SCIENCE CHINA
Chemistry

• ARTICLES •

November 2011 Vol.54 No.11: 1711–1717
doi: 10.1007/s11426-011-4372-1

Stereoselective synthesis of *cis*- and *trans*-4-acyl-β-lactams from vicinal diketones and ketoaldehydes

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Received June 28, 2011; accepted July 12, 2011; published online August 25, 2011

4-Acyl-β-lactams are important synthetic intermediates in both pharmaceutical and organic chemistry. *Cis*- and *trans*-4-acyl-β-lactams were synthesized stereoselectively from vicinal diketones via the formation of bulky and less bulky diimines as key intermediates, respectively. The diimines reacted with acyl chloride in the presence of triethylamine to give rise to the corresponding 4-imino-β-lactams, which were further hydrolyzed to afford 4-acyl-β-lactams. The *cis*- and *trans* selectivity is depended on the steric hindrance of the imine *N*-substituents. A series of *cis*-4-acyl-β-lactams were synthesized from vicinal ketoaldehydes via the formation of their monoimines and diimines as intermediates. Pyruvic aldehyde produced *cis*-4-acetyl-β-lactams and *cis*-4-formyl-β-lactams, respectively, through the reactions of its monoimine and diimine with acyl chlorides. Phenylglyoxal generated *cis*-4-benzoyl-β-lactams via its monoaldimine.

4-acyl-β-lactam, diimine, diketone, imine, ketoaldehyde, β-lactam, stereoselectivity

1 Introduction

4-Acyl-β-lactams are important synthetic intermediates in both pharmaceutical and organic chemistry [1, 2]. They have been widely used for the synthesis of α-amino acid derivatives [3, 4] and β-amino acid derivatives [5, 6] via ring-opening reactions. They have also been applied in the preparation of heterocycles [7–18], polycyclic heterocyclic compounds [19–25], alkaloids [23, 26], antibiotics [27–31], and even more complex natural products [23, 32] via ring enlargements. 4-Formyl-β-lactams have been prepared in different ways, including the Swern oxidation from the corresponding 4-hydroxymethyl-β-lactams [33], ozonolysis and reduction from 4-styryl-β-lactams [34], and acidic hydrolysis from 4-imino-β-lactams [35]. Additionally, optically pure 4-formyl-β-lactams were prepared from optically pure 4-(1,3-dioxol-4-yl)-β-lactams or 4-(1,3-oxazolidin-4-yl)-β-lactams via periodinate oxidation [36–38]. However, the above-mentioned methods can only be used for the synthesis of *cis*-4-acyl-β-lactams. *Trans*-β-lactams have been previously prepared from the 3-unsubstituted 4-hydroxymethyl-β-lactams via alkylation and the Swern oxidation [39], or from *N*-2-oxoalkyl-2,3-epoxyalkanamides via an intramolecular nucleophilic ring-open reaction of the oxirane ring [40]. It is still in demand to develop efficient methods to stereoselectively prepare both *cis*- and *trans*-4-acyl-β-lactams with different acyl groups from simple starting materials. Herein, we reported our preliminary work on the stereoselective synthesis of both *cis*- and *trans*-4-acyl-β-lactams with different acyl groups from vicinal diketones and ketoaldehydes.

2 Experiments

2.1 Materials and measurements

All commercially available reagents and solvents were

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used without further purification unless otherwise noted. Monoimines and diimines were prepared from diketones and ketoaldehydes according to the previously reported methods [41]. Reactions of propionyl chloride and imines were carried out under nitrogen atmosphere in anhydrous solvents. Melting points were measured on a melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 200, 300, or 400 MHz in $CDCl_3$ with TMS as the internal standard. ^{13}C NMR spectra were recorded at 50.3, 75.5, or 100.6 MHz in $CDCl_3$ with $CDCl_3$ as the internal standard at 77.0 ppm. IR spectra were determined directly. HRMS spectra were performed on an LC/MSD TOF mass spectrometer.

2.2 Preparation of diimines (1a–c) of vicinal diketones

*N,N'-Bis(diphenylmethyl)-2,3-butanediimine (**1a**)*

Butanedione (0.86 g, 10 mmol) and diphenylmethylamine (3.84 g, 21 mmol)) were dissolved in freshly distilled anhydrous EtOH (15 mL). To the resulting solution were added a drop of 98% formic acid and $MgSO_4$ (2 g). The mixture was stirred at room temperature for 24 h. Dichloromethane (20 mL) was added to fully dissolve the product. After filtration and evaporation of the solvent under reduced pressure, the residue was purified by recrystallization in EtOH to afford **1a** as colorless crystals (1.83 g, yield 43.9 %). m.p. 185–187 °C. Lit. [41] m.p. 185–186 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.50–7.16 (m, 20H, ArH), 5.83 (s, 2H, 2CH), 2.31 (s, 6H, $2CH_3$).

*N,N'- Bis(4-methoxyphenyl)-2,3-butanediimine (**1b**)*

An ethanolic solution (100 mL) of 4-methoxyaniline (2.46 g, 20 mmol) was added dropwise to an ethanolic solution (100 mL) of 2,3-butanedione (0.86 g, 10 mmol). The resulting solution was refluxed in a water bath for 8 h. The yellow crystalline product was filtered, recrystallized from ethanol, and washed with *n*-hexane to afford **1b** as yellow crystals (1.51 g, yield 50.6 %). m.p. 187–188 °C. Lit. [42] m.p. 185–186 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.93–6.75 (m, 8H, ArH), 3.82 (s, 6H, $2OCH_3$), 2.17 (s, 6H, $2CH_3$).

