1227, 1159, 1105, 1033, 976, 935, 868, 829, 750, 686, 589, 524, 493 cm^{-1}; ESI-MS *m/z* (%): 311 (M^+, 100); HR-MS (TOF ES^+) calcd for $C_{18}H_{17}NO_4$ $[M+Na]^+$ 334.1056, found 334.1050.

General procedure for the preparation of organocopper reagents

A three-necked flask with a magnetic bar was placed with magnesium scraps (500 mg, 20.8 mmol) in dry ether or THF (50 mL). A few drops of bromoethane and a bit of iodine were added. When the reaction liquid showed signs of fading, more bromoethane (1.5 mL) diluted in THF (30 mL) was added into the reaction flask dropwise under nitrogen over 30 min and the reaction was stirred at room temperature for 1 h. The Grignard reagent EtMgBr (19.2 mmol) was prepared, then cooled to 0 ℃ before being transferred via a cannula to a stirring slurry of copper(I) bromide-dimethyl sulfide complex (1 g, 4.8 mmol) in THF (50 mL) at −78 ℃. The grey mixture was warmed to 0 ℃ and stirred for 30 min. The mixture turned black over time, at which point it was ready for conjugate additions.

General procedure for conjugate additions

To the above mixture of EtMgBr (19.2 mmol, 2 equiv.) and $CuBr{\bullet}SMe_2$ (1 g, 4.8 mmol, 0.5 equiv.) in 130 mL THF at −78 ℃, a solution of (*E*)-3-(3-(furan-2-yl)acryloyl)-5,5-dimethyl-4-phenyl-oxazolidin-2-one (**2**) (3 g, 9.6 mmol) in 50 mL of THF was added dropwise. The resulting mixture was stirred at −78 ℃ for 15 min, 0 ℃ for 2 h, and then at room temperature for 1 h under nitrogen. The process was monitored by TLC and the reaction was quenched by adding saturated ammonium chloride cautiously at 0 ℃. The organic phase was separated and the aqueous layer was extracted by ether (50 mL×2). The combined organic extracts were washed with brine (30 mL×2) and water (30 mL), dried over anhydrous magnesium sulfate and rotary evaporated to give the crude product which was purified by column chromatography.

(*R*)-3-((*R*)-3-(Furan-2-yl)pentanoyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (**3a**): Yield 84%; m.p. 110—112 ℃; $[\alpha]_D^{20}$ −70.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 7.37—6.00 (m, 8H, Ar), 5.01 (s, 1H, PhCH), 3.44 (q, *J*=8.6 Hz, 1H, furanyl-C**H**-C_2H_5), 3.23—3.13 (m, 2H, CH_2CO), 1.61 (s, 3H, CH_3), 1.67—1.64 (m, 2H, CHC**H**$_2$CH$_3$), 0.97 (s, 3H, CH_3), 0.79 (t, *J*=7.4 Hz, 3H, CH_2C**H**$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 172.4, 158.0, 154.1, 141.9, 137.2, 129.7, 129.5, 127.2, 110.8, 106.2, 83.3, 68.0, 40.4, 37.4, 29.8, 28.1, 24.5, 12.4; IR (KBr) *v*: 3127, 2925, 2861, 1785, 1692, 1597, 1500, 1456, 1384, 1329, 1266, 1222, 1159, 1082, 1016, 975, 944, 856, 807, 738, 699, 631, 599, 527, 467 cm^{-1}; ESI-MS *m/z* (%): 364 ($[M+Na]^+$, 100); HR-MS (TOF ES^+) calcd for $C_{20}H_{23}NO_4$ $[M+Na]^+$ 364.1525, found 364.1519.

