Synthesis of ferrocene tethered open and macrocyclic bis-β-lactams and bis-β-amino acid derivatives†

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Received 12th June 2009, Accepted 11th August 2009
First published as an Advance Article on the web 2nd September 2009
DOI: 10.1039/b911450e

New bioorganometallic ferrocene derivatives are synthesized through a Diversity Oriented Synthesis strategy. Easily available ferrocene bisimines have been transformed into open ferrocenyl bis-β-lactams. These compounds have demonstrated to be versatile synthons used in further transformations into new ferrocene bis-β-amino acids. Carefully selected substituents submitted to ring closing metathesis (RCM) and Cu-catalyzed oxidative alkyne coupling conditions have also allowed the conversion of open substrates into ferrocenic macrocyclic bis-β-lactams.

Introduction

Ferrocene plays a pivotal role in bio-organometallic chemistry.[1] The stability of the ferrocene moiety in aqueous or aerobic media, its electrochemical properties together with a well established chemistry that allows the preparation of a wide variety of derivatives, make ferrocenes interesting starting points for the development of new properties in already bioactive compounds.[2] Ferrocene derived β-lactams are good candidates for the construction of new bio-organometallic structures and also as intermediates to prepare new types of metalla amino acids and peptides. Nevertheless, compounds having a ferrocene fragment incorporated into a β-lactam nucleus are scarce,[3] and among them some penicillin and cephalosporin derivatives having 6- and 7-positions acylated with ferrocenyl fragments have been prepared (Chart 1).[4,5]

Our research group has described a method to easily incorporate the ferrocene unit at the N1 and/or C4 positions of the 2-azetidinone ring by reacting a photogenerated ketene derived from a chromium(0) carbene with the adequate ferrocenylimines (Scheme 1).[3a]

The access to bis-β-lactams **2** from the easily available ferrocene diimines **1** will allow the preparation of different compounds (Chart 2). Thus, the ring opening of both 2-azetidinone rings will yield bis-β-amino acids **3** tethered by a ferrocene nucleus, while the metathesis or the intramolecular alkyne coupling in suitably functionalized **2** would yield new bis-β-lactam macrocyles **4** and **5**.[6] Reported here is the development of the synthesis of ferrocenyl bis-β-lactams **2** and their use in the preparation of unusual bis-aminoacid derivatives and strained macrocycles **4–5**. Therefore, access from diimines **1** to the final products can be gained in three or four steps, being an archetypical example of diversity oriented organic synthesis (DOS).[7]

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† Electronic supplementary information (ESI) available: Copies of the NMR spectra for the synthesized compounds. See DOI: 10.1039/b911450e

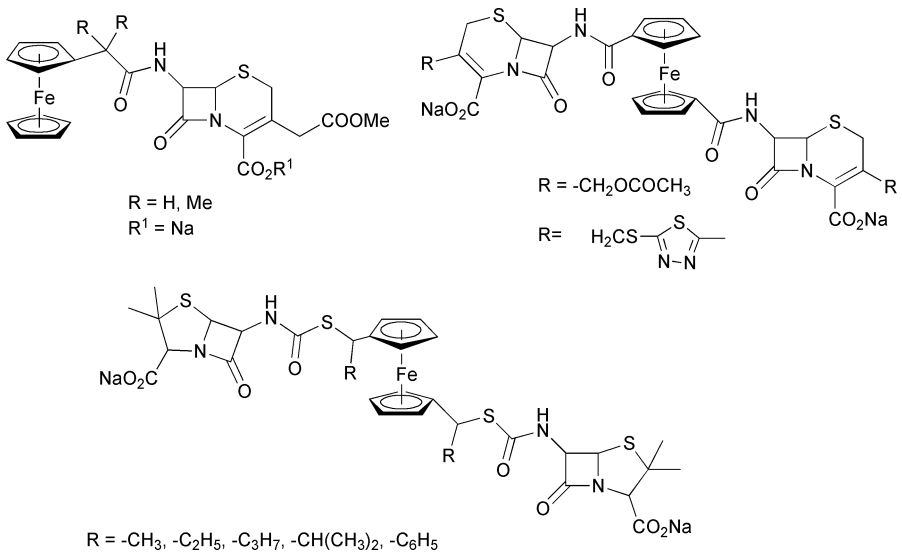
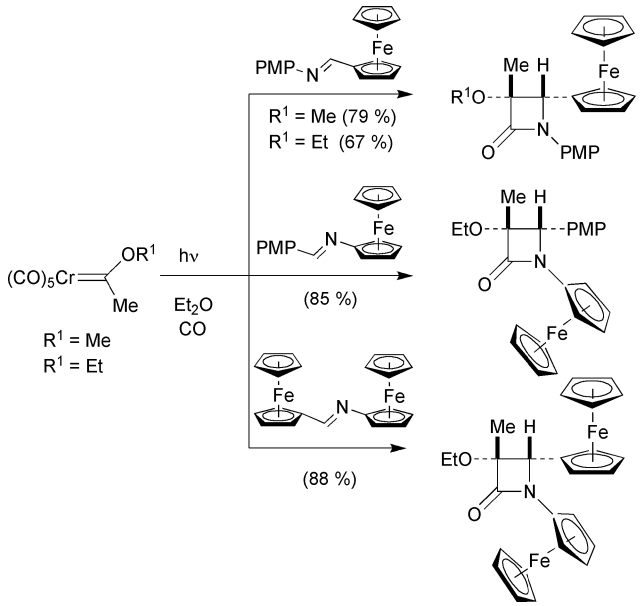
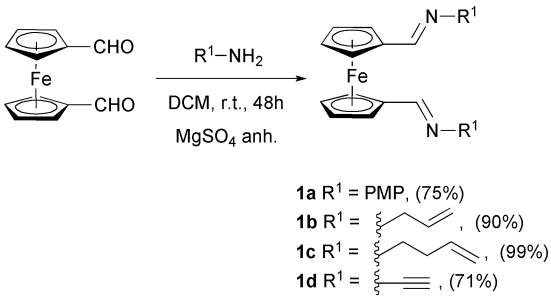