*N,N'-Bis(4-methoxyphenyl)-1,2-diphenyl-1,2-ethanediimine (**1c**)*

An ethanolic solution (100 mL) of benzil (2.10 g, 10 mmol) and 4-methoxyaniline (2.46 g, 20 mmol) was refluxed in a water bath for 24 h. The reaction mixture was concentrated to one-third of its volume and kept overnight in a sulfuric acid desiccator. The yellow crystalline product was filtered, recrystallized from ethanol, and washed with diethyl ether and hexane (1:1, *v/v*) to afford **1c** as yellow crystals (2.46 g, yield 58.6 %). m.p. 173–174 °C. Lit. [43] m.p. 171–172 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.88–7.31 (m, 12H, ArH), 6.65 (s, 6H, ArH), 3.72 (s, 6H, $2CH_3O$).

2.3 Preparation of diimines (1d, e) of vicinal ketoaldehydes

*N,N'-Bis(diphenylmethyl)-1,2-propanediimine (**1d**)*

A round-bottom flask was charged with a solution of pyruvic aldehyde (14 mmol, 3.33 g of 30 % aqueous solution) and diphenylmethylamine (5.34 g, 29 mmol) in diethyl ether (30 mL). The mixture was stirred at room temperature for 24 h and filtered. The colorless crystals were further recrystallized from ethanol and washed with *n*-hexane to afford **1d** as colorless crystals (3.72 g, yield 66.2 %). m.p. 141.0–142.5 °C. Lit. [41] m.p. 141–142 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.15 (s, 1H, CH=N), 7.23–7.37 (m, 20H, ArH), 5.87 (s, 1H, CH), 5.56 (s, 1H, CH), 2.26 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$). δ: 167.0, 164.5, 143.5, 143.3, 128.48, 128.45, 127.59, 127.53, 127.1, 126.9, 77.5, 68.8, 13.5. IR (KBr): ν (cm^{-1}) 1635 (C=N).

*N,N'- Bis(4-methoxyphenyl)-1,2-propanediimine (**1e**)*

A round-bottom flask was charged with a solution of pyruvic aldehyde (7 mmol, 1.67 g of 30 % aqueous solution) and 4-methoxyaniline (1.85 g, 15 mmol) in diethyl ether (20 mL). The mixture was stirred at 0 °C for 12 h. After removal of the solvent under reduced pressure, the residue was purified by crystallization in EtOH to afford **1e** as yellow crystals (1.01 g, yield 51.0 %). m.p. 108–109 °C. Lit. [44] m.p. 106–108 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.29 (s, 1H, N=CH), 7.34–6.82 (m, 8H, ArH), 3.84 (s, 3H, CH_3O), 3.83 (s, 3H, CH_3O), 2.23 (s, 3H, CH_3).

2.4 Preparation of ketoaldimines (1f, g) of vicinal ketoaldehydes

*1-(4-Methoxyphenylimino)propan-2-one (**1f**)*

A round-bottom flask was charged with a solution of pyruvic aldehyde (28 mmol, 6.73 g of 30 % aqueous solution) and 4-methoxyaniline (2.46 g, 20 mmol) in diethyl ether (20 mL). The mixture was stirred at 0 °C for 3 h and washed with water. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified via flash column chromatography (silica gel, hexanes:EtOAc = 4:1, *v/v*) to afford **1f** as yellow crystals (0.9 g, yield 25.4 %). m.p. 70.0–72.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88 (m, 1H, CH=N), 7.34 (d, J =9.0 Hz, 2H, ArH), 6.94 (d, J=9.0 Hz, 2H, ArH), 3.84 (s, 3H, OCH_3), 2.52 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 200.1, 160.5, 154.0, 141.0, 123.9, 123.8, 114.5, 55.5, 24.6.

*2-(4-Methoxyphenylimino)-1-phenylethanone (**1g**)*

A mixture of phenylglyoxal hydrate (1.13 g, 7.46 mmol), 4-methoxyaniline (0.97 g, 7.40 mmol), and anhydrous magnesium sulfate (2 g) in dichloromethane (25 mL) was stirred at 0 °C for 1 h, warmed to rt, filtered through Celite, and concentrated under reduced pressure. The resulting residue was purified via flash column chromatography (silica

gel, hexanes:EtOAc = 8:1, *v/v*) to afford **1g** as an orange oil (1.0 g, yield 60 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (s, 1H, CH), 8.33–6.98 (m, 9H, 2CH), 3.871 (s, 3H, OCH_3).

2.5 General procedure for the reaction of propionyl chloride and imines

A solution of propionyl chloride (111 mg, 1.2 mmol) in anhydrous benzene (5 mL) was added dropwise to a solution of imine (1 mmol) and triethylamine (0.152 g, 1.5 mmol) in toluene (10 mL). The resulting mixture was stirred at 80 °C under nitrogen for 4–16 h (monitoried by TLC), diluted with CH_2C1_2 (20 mL), and washed with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (2 x 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified via recrystallization in a mixture of EtOAc and hexanes (for crystalline products) or via flash column chromatography (silica gel, a mixture of hexanes and EtOAc as eluent) (for liquid products) to afford the products.

*Cis-1-diphenylmethyl-4-[(E)-1-(diphenylmethylimino)ethyl]-3,4-dimethylazetidin-2-one (**2a**)*

Colorless crystals 0.200 g, yield 42.3%, m.p. 164.0–166.0 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.46–7.18 (m, 20H, ArH), 5.70 (s, 1H, CH), 5.67 (s, 1H, CH), 2.95 (q, J = 7.5 Hz, 1H, CH), 1.84 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.05 (d, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.9, 167.5, 144.0, 143.9, 141.9, 140.0, 128.8, 128.5, 128.4, 128.33, 128.27, 127.8, 127.4, 127.34, 127.28, 126.85, 126.79, 126.7, 68.4, 68.0, 62.9, 54.8, 22.8, 16.7, 10.6. IR (KBr): ν (cm^{-1}) 1743 (C=O), 1653 (C=N). HRMS (ESI) calcd for $C_{33}H_{33}N_2O$ $[M+H]^+$ *m/z*: 473.2587, found 473.2591.