(*S*)-3-((*S*)-3-(Furan-2-yl)pentanoyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (**3b**): Yield 81%; m.p. 110—112 ℃; $[\alpha]_D^{20}$ +70.6 (*c* 1.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 7.40—6.02 (m, 8H, Ar), 5.04 (s, 1H, PhCH), 3.50 (q, *J*=8.5 Hz, 1H, furanyl-C**H**-C_2H_5), 3.29—3.17 (m, 2H, CH_2CO), 1.57 (s, 3H, CH_3), 1.73—1.62 (m, 2H, CHC**H**$_2$CH$_3$), 1.00 (s, 3H, CH_3), 0.85 (t, *J*=7.2 Hz, 3H, CH_2C**H**$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 172.4, 158.0, 154.1, 141.9, 136.7, 129.2, 129.8, 126.8, 110.3, 106.2, 83.29, 68.0, 40.4, 37.4, 29.8, 28.1, 24.5, 12.42; IR (KBr) *v*: 3129, 1785, 1692, 1602, 1386, 1329, 1265, 1221, 1159, 1080, 1016, 807, 748, 696, 627, 470 cm^{-1}; ESI-MS *m/z* (%): 364 ($[M+Na]^+$, 100); HR-MS (TOF ES^+) calcd for $C_{20}H_{23}NO_4$ $[M+Na]^+$ 364.1515, found 364.1519.

General procedure for the direct azidation reaction

Potassium bis(trimethylsilyl) amide (KHMDS) (7.2 mL, 0.91 mol•L^{-1} in THF, 6.6 mmol, 1.5 equiv.) and NaH (280 mg, 60% in oil, 1.5 equiv.) were added via a syringe to a solution of *N*-acyloxazolidinone **3a** or **3b** (1.5 g, 4.4 mmol) in 50 mL of THF at −78 ℃ under nitrogen. The mixture was stirred at −78 ℃ under nitrogen for 30 min. A pre-cooled solution of trisyl azide (2 g, 6.6 mmol, 1.5 equiv.) in THF (40 mL) was added

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via a cannula. The reaction mixture was stirred at −78 ℃ for 15 min and then quenched with acetic acid (1.2 mL, 20.2 mmol, 4.6 equiv.). The reaction flask was immediately immersed in a water bath at 35 ℃ for 40 min with stirring, and the reaction was monitored by TLC. When the majority of the starting substance had been reacted, 100 mL of brine was added and the organic phase was separated. The aqueous phase was extracted with ether (50 mL×2). The combined organic phase was washed with brine (40 mL×2) and water (40 mL×2), and dried over anhydrous magnesium sulfate. Removal of the solvents gave the crude product as a light yellow oil, which was purified by silica gel column chromatography to obtain the *α*-azido compound **4a** or **4b**.

(*R*)-3-((2*R*,3*R*)-2-Azido-3-(furan-2-yl)pentanoyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (**4a**): Yield 85%; colourless sticky liquid; $[\alpha]_D^{20}$ −139.6 (*c* 0.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 7.38—6.16 (m, 8H, Ar), 5.54 (d, *J*=10 Hz, 1H, CHN_3), 4.86 (s, 1H, PhCH), 3.27—3.24 (m, 1H, franyl-C**H**-C_2H_5), 1.99—1.78 (m, 2H, CHC**H**$_2$CH$_3$), 1.37 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.85 (t, *J*=7.4 Hz, 3H, CH_2C**H**$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 169.6, 153.5, 152.9, 142.5, 142.5, 141.4, 135.9, 129.4, 129, 126.6, 110.8, 109.1, 83.4, 67.5, 61.8, 43.0, 29.0, 24.3, 23.9, 12.0; IR (KBr) *v*: 3126, 2104, 1776, 1708, 1496, 1397, 1328, 1267, 1224, 1160, 1098, 1010, 953, 815, 740, 707, 631, 531 cm^{-1}; ESI-MS *m/z* (%): 405 ([M+Na]$^+$, 100); HR-MS (TOF ES$^+$) calcd for $C_{20}H_{22}N_4O_4$ [M+Na]$^+$ 405.1539, found 405.1533.

(*S*)-3-((2*S*,3*S*)-2-Azido-3-(furan-2-yl)pentanoyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (**4b**): Yield 76%; colourless sticky liquid; $[\alpha]_D^{20}$ +126.4 (*c* 0.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 7.39—6.00 (m, 8H, Ar), 5.51 (d, *J*=10.1 Hz, 1H, CHN_3), 5.13 (s, 1H, PhCH), 3.30 (q, *J*=6.8 Hz, 1H, C**H**C_2H_5), 1.88—1.68 (m, 2H, CHC**H**$_2$CH$_3$), 1.62 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.85 (t, *J*=7.3 Hz, 3H, CH_2C**H**$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 169.6, 153.5, 152.9, 142.5, 135.9, 129.4, 126.5, 110.7, 108.3, 83.3, 67.5, 61.8, 43, 29, 24, 11.8; IR (KBr) *v*: 3125, 2870, 2105, 1775, 1709, 1601, 1451, 1397, 1330, 1268, 1226, 1161, 1106, 1016, 938, 815, 741, 705, 632, 545, 450 cm^{-1}; ESI-MS *m/z* (%): 405 ([M+Na]$^+$, 100); HR-MS (TOF ES$^+$) calcd for $C_{20}H_{22}N_4O_4$ [M+Na]$^+$ 405.1535, found 405.1533.

General procedure for the asymmetric bromination of *N*-acyloxazolidinone

To obtain the two other isomers of **4c** and **4d** with different stereochemistry of the *α*-carbon, an electrophilic bromination reaction was utilized. This was achieved by stereoselective halogenation of the metal-chelated enolate formed by the addition of the ethylcuprate to the *α*,*β*-unsaturated acyloxazolidinones, namely a one-pot tandem asymmetric conjugation addition followed by bromination to furnish the *α*-bromo products **3c** and **3d**. To a mixture of EtMgBr (19.2 mmol, 2 equiv.) and CuBr•SMe_2 (1 g, 4.8 mmol, 0.5 equiv.) in 130 mL of THF at −78 ℃, a solution of (*E*)-3-(3-(furan-2-yl)acryloyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (**2**) (3 g, 9.6 mmol) in 50 mL of THF was added dropwise. The resulting mixture was stirred at −78 ℃ for 15 min, 0 ℃ for 2 h and then at room temperature for 1 h under nitrogen atmosphere. The process was monitored by TLC. When the reaction was finished, the reaction liquid was cooled to −78 ℃ for 15 min and an excess of NBS (2.65 g, 15 mmol, 2.3 equiv.) was added. As the reaction began to slow down, the reaction liquid was continually stirred at −78 ℃ for 2 h. After the reaction had finished, the reaction flask was transferred to an ice bath for 1 h. Then, a liquid of mixture of 0.5 mol•L^{-1} bisulfate and saturated brine (80 mL, *V*/*V*=1∶1) was added to quench the reaction and the organic phase was separated. The aqueous phase was extracted with ether (50 mL×2), the combined organic phase was washed with 0.5 mol•L^{-1} hyposulphite (40 mL×2), brine (40 mL) and water (40 mL) and dried over anhydrous magnesium sulfate. Removal of the solvents gave the crude product as a light yellow oil, which was further purified by silica gel column chromatography.

(*R*)-3-((2*R*,3*S*)-2-Bromo-3-(furan-2-yl)pentanoyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (**3c**): Yield 82%; colourless sticky liquid; $[\alpha]_D^{20}$ −82.9 (*c* 1.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 7.40—6.08 (m, 8H, Ar), 6.05 (d, *J*=11 Hz, 1H, CHBr), 4.94 (s, 1H, PhCH), 3.40 (q, *J*=10.5 Hz, 1H, C**H**C_2H_5), 1.78—1.67 (m, 2H, CHC**H**$_2$CH$_3$), 1.44 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 0.84 (t, *J*=7.1 Hz, 3H, CH_2C**H**$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 168.9, 158.0, 154.2, 142.9, 136, 129.8, 127.2, 111.2, 108.7, 106.3, 83.6, 68.3, 67.8, 46.4, 44.1, 29.5, 26.1, 24.5, 11.9; IR (KBr) *v*: 3510, 3130, 2967, 2874, 1769, 1597, 1557, 1480, 1398, 1319, 1257, 1217, 1165, 1115, 1039, 932, 884, 850, 809, 752, 702, 657, 566, 471 cm^{-1}; ESI-MS *m/z* (%): 443 ([M+Na]$^+$, 100); HR-MS (TOF ES$^+$) calcd for $C_{20}H_{22}NO_4Br$ [M+Na]$^+$ 442.0630, found 442.0624.