*Trans-1-(4-methoxyphenyl)-4-[(E)-1-(4-methoxyphenylimino) ethyl]-3,4-dimethylazetidin-2-one (**2b**)*

Colorless crystals 0.249 g, yield 70.7 %, m.p. 188.0–190.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41–6.63 (m, 8H, ArH), 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.33 (q, J =7.5 Hz, 1H, CH), 1.88 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 1.32 (d, J = 7.6 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 170.7, 166.8, 156.1, 155.9, 143.8, 131.0, 120.0, 118.7, 114.3, 114.2, 67.5, 56.5, 55.4, 21.7, 17.9, 9.3. IR (KBr): ν (cm^{-1}) 1742 (C=O), 1652 (C=N). HRMS (ESI) calcd for $C_{21}H_{25}N_2O_3$ $[M+H]^+$ *m/z*: 353.1860, found 353.1864.

*Trans-1-(4-methoxyphenyl)-4-[(E)-(4-methoxyphenylimino) (phenyl)methyl]-3-methyl-4-phenylazetidin-2-one (**2c**)*

Yellow oil 0.239 g, yield 50.3 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50–6.59 (m, 18H, ArH), 3.88 (q, J =7.5 Hz, 1H, CH), 3.71 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 1.59 (d, J =7.4 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.5, 166.5, 156.3, 156.0, 142.5, 139.6, 135.5, 130.7, 128.5, 128.4, 127.9, 127.8, 127.4, 122.1, 121.5, 113.8, 113.5, 73.5, 60.4, 55.2, 12.3. IR (KBr): ν (cm^{-1}) 1747 (C=O), 1626 (C=N). HRMS (ESI) calcd for $C_{31}H_{29}N_2O_3$ $[M+H]^+$ *m/z*: 477.2173, found 477.2173.

*Cis-1-diphenylmethyl-4-[(E)-(diphenylmethylimino)methyl]-3,4-dimethylazetidin-2-one (**2d**)*

Colorless crystals 0.339 g, yield 74.1 %, m.p. 113.0–115.0 °C. ^{1}H NMR (200MHz, $CDCl_3$) δ: 7.62 (s, 1H, CHN), 7.26–7.20 (m, 20H, ArH), 5.55 (s, 1H, ArCH), 5.28 (s, 1H, ArCH), 3.10 (q, J =7.6 Hz, 1H, CH), 1.50 (s, 3H, CH_3), 1.04 (d, J =7.6 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 169.4, 163.9, 143.2, 143.1, 140.0, 128.43, 128.39, 128.30, 128.27, 127.5, 127.4, 127.3, 127.3, 127.0, 77.6, 63.9, 61.7, 55.7, 21.4, 9.9. IR (KBr): ν (cm^{-1}) 1748 (C=O), 1653(C=N). HRMS calcd for $C_{32}H_{31}N_2O$ $[M+H]^+$ *m/z*: 459.2431, found 459.2440.

*Cis-1-(4-methoxyphenyl)-4-[(E)-(4-methoxyphenylimino)-methyl]-3,4-dimethylazetidin-2-one (**2e**)*

Yellow oil 0.260 g, yield 76.9 %. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.99 (s, 1H, CH=N), 7.30–6.72 (m, 8H, ArH), 3.70 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.21 (q, J=7.6 Hz, 1H, CH), 1.76 (s, 3H, CH_3), 1.21 (d, J=7.6 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 167.0, 162.4, 158.5, 155.9, 143.5, 130.6, 121.9, 118.3, 114.3, 114.2, 63.7, 56.6, 55.3, 55.2, 19.9, 9.9. IR (KBr): ν (cm^{-1}) 1742 (C=O), 1644 (C=N). HRMS (ESI) calcd for $C_{20}H_{23}N_2O_3$ $[M+H]^+$ *m/z*: 339.1703, found 339.1709.

*Cis-4-acetyl-1-(4-methoxyphenyl)-3-methylazetidin-2-one (**3f**)*

Colorless crystals 0.268 g, yield 76.6 %, m.p. 118.0–120.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.20 (d, J = 9.0 Hz, 2H, ArH), 6.85 (d, J = 9.0 Hz, 2H, ArH), 4.62 (d, J = 6.4 Hz, 1H, NCH), 3.77 (s, 3H, OCH_3), 3.72-3.65 (dq, J = 6.4, 7.6 Hz 1H, CH), 2.21 (s, 3H, CH_3), 1.23 (d, J = 7.6 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 204.8, 166.0, 156.4, 131.1, 117.9, 114.5, 61.6, 55.5, 47.7, 28.2, 9.5. IR (KBr): ν (cm^{-1}) 1715 (C=O), 1743 (C=O, in amide). HRMS (ESI) calcd for $C_{13}H_{16}NO_3$ $[M+H]^+$ *m/z*: 234.1125, found 234.1129.

*Cis-4-benzoyl-1-(4-methoxyphenyl)-3-methylazetidin-2-one (**3g**)*

Colorless crystals 0.293 g, yield 80 %, m.p. 160.0–162.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98–6.81 (m, 9H, ArH), 5.54 (d, J = 6.2 Hz, 1H, CH), 3.83 (dq, J = 6.2, 7.4 Hz, 1H, CH), 3.76 (s, 3H, OCH_3), 1.11 (d, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.9, 165.7, 156.2, 135.2, 134.3, 131.3, 129.2, 128.2, 118.4, 114.3, 59.1, 55.5, 48.4, 10.0. IR (KBr) ν (cm^{-1}): 1699 (C=O), 1746 (C=O in amide). HRMS (ESI) calcd for $C_{18}H_{18}NO_3$ $[M+H]^+$ *m/z*: 296.1281, found 296.1277.

2.6 General procedure for hydrolysis of 4-imino-β-lactams

A round-bottom flask was charged with a solution of 4-imino-β-lactams (30 mg) and 1 mol/L aqueous HCl (6 mL) in THF (6 mL). The mixture was stirred at reflux for 3 h. After removal of solvent under reduced pressure, the residue was diluted with CH_2C1_2 (10 mL) and subsequently washed with 1 mol/L aqueous HCl (6 mL) and water (6 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the desired products.

*Cis-4-acetyl-1-diphenylmethyl-3,4-dimethylazetidin-2-one (**3a**)*

Yellowish oil 17.9 mg, yield 92 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44–7.25 (m, 10H, ArH), 5.46 (s, 1H, NCH), 3.05 (q, J = 7.5 Hz, 1H, CH), 2.09 (s, 3H, $COCH_3$), 1.43 (s, 3H, CH_3), 1.20 (d, J = 7.6 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.4, 168.2, 140.4, 139.1, 128.6, 128.3, 128.2, 127.6, 127.4, 69.9, 62.9, 55.1, 27.8, 21.2, 10.3. IR (KBr): ν (cm^{-1}) 1711 (C=O), 1742 (C=O, in amide). HRMS (ESI) calcd for $C_{20}H_{22}NO_2$ $[M+H]^+$ *m/z*: 308.1645, found 308.1649.

*Trans-4-acetyl-1-(4-methoxyphenyl)-3,4-dimethylazetidin-2-one (**3b**)*

Yellowish oil 19.7 mg, yield 94 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28 (d, J = 9.1 Hz, 2H, ArH), 6.87 (d, J = 9.1 Hz, 2H, ArH), 3.78 (s, 3H, OCH_3), 3.24 (q, J = 7.6 Hz, 1H, CH), 2.24 (s, 3H, $COCH_3$), 1.77 (s, 3H, CH_3), 1.23 (d, J = 7.6 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.7, 166.2, 156.2, 130.3, 118.7, 114.5, 69.5, 56.2, 55.4, 28.0, 19.8, 9.4. IR (KBr): ν (cm^{-1}) 1715 (C=O), 1743 (C=O, in amide). HRMS (ESI) calcd for $C_{14}H_{18}NO_3$ $[M+H]^+$ *m/z*: 248.1281, found 248.1276.

*Trans-4-benzoyl-1-(4-methoxyphenyl)-3-methyl-4-phenylazetidin-2-one (**3c**)*

Yellow oil 19.3 mg, yield 94%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50–6.59 (m, 14H, ArH), 4.14 (q, J =7.4 Hz, 1H, CH), 3.71 (s, 3H, OCH_3), 1.24 (d, J =7.4 Hz, 3H, CH_3). IR (KBr): ν (cm^{-1}) 1686 (C=O), 1747 (C=O in amide). HRMS (ESI) calcd for $C_{24}H_{22}NO_3$ $[M+H]^+$ *m/z*: 372.1594, found 372.1591.

*Cis-1-diphenylmethyl-2,3-dimethylazetidin-2-one-4-carbaldehyde (**3d**)*

Yellowish oil 18.2 mg，yield 91 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.37 (s, 1H, CHO), 7.36–7.25 (m, 10H, ArH), 5.79 (s, 1H, NCH), 3.16 (q, J = 7.7 Hz, 1H, CH), 1.39 (s, 3H, CH_3), 1.21 (d, J = 7.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.1, 169.1, 138.9, 138.6, 128.9, 128.8, 128.6, 128.3, 128.0 127.8, 67.6, 61.7, 55.6, 18.4, 9.4. IR (KBr): ν (cm^{-1}) 1659 (C=O), 1742 (C=O in amide). HRMS (ESI) calcd for $C_{19}H_{20}NO_2$ $[M+H]^+$ *m/z*: 294.1489, found 294.1492.

*Trans-1-(4-methoxyphenyl)-2,3-dimethylazetidin-2-one-4-carbaldehyde (**3e**)*

Yellowish oil 18.6 mg, yield 90 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.83 (s, 1H, CHO), 7.16 (d, J = 9.0 Hz, 2H, ArH), 6.78 (d, J = 9.0 Hz, 2H, ArH), 3.70 (s, 3H, OCH_3), 3.19 (q, J = 7.7 Hz, 1H, CH), 1.60 (s, 3H, CH_3), 1.22 (d, J = 7.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.1, 166.4, 156.5, 130.0, 118.6, 114.6, 66.8, 56.3, 55.5, 17.0, 9.5. IR (KBr): ν (cm^{-1}) 1658 (C=O), 1741 (C=O in amide). HRMS (ESI) calcd for $C_{13}H_{16}NO_3$ $[M+H]^+$ *m/z*: 234.1125, found 234.1140.