(*S*)-3-((2*S*,3*R*)-2-bromo-3-(furan-2-yl)pentanoyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (**3d**): Yield 80%; colourless sticky liquid; $[\alpha]_D^{20}$ +57.5 (*c* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 7.35—6.12 (m, 8H, Ar), 6.05 (d, *J*=11.1 Hz, 1H, CHBr), 4.90 (s, 1H, PhCH), 3.36 (q, *J*=9.8 Hz, 1H, C**H**C_2H_5), 1.77—1.69 (m, 2H, CHC**H**$_2$CH$_3$), 1.39 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 0.80 (t, *J*=7.3 Hz, 3H, CH_2C**H**$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 168.9, 154.1, 153.1, 142.9, 136, 129.8, 127.2, 111.2, 108.6, 83.6, 68.2, 67.5, 46.4, 44.1, 29.5, 26.0, 24.5, 11.9; IR (KBr) *v*: 3129, 1770, 1707, 1621, 1399, 1332, 1271, 1221, 1163, 1099, 1019, 735, 597, 469 cm^{-1}; ESI-MS *m/z* (%): 443 ([M+Na]$^+$, 100); HR-MS (TOF ES$^+$) calcd for $C_{20}H_{22}NO_4Br$ [M+Na]$^+$ 442.0629, found 442.0624.

General procedure for azide displacement

The bromo-compound **3c** or **3d** (800 mg, 1.9 mmol) and NaN_3 (200 mg, 1.6 equiv.) were dissolved in DMF (50 mL). The solution was stirred under nitrogen at room temperature overnight. A little water was added to

the reaction flask and stirred for a short period of time before being extracted with ethyl acetate (30 mL×3). The combined organic phase was washed with water (30 mL×2) and dried over anhydrous sodium sulfate. Removal of the solvents gave the crude product as a light yellow oil, which was purified by silica gel column chromatography.

(*R*)-3-((2*S*,3*R*)-2-Azido-3-(furan-2-yl)pentanoyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (**4c**): Yield 74%; colourless sticky liquid; $[\alpha]_D^{20}$ −85.8 (*c* 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 7.41—6.00 (m, 8H, Ar), 5.28 (d, *J*=6.6 Hz, 1H, CHN_3), 5.13 (s, 1H, PhCH), 3.38 (q, *J*=4.2 Hz, 1H, C**H**C_2H_5), 1.87—1.68 (m, 2H, CHC**H**$_2$$CH_3$), 1.63 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.86—0.78 (m, 3H, CH_2C**H**$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 170.4, 153.7, 153.1, 142.8, 136.4, 129.7, 127.8, 111.1, 108.9, 84.3, 68.2, 63.6, 43.7, 29.9, 24.9, 24.6, 12.5; IR (KBr) *v*: 3125, 2972, 2866, 2107, 1774, 1708, 1600, 1457, 1392, 1330, 1268, 1225, 1160, 1106, 1011, 939, 874, 815, 740, 697, 632, 543, 454 cm^{-1}; ESI-MS *m/z* (%): 405 ([M+Na]$^+$, 100); HR-MS (TOF ES$^+$) calcd for $C_{20}H_{22}N_4O_4$ [M+Na]$^+$ 405.1531, found 405.1533.

(*S*)-3-((2*R*,3*S*)-2-Azido-3-(furan-2-yl)pentanoyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (**4d**): Yield 80%; colourless sticky liquid; $[\alpha]_D^{20}$ +85.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 7.38—6.00 (m, 8H, Ar), 5.29 (d, *J*=6.6 Hz, 1H, CHN_3), 4.86 (s, 1H, PhCH), 3.24—3.28 (m, 1H, franyl-C**H**-C_2H_5), 1.99—1.77 (m, 2H, CHC**H**$_2$$CH_3$), 1.37 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 0.85—0.94 (m, 3H, CH_2C**H**$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 170.4, 153.7, 153.1, 142.8, 136.4, 129.7, 127.8, 111.1, 109, 84.3, 68.2, 63.6, 43.0, 29.0, 23.9, 23.9, 11.8; IR (KBr) *v*: 3127, 2356, 1773, 1708, 139, 1331, 1266, 1221, 1164, 1099, 1024, 751, 705, 629 cm^{-1}; ESI-MS *m/z* (%): 405 ([M+Na]$^+$, 100); HR-MS (TOF ES$^+$) calcd for $C_{20}H_{22}N_4O_4$ [M+Na]$^+$ 405.1541, found 405.1533.