3 Results and discussion

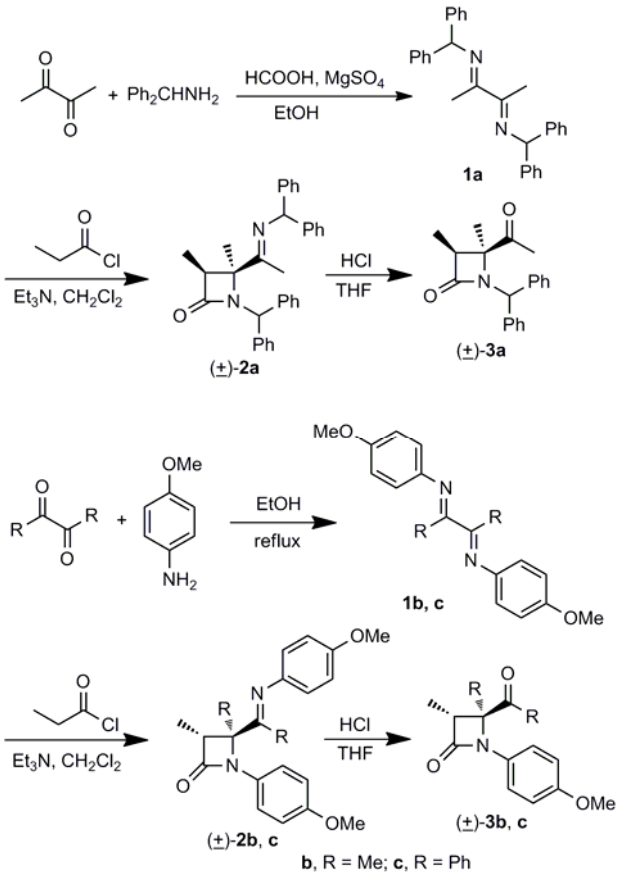
3.1 Synthesis of *cis*- and *trans*-4-acyl-β-lactams from symmetric vicinal diketones

Although it is an economic and convenient route to prepare 4-acyl-β-lactams from vicinal diketones and acyl chlorides in the presence of tertiary amine via monoimine derivatives of diketones, the reaction of diketones and amines, even in a molar ratio of 1:1, generally produces a mixture of monoimine and diimine derivatives of diketones that are difficult to separate due to their similar polarity and unstability in a silica gel column. Thus, it is more practical to prepare 4-acyl-β-lactams from vicinal diketones and acyl chlorides via diimines of diketones followed by subsequent hydrolysis. According to our proposal on the stereocontrol in the synthesis of β-lactams [45, 46], we hoped to synthesize the *cis*- and *trans*-4-acyl-β-lactams via the diketone diimines with bulky and less steric N-substituents, respectively.

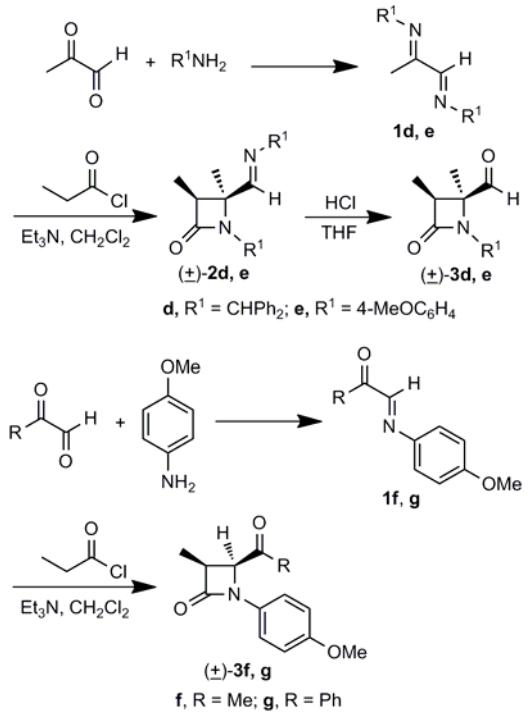
First, 2,3-butanedione reacted with diphenylmethylamine and *p*-methoxyaniline to prepare the corresponding diimines **1a** and **1b**, respectively. Diimines **1a** and **1b** reacted with propionyl chloride in the presence of triethylamine in dichloromethane to give rise to the *cis*- and *trans*-4-imino-β-lactams **2a** and **2b**, respectively, which were further hydrolyzed to produce the *cis*- and *trans*-4-acetyl-β-lactams **3a** and **3b**. Similarly, the *trans*-4-benzoyl-β-lactam **3c** was synthesized from 1,2-diphenyl-1,2-ethanedione. The stereostructures of products **2** and **3** were identified on the basis of their NOESY spectra [45]. For example, the correlation between the C3 proton and the C4 methyl group of β-lactams was observed in **2a**, but not in **2b**. Unfortunately, the reaction of 1,2-diphenyl-1,2-ethanedione and bulky diphenylmethylamine did not occur (Scheme 1).

3.2 Synthesis of *cis*-4-acyl-β-lactams from unsymmetric vicinal ketoaldehydes

Pyruvic aldehyde reacted with amines in different molar ratios to generate diimines **1d, 1e,** and ketoaldimine **1f**, re-



Scheme 1 Synthesis of *cis*- and *trans*-4-acyl-β-lactams **3** from vicinal diketones.



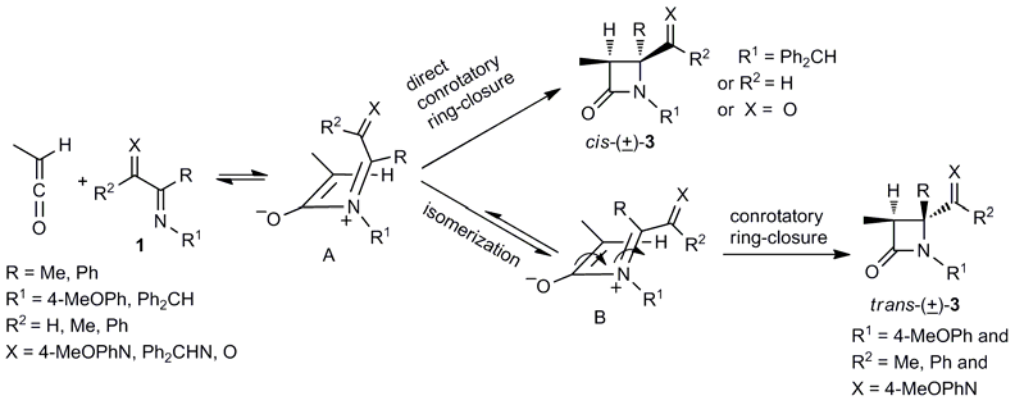
Scheme 2 Synthesis of *cis*-4-acyl-β-lactams **3** from vicinal ketoaldehydes.