General procedure for hydrolysis of azido compounds

Into a solution of *α*-azido compounds **4a**—**4d** (500 mg, 1.3 mmol) in THF (60 mL), 20 mL of H_2O was added. After the solution was cooled to 0 ℃ for 15 min, 0.8 mL of 30% hydrogen peroxide (7.7 mmol, 6 equiv.) was added dropwise, followed by the dropwise addition of 370 mg lithium hydroxide monohydrate (8.8 mmol, 6.7 equiv.). The resulting mixture was stirred at 0 ℃ for 4 h. The reaction was quenched by the addition of saturated sodium sulfite (50 mL) and stirred at room temperature for 30 min. The aqueous phase was separated and extracted with dichloride methane (DCM) (30 mL×3) for the recovery of the auxiliary. Then, the remaining aqueous phase was cooled to 0 ℃, acidified with 6 mol•L^{-1} HCl to pH 1 and extracted with DCM (30 mL×3). The combined organic phases were dried over anhydrous magnesium sulfate and evaporated *in vacuo* to give the light yellow oils **5a**—**5d**.

(2*R*,3*R*)-2-Azido-3-(furan-2-yl)pentanoic acid (**5a**): Yield 85%; colourless sticky liquid; $[\alpha]_D^{20}$ −17.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 10.22 (broad, 1H, COOH), 7.36—6.05 (m, 3H, Ar), 4.18 (d, *J*=6.0 Hz, 1H, CHN_3), 3.25—3.22 (m, 1H, C**H**C_2H_5), 1.89—1.77 (m, 2H, CHC**H**$_2$$CH_3$), 0.98 — 0.85 (m, 3H, CH_2C**H**$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 178.3, 153.3, 142.4, 110.7, 108.8, 65.7, 43.4, 22.8, 12.1; IR (KBr) *v*: 3126, 2112, 1719, 1635, 1400, 1270, 1011, 733, 449 cm^{-1}; ESI-MS *m/z* (%): 210 ([M+H]$^+$, 100).

(2*S*,3*S*)-2-Azido-3-(furan-2-yl)pentanoic acid (**5b**): Yield 80%; colourless sticky liquid; $[\alpha]_D^{20}$ +17.5 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 10.31 (broad, 1H, COOH), 7.38—6.06 (m, 3H, Ar), 4.21 (d, *J*=6.1 Hz, 1H, CHN_3), 3.27—3.23 (m, 1H, C**H**C_2H_5), 1.89—1.79 (m, 2H, CHC**H**$_2$$CH_3$), 0.95 — 0.85 (m, 3H, CH_2C**H**$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 177.0, 155.2, 144.4, 112.7, 110.2, 67.6, 45.3, 24.8, 14.2; IR (KBr) *v*: 3126, 2972, 2878, 2112, 1721, 1605, 1504, 1400, 1232, 1012, 932, 805, 732, 588, 561 cm^{-1}; ESI-MS *m/z* (%): 209 (M$^+$, 100).

(2*S*,3*R*)-2-Azido-3-(furan-2-yl)pentanoic acid (**5c**): Yield 91%; colourless sticky liquid; $[\alpha]_D^{20}$ −59.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 10.25 (broad, 1H, COOH), 7.37—6.20 (m, 3H, Ar), 4.11 (d, *J*=5.8 Hz, 1H, CHN_3), 3.30—3.23 (m, 1H, C**H**C_2H_5), 1.94—1.70 (m, 2H, CHC**H**$_2$$CH_3$), 0.99 — 0.86 (m, 3H, CH_2C**H**$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 174.6, 157.6, 142.1, 112.7, 110.8, 106.2, 65.5, 43.8, 25.0, 12.3; IR (KBr) *v*: 3126, 2113, 1723, 1632, 1400, 1230, 1011, 803, 733, 452 cm^{-1}; ESI-MS *m/z* (%): 232 ([M+Na]$^+$, 100).

(2*R*,3*S*)-2-Azido-3-(furan-2-yl)pentanoic acid (**5d**): Yield 83%; colourless sticky liquid; $[\alpha]_D^{20}$ +58.5 (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 10.25 (broad, 1H, COOH), 7.37—6.20 (m, 3H, Ar), 4.11 (d, *J*=5.9 Hz, 1H, CHN_3), 3.30—3.26 (m, 1H, C**H**C_2H_5), 1.94—1.71 (m, 2H, CHC**H**$_2$$CH_3$), 0.95—0.88 (m, 3H, CH_2C**H**$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 175.9, 152.7, 142.4, 110.7, 108.8, 64.9, 43.3, 24.0, 12.1; IR (KBr) *v*: 3125, 2988, 2113, 1723, 1623, 1503, 1399, 1230, 1108, 1011, 805, 738, 612, 547 cm^{-1}; ESI-MS *m/z* (%): 232 ([M+Na]$^+$, 100).

General procedure for reduction of azido acids

A solution of azido acid **5a**—**5d** (100 mg, 0.54 mmol) in methanol (3 mL) and 6 mol•L^{-1} HCl (0.5 mL) was placed in a hydrogenation vessel. Then, 10% Pd/C (20 mg) was added. The hydrogenation vessel was vacuumed and refilled with hydrogen three times and stirred under 138—207 kPa hydrogen for 2 h. The catalyst was filtered, and the volatile was removed by rotary evaporation. The residue was loaded on a coolant jacketed ion-exchange column filled with Amberlite IR-120 (H^+) resin. The column was washed with deionized water until the eluent was neutral. The free amino acid was washed off the column with a solution (28% NH_3•H_2O : H_2O, *V*/*V*) in a volume ratio of 2 : 3. The fractions containing the product were combined and evaporated to remove the NH_3, then frozen and lyophilized to give the title compounds **6a**—**6d**.

(2*R*,3*R*)-2-Amino-3-(furan-2-yl)pentanoic acid (**6a**):

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Yield 87%; white solid, $[\alpha]_D^{20}$ −18.4 (*c* 0.55, 1 mol•L^{-1} HCl); ^{1}H NMR (D_2O, 500 MHz) *δ*: 7.39—6.26 (m, 3H, Ar), 4.20—4.19 (m, 1H, C**H**NH_2), 3.26—3.25 (m, 1H, C**H**C_2H_5), 0.92—0.74 (m, 5H, C_2H_5); ^{13}C NMR (D_2O, 125 MHz) *δ*: 171.1, 151.7, 143.9, 111.1, 109.5, 56.7, 42.0, 23.2, 11.7; IR (KBr) *v*: 3433, 3136, 1632, 1400, 1118, 600 cm^{-1}; ESI-MS *m/z* (%): 184 ([M+H]$^+$, 100); HR-MS (TOF ES$^+$) calcd for $C_9H_{13}NO_3$ [M+H]$^+$ 184.0974, found 184.0972.

(2*S*,3*S*)-2-Amino-3-(furan-2-yl)pentanoic acid (**6b**): Yield 88%; white solid, $[\alpha]_D^{20}$ +17.6 (*c* 0.55, 1 mol•L^{-1} HCl); ^{1}H NMR (D_2O, 500 MHz) *δ*: 7.38—6.20 (m, 3H, Ar), 4.21—4.20 (m, 1H, C**H**NH_2), 3.28—3.24 (m, 1H, C**H**C_2H_5), 0.81—0.76 (m, 5H, C_2H_5); ^{13}C NMR (D_2O, 125 MHz) *δ*: 171.2, 151.7, 143.8, 111.1, 109.5, 56.7, 41.4, 22.9, 11.6; IR (KBr) *v*: 3433, 3136, 1632, 1400, 1118, 600 cm^{-1}; ESI-MS *m/z* (%): 184 ([M+H]$^+$, 100); HR-MS (TOF ES$^+$) calcd for $C_9H_{13}NO_3$ [M+H]$^+$ 184.0974, found 184.0965.