spectively, because the ketone and aldehyde groups showed obviously different reactivity with amines. The diimines **1d** and **1e** reacted with propionyl chloride in the presence of triethylamine to give rise to the *cis*-4-aldimino-β-lactams **2d** and **2e**, respectively. Their stereostructures were identified on the basis of the NOESY spectra. Lactams **2d** and **2e** were further hydrolyzed to produce *cis*-4-formyl-β-lactams **3d** and **3e**. As comparison, the ketoaldimine **1f** reacted with propionyl chloride to afford *cis*-4-acetyl-β-lactam **3f** directly (Scheme 2). This is because ketimines reacted more predominantly with the acyl chloride than aldimines due to their higher electron density and less steric hindrance in the attacking of imines to ketenes generated from propionyl chloride in the presence of triethylamine. Similarly, *cis*-4-benzoyl-β-lactam **3g** was synthesized from ketoaldimine **1g** generated from phenylglyoxal with 4-methoxyaniline (Scheme 2). The stereostructures of products **3f** and **3g** were identified on the basis of the coupling constants between the C3 protons and C4 protons of β-lactams (6.4 and 6.2 Hz, respectively) because the coupling constant of *cis*-protons ranges from 4 to 6 Hz, while that for *trans*-protons is less than 4 Hz [45]. Unfortunately, attempts to prepare the phenylglyoxal-derived diimines failed.

The results indicate that both *cis*- and *trans*-4-acyl-lactams were prepared from 2,3-butanedione via its diimines with more or less bulky *N*-substituents (Scheme 1). However, only *cis*-4-formyl-β-lactams were prepared from diimines generated from pyruvic aldehyde no matter whether they possess bulky or less bulky *N*-substituents. This is because the ketimine moiety in the diimines predominately reacted with the acyl chloride due to its higher electron density. It is also because the generated zwitterionic intermediates prefer to direct ring closure due to their iminium moiety with electron-withdrawing aldimine substituents. Although only *cis*-4-acyl-β-lactams were obtained from pyruvic aldehyde, both *cis*-4-acetyl-β-lactams and *cis*-4-formyl-β-lactams were synthesized via its monoimine and diimine derivatives, respectively. The diastereoselectivity follows our previous proposal on the stereoselectivity of the Staudinger reaction [47, 48]. That is, the diastereoselectivity is a result of the competition between the direct conrotatory ring closure and the isomerization of the iminium moiety in the zwitterionic intermediates generated from ketenes and imines (Scheme 3). Strong electron-donating ketene substituents, strong electron-withdrawing imine *C*-substituents, and bulky imine *N*-substituents prefer the formation of *cis*-β-lactams, while weak electron-donating and electron-withdrawing ketene substituents dominate the formation of *trans*-β-lactams.

4 Conclusions

Cis- and *trans*-4-acyl-β-lactams were stereoselectively syn-



Scheme 3 Selectivity in synthesis of *cis*- and *trans*-4-acyl-β-lactams **3** from vicinal diketones and ketoaldehydes.

thesized from vicinal diketones while *cis*-4-acyl-β-lactams were synthesized from ketoaldehydes. Diketones and ketoaldehydes reacted with amines to afford diimines. The diimines reacted with propionyl chloride in the presence of triethylamine to give rise to the corresponding 4-imino-β-lactams, which were further hydrolyzed to afford 4-acyl-β-lactams. *Cis*- and *trans*- selectivity depends on the steric hindrance of the imine *N*-substituents and on the electronic property of the imine *C*-substituents. Pyruvic aldehyde produced *cis*-4-acetyl-β-lactams and *cis*-4-formyl-β-lactams, respectively, through the reactions of its monoimines and diimines with propionyl chlorides. Phenylglyoxal generated *cis*-4-benzoyl-β-lactams via its monoaldimines.

The authors express their thanks to the support from the National Natural Science Foundation of China (20972013 and 20772005), Beijing Natural Science Foundation (2092022), the Fundamental Research Funds for the Central Universities (ZZ1020). and the Doctoral Fund of Ministry of Education of China (200800100010).

1 Alcaide B, Almendros P. 4-Oxoazetidine-2-carbaldehydes as useful building blocks in stereocontrolled synthesis. *Chem Soc Rev*, 2001, 30: 226–240
2 Alcaide B, Almendros P, Aragoncillo C. β-Lactams: Versatile building blocks for the stereoselective synthesis of non-β-lactam products. *Chem Rev*, 2007, 107: 4437–4492
3 Palomo C, Aizpurua CJM, Ganboa I, Carreaux F, Cuevas C, Maneiro E, Ontoria JM. New synthesis of α-amino acid *N*-carboxy anhydrides through Baeyer-Villiger oxidation of α-keto-β-lactams. *J Org Chem*, 1994, 59: 3123–3130
4 Palomo C, Aizpurua CJM, Ganboa I, Odriozola B, Urchegui R, Gorls H. Concise synthesis of α-alkyl-α-amino acids and their incorporation into peptides via β-lactam-derived α-amino acid *N*-carboxy anhydrides. *Chem Commun*, 1996: 1269–1270
5 Robinson RP, Donahue KM. Synthesis of a peptidyl difluoro ketone bearing the aspartic acid side chain: An inhibitor of interleukin-1 converting enzyme. *J Org Chem*, 1992, 57: 7309–7314
6 Palomo C, Arrieta A, Cossío FP, Aizpurua JM, Mielgo A, Aurrekoetxea N. Highly stereoselective synthesis of α-hydroxy-β-amino acids through β-lactams: application to the synthesis of the taxol and bestatin side chains and related systems. *Tetrahedron Lett*, 1990, 31: 6429–6432
7 Kale AS, Deshmukh ARAS. An efficient synthesis of 2,3-aziridino-γ-lactones from azetidin-2-ones. *Synlett*, 2005: 2370–2372
8 J Alcaide B, Martın-Cantalejo Y, Rodrıguez-Lopez J, Sierra MA. New reactivity patterns of the β-lactam ring: tandem C3–C4 bond breakage-rearrangement of 4-acyl- or 4-imino-3,3-dimethoxy-2-azetidinones promoted by stannous chloride ($SnCl_2$-$2H_2O$). *J Org Chem*, 1993, 581: 4767–4770
9 Alcaide B, Domınguez G, Martın-Domenech A, Plumet J, Monge A, Perez-Garcıa V. Ring expansion of 4-benzoyl-β-lactams. *Heterocycles*, 1987, 26: 1461–1466
10 Alcaide B, Almendros P, Cabrero G, Ruiz MP. Organocatalytic ring expansion of β-lactams to γ-lactams through a novel N1-C4 bond cleavage. Direct synthesis of enantiopure succinimide derivatives. *Org Lett*, 2005, 7: 3981–3984
11 Alcaide B, Almendros P, Cabreroa G, Ruiza MP. Direct organocatalytic synthesis of enantiopure succinimides from β-lactam aldehydes through ring expansion promoted by azolium salt precatalysts. *Chem Commun*, 2007: 4788–4790
12 Li GQ, Li Y, Dai LX, You SL. *N*-heterocyclic carbene catalyzed ring expansion of 4-formyl-beta-lactams: Synthesis of succinimide derivatives. *Org Lett*, 2007, 9: 3519–3521
13 Domingo LR, Aurell MJ, Arno M. Understanding the mechanism of the *N*-heterocyclic carbene-catalyzed ring-expansion of 4-formyl-β-lactams to succinimide derivatives. *Tetrahedron*, 2009, 65: 3432–3440
14 Alcaide B, Aly M, Rodrıguez C, Rodrıguez-Vicente A. Base-promoted isomerization of *cis*-4-formyl-2-azetidinones: chemoselective C4-epimerization vs rearrangement to cyclic enaminones. *J Org Chem,* 2000, 65: 3453–3459
15 Krishnaswamy D, Govande VV, Deshmukh ARAS. 4-Formylazetidin-2-ones, synthon for the facile synthesis of enantiopure 4-aminopiperidin-2-one. *Synthesis*, 2003: 1903–1908
16 Bailey PD, Millwood PA, Smith PD. Asymmetric routes to substituted piperidines. *Chem Commun*, 1998: 633–640
17 Parr IB, Horenstein BA. New electronic analogs of the sialyl cation: N-functionalized 4-acetamido-2,4-dihydroxypiperidines. Inhibition of bacterial sialidases. *J Org Chem*, 1997, 62: 7489–7494
18 Alcaide B, Almendros P, Cabrero G, Ruiz MP. Stereocontrolled access to orthogonally protected anti,anti-4-aminopiperidine-3,5-diols through chemoselective reduction of enantiopure β-lactam cyanohydrins. *J Org Chem*, 2007, 72 : 7980–7991
19 Kale AS, Puranik VG, Rakeeb A, Deshmukh AS. A practical formal synthesis of D-(+)-biotin from 4-formylazetidin-2-one. *Synthesis*, 2007, 17: 1159–1164
20 Alcaide B, Almendros P, Alonso JM. A practical ruthenium-catalyzed cleavage of the allyl protecting group in amides, lactams, imides, and congeners. *Chem Eur J*, 2006, 12: 2874–2879
21 Buttero PD, Molteni G, Papagnib A, Pilati T. The intramolecular aromatic nucleophilic substitution as a route to tricyclic β-lactams. Synthesis of the novel 4-oxa-7-azabicyclo[4.2.0]octane skeleton.