(2*S*,3*R*)-2-Amino-3-(furan-2-yl)pentanoic acid (**6c**): Yield 86%; white solid, $[\alpha]_D^{20}$ −13.6 (*c* 0.55, 1 mol•L^{-1} HCl); ^{1}H NMR (D_2O, 500 MHz) *δ*: 6.90—5.78 (m, 3H, Ar), 3.74—3.73 (m, 1H, C**H**NH_2), 2.91—2.88 (m, 1H, C**H**C_2H_5), 0.40—0.29 (m, 5H, C_2H_5); ^{13}C NMR (D_2O, 125 MHz) *δ*: 171.2, 151.7, 143.8, 111.2, 109.5, 56.7, 42.0, 23.2, 11.7; IR (KBr) *v*: 3433, 3136, 1632, 1400, 1118, 600 cm^{-1}; ESI-MS *m/z* (%): 184 ([M+H]$^+$, 100); HR-MS (TOF ES$^+$) calcd for $C_9H_{13}NO_3$ [M+H]$^+$ 184.0974, found 184.0973.

(2*R*,3*S*)-2-Amino-3-(furan-2-yl)pentanoic acid (**6d**): Yield 80%; white solid, $[\alpha]_D^{20}$ +12.6 (*c* 0.55, 1 mol•L^{-1} HCl); ^{1}H NMR (D_2O, 500 MHz) *δ*: 7.38—6.24 (m, 3H, Ar), 4.13—4.12 (m, 1H, C**H**NH_2), 3.37—3.36 (m, 1H, C**H**C_2H_5), 0.80—0.75 (m, 5H, C_2H_5); ^{13}C NMR (D_2O, 125 MHz) *δ*: 171.9, 151.3, 143.9, 111.1, 109.4, 56.9, 41.5, 23.0, 11.6; IR (KBr) *v*: 3433, 3136, 1632, 1400, 1118, 600 cm^{-1}; ESI-MS *m/z* (%): 184 ([M+H]$^+$, 100); HR-MS (TOF ES$^+$) calcd for $C_9H_{13}NO_3$ [M+H]$^+$ 184.0974, found 184.0963.

Conclusions

In summary, we have reported stereoselective synthesis of the four individual isomers of the novel heterocycle-containing amino acid 2-amino-3-furan-2-yl-pentanoic acid. Davies' "SuperQuats" chiral auxiliary 4(*R*/*S*)-5,5-dimethyl-4-phenyl-oxazolidin-2-one was used to replace Hruby's 4(*R*/*S*)-4-phenyl-oxazolidin-2-one, and could control the entire synthesis with high stereoselectivity via asymmetric 1,4-Michael addition and direct or indirect azidation reactions with a greater than 90% *de* and 33%—44% overall yield. The target compounds represent attractive conformationally constrained amino acids that could be incorporated into peptidomimetic structures with potential biological activities. Further application of these compounds for the preparation of novel non-proteinogenic *α*-amino acids is currently underway.

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References

[1] (a) Hruby, V. J. *Prog. Brain Res.* **1992**, *92*, 215; (b) Hruby, V. J.; Al-Obedi, F.; Kazmierski, W. *Biochem J.* **1990**, *268*, 249; (c) Hruby, V. J. *Life Sci.* **1982**, *38*, 189; (d) Qian, X. H.; Russell, K. C.; Boteju, L. W.; Hruby, V. J. *Tetrahedron* **1995**, *51*, 1033; (e) Qian, X. H.; Shenderovich, M. D.; Kover, K. E.; Davis, P.; Horvath, R.; Zalewska, T.; Yammamura, H.; Porreca, F.; Hruby, V. J. *J. Am. Chem. Soc.* **1996**, *118*, 7280.

[2] (a) Wang, S. H.; Tang, X. J.; Hruby, V. J. *Tetrahedron Lett.* **2000**, *41*, 1307; (b) Wang, W.; Xiong, C. Y.; Yang, J. Q.; Hruby, V. J. *Tetrahedron Lett.* **2001**, *42*, 7717; (c) Wang, W.; Zhang, J. Y.; Xiong, C. Y.; Hruby, V. J. *Tetrahedron Lett.* **2002**, *43*, 2137; (d) Wang, W.; Xiong, C. Y.; Yang, J. Q.; Hruby, V. J. *Tetrahedron* **2002**, *58*, 3101.