Tetrahedron, 2003, 59: 5259–5263
22 Alcaide B, Almendros P, Alonso JM, Aly MF. Useful dual Diels-Alder behavior of 2-azetidinone-tethered aryl imines as azadienophiles or azadienes: A β-lactam-based stereocontrolled access to optically pure highly functionalized indolizidine systems. *Chem Eur J*, 2003, 9: 3415–3426
23 Alcaide B, Almendros P, Alonso JM, Aly MF. 1,3-Dipolar cycloaddition of 2-azetidinone-tethered azomethine ylides. application to the rapid, stereocontrolled synthesis of optically pure highly functionalized pyrrolizidine systems. *Chem Commun*, 2000: 485–486
24 Alcaide B, Almendros P, Alonso JM, Aly MF. Rapid and stereocontrolled synthesis of racemic and optically pure highly functionalized pyrrolizidine systems via rearrangement of 1,3-dipolar cycloadducts derived from 2-azetidinone-tethered azomethine ylides. *J Org Chem*, 2001, 66: 1351–1358
25 Alcaide B, Polanco C, Sierra MA. Alkyne-$Co_2(CO)_6$ complexes in the synthesis of fused tricyclic β-lactam and azetidine system. *J Org Chem*, 1998, 63: 6786–6796
26 Ojima I, Lin S, Inoue T. Miller ML, Borella CP, Geng X, Walsh JJ. Macrocycle formation by ring-closing metathesis. Application to the syntheses of novel macrocyclic taxoids. *J Am Chem Soc*, 2000, 122: 5343–5353
27 Hart DJ, Lee CS. Asymmetric synthesis of β-lactams and the carbapenem antibiotic (+)-PS-5. *J Am Chem Soc*, 1986, 108: 6054–6056
28 Georg GI, Kant J, Gill HS. Symmetric synthesis of (1'*R*,3*R*,4*R*)-4-acetoxy-3-[1'-((*tert*-butyldimethylsilyl)oxy)ethyl]-2-azetidinone and other 3-(1'-hydroxyethyl)-2-azetidinones from (*S*)-(+)-ethyl 3-hydroxybutanoate: formal total synthesis of (+)-thienamycin. *J Am Chem Soc*, 1987, 109: 1129–1135
29 Evans DA, Sjogren EB. The asymmetric synthesis of β-lactam antibiotics II The first enantioselective synthesis of the carbacephaloporin nucleus. *Tetrahedron Lett*, 1985, 26, 3783–3787
30 Fujisawa T, Shibuya A, Sato D, Shimizu M. Stereoselective synthesis of monocyclic β-lactam related to a carmonam precursor via ketene-imine reaction. *Synlett*, 1995, 39: 1067–1068
31 Tsubouchi H, Tsuji K, Yusumura K, Tada N, Nishitani S, Minamikawa J, Ishikawa H. A convenient one pot asymmetric synthesis of *cis*-β-lactams: Key precursors for optically active 2-oxaisocephems. *Tetrahedron: Asymmetry*, 1994, 5: 441–452
32 Broady SD, Rexhausen JE, Thomas EJ. Total synthesis of AI-77-B: Stereoselective hydroxylation of 4-alkenylazetidinones. *J Chem Soc, Perkin Trans 1*, 1999:1083–1094
33 Myers AG, Zhong B, Movassaghi M, Kung DW, Lanman BA, Kwon S. Synthesis of highly epimerizable N-protected α-amino aldehydes of high enantiomeric excess. *Tetrahedron Lett*, 2000, *41*, 1359–1362
34 Garcia-Martin M, Violante de Paz Banez M, Garcia-Alvarez M, Munoz-Guerra S, Galbis JA. Synthesis and structural studies of 2,3-disubstituted poly(β-peptide)s. *Macromolecules,* 2001, 34: 5042–5047
35 Alcaide B, Yolanda MC, Javier PC, Julih RL, Miguel AS. The stereoselective preparation of mono- and bis-β-lactams by the 1,4-diaza-l,3-diene-acid chloride condensation: scope and synthetic applications. *J Org Chem*, 1992, *57*: 5921–5931
36 Evans DA, Williams JM. The asymmetric synthesis of β-lactam antibiotics-V application of chiral α,β-epoxyimines in ketene-imine cycloaddition reactions leading to homochiral 3-aminoazetidinones *Tetrahedron Lett*, 1988, 29: 5065–5068
37 Jayaraman M, Deshmukh AR, Bhawal BM. Application of (+)-(1*S*,2*S*)-2-amino-1-phenylpropan-1,3-diol in the formal total synthesis of carbapenems, novel 4-cyano-β-lactams and β-hydroxy aspartates. *Tetrahedron*, 1996, 52: 8989–9004
38 Shirode NM, Rakeeb A, Deshmukh AS. 4-Formylazetidin-2-ones, synthon for the synthesis of (2*R*,3*S*) and (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid (AHDA) *Tetrahedron*, 2006, 62: 4615–4621
39 Cundy DJ, Donohue AC, McCarthy TD. An asymmetric synthesis of ADDA and ADDA-glycine dipeptide using the β-lactam synthon method. *J Chem Soc Perkin Trans 1*, 1999, 5: 559–568
40 Laurent M, Cérésiat M, Marchand-Brynaert J. Synthesis of (1*R*,3*S*,4*S*)-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]-4-(cyclopropylcarbonyloxy)azetidin-2-one. *Eur J Org Chem*, 2006: 3755–376
41 Pansuriya PB, Patel MN. Synthesis, spectral, thermal, DNA I nteraction and antimicrobial properties of novel Cu(II) heterochelates. *Appl Organomet Chem*, 2007, 21: 739–749
42 Lemp E, Zanocco AL, Guenther G, Pizarro N. Solvent effect on the sensitized photooxygenation of cyclic and acyclic α-diimines *Tetrahedron*, 2006, 62: 10734–10746
43 Jin W, Makioka Y, Kitamura T, Fujiwara Y. A novel reductive dimerization/oxidative dehydrogenation of aldimines mediated by lanthanoid metals. *J Org Chem*, 2001, 66: 514–520
44 Jose B, Fernando A, Ramon L. Oxidative aminomercuration of prop-2-ynol. Syntheses of substituted propane-1,2-diimines and 2-aminopropionamidines. *J Chem Soc Chem Comm,* 1981, 22: 1181–1182
45 Liang Y, Jiao L, Zhang SW, Yu ZX, Xu JX. New insights into the torquoselectivity of the Staudinger reaction. *J Am Chem Soc*, 2009, 131: 1542–1549
46 Li BN, Wang YK, Du DM, Xu JX. Notable and obvious ketene substituent-dependent effect of temperature on the stereoselectivity in the Staudinger reaction. *J Org Chem*, 2007, 72: 990–997
47 Jiao L, Liang Y, Xu JX. Origin of the relative stereoselectivity of the β-lactam formation in the Staudinger Reaction. *J Am Chem Soc*, 2006, 128: 6060–6069
48 Qi HZ, Li XY, Xu JX. Stereoselective control in the Staudinger reactions involving monosubstituted ketenes with electron acceptor substituents: Experimental investigation and theoretical rationalization. *Org Biomol Chem*, 2011, 9: 2702–2714