[3] (a) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron*: *Asymmetry* **2000**, *11*, 645; (b) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron*: *Asymmetry* **2007**, *18*, 569; (c) Konno, H.; Aoyama, S.; Nosaka, K.; Akaji, K. *Synthesis* **2007**, *23*, 3666; (d) Cranfill, D. C.; Lipton, M. A. *Org. Lett.* **2007**, *9*, 3511; (e) Cativiela, C.; Ordonez, M. *Tetrahedron*: *Asymmetry* **2009**, *20*, 1; (f) Martens, J. *ChemCatChem* **2010**, *2*, 379; (g) Drummond, L. J.; Sutherland, A. *Tetrahedron* **2010**, *66*, 5349; (h) Fustero, S.; Mateu, N.; Simon-Fuentes, A.; Acena, J. L. *Org. Lett.* **2010**, *12*, 3014; (i) Radchenko, D. S.; Grygorenko, O. O.; Komarov, I. V. *Amino Acids* **2010**, *2*, 515; (j) Iosub, V.; Haberl, A. R.; Leung, J.; Tang, M.; Vembaiyan, K.; Parvez, M.; Back, T. G. *J. Org. Chem.* **2010**, *75*, 1612.

[4] (a) Nicolás, E.; Russel1, K. C.; Knollenberg; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 7565; (b) Li, G. G.; Keith C; Russel; Jarosinski, M. A.; Hruby, V. J. *Tetrahedron Lett.* **1993**, *34*, 2565 (c) Boteju, L. W.; Wegner, K.; Qian, X. H.; Hruby, V. J. *Tetrahedron* **1994**, *50*, 2391 (d) Xiang, L.; Wu, H. W.; Hruby, V. J. *Tetrahedron*: *Asymmetry* **1995**, *6*, 83; (e) Liao, S. B.; Hruby, V. J. *Tetrahedron Lett.* **1996**, *37*, 1563; (f) Liao, S. B.; Han, Y. L.; Qiu, W.; Bruck, M.; Hruby, V. J. *Tetrahedron Lett.* **1996**, *37*, 7917; (g) Liao, S. B.; Shenderovich, M. D.; Lin, J.; Hruby, V. J. *Tetrahedron* **1997**, *53*, 16645; (h) Han, Y. L.; Liao, S. B.; Qiu, W.; Cai, C. Z.; Hruby, V. J. *Tetrahedron Lett.* **1997**, *38*, 5135; (i) Yuan, W.; Hruby, V. J. *Tetrahedron Lett.* **1997**, *38*, 3853; (j) Lin, J.; Liao, S. B.; Hruby, V. J. *Tetrahedron Lett.* **1998**, *39*, 3117; (k) Lin, J.; Liao, S. B.; Han, Y. L.; Qiu, W.; Hruby, V. J. *Tetrahedron*: *Asymmetry* **1997**, *8*, 3213; (l) Wang, S. H.; Tang, X. J.; Hruby, V. J. *Tetrahedron Lett.* **2000**, *41*, 1307; (m) Lin, J.; Liao, S. B.; Hruby, V. J. *J. Peptide Res.* **2005**, *65*(1), 105.

[5] (a) Davies, S. G.; Sanganee, H. J. *Tetrahedron*: *Asymmetry* **1995**, *6*, 671; (b) Bull, S. G.; Davies, S. G.; Jones, S.; Polywka, M. E. C.; Prasad, R. S.; Sanganee, H. J. *Synlett* **1998**, 519; (c) Davies, S. G.; Sanganee, H. J.; Szolcsanyi, P. *Tetrahedron* **1999**, *55*, 3337; (d) Bull, S. D.; Davies, S. G.; Nicholson, R. L.; Sanganee, H. J.; Smith, A. D. *Tetrahedron*: *Asymmetry* **2000**, *11*, 3475.

[6] (a) Evans, D. A.; Sjogren, B. *Tetrahedron Lett.* **1986**, *26*, 3783; (b) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757.

[7] Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc*. **1990**, *112*, 4011.

[8] (a) Li, G. G.; Jarosinski, M. A.; Hruby, V. J. *Tetrahedron Lett.* **1993**, *34*, 2561; (b) Li, G. G.; Keith, C.; Russel; Jarosinski, M. A.; Hruby, V. J. *Tetrahedron Lett.* **1993**, *34*, 2565; (c) Boteju, L. W.; Wegner, K.; Hruby, V. J. *Tetrahedron Lett.* **1992**, *33*, 7491.

[9] Li, G.; Patel, D.; Hruby, V. J. *J. Chem. Soc*., *Perkin Trans. 1* **1994**, 3057.

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