Chart 1



Scheme 1



Scheme 2

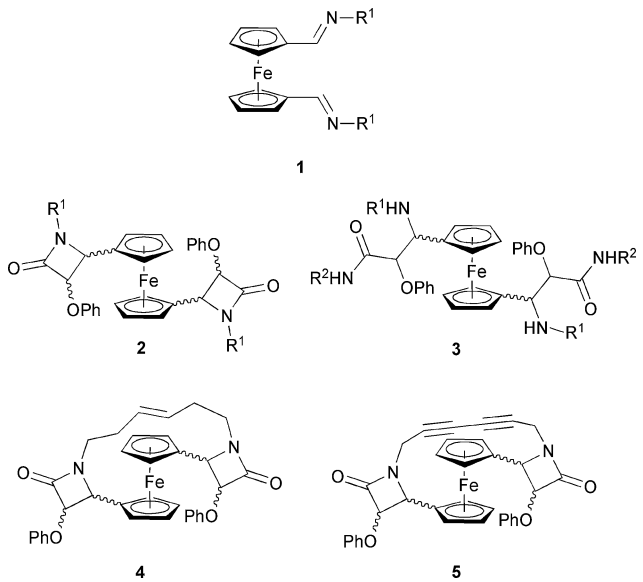
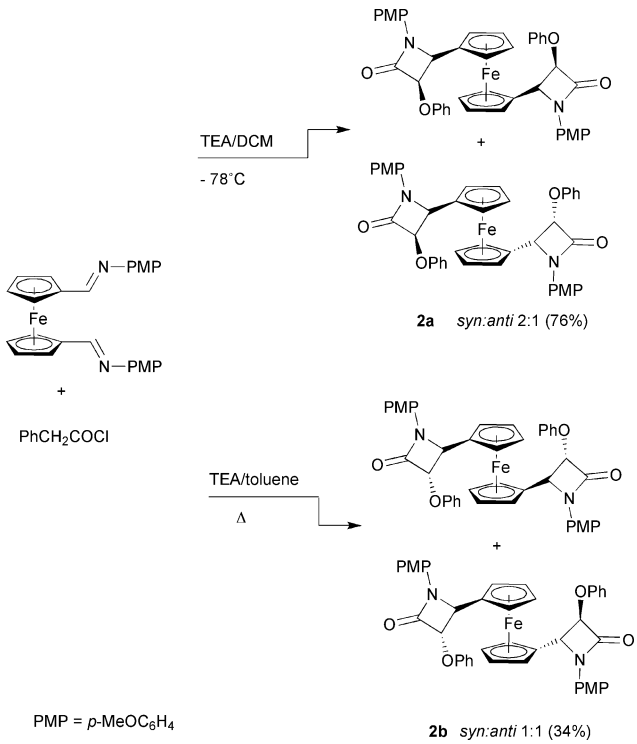


Chart 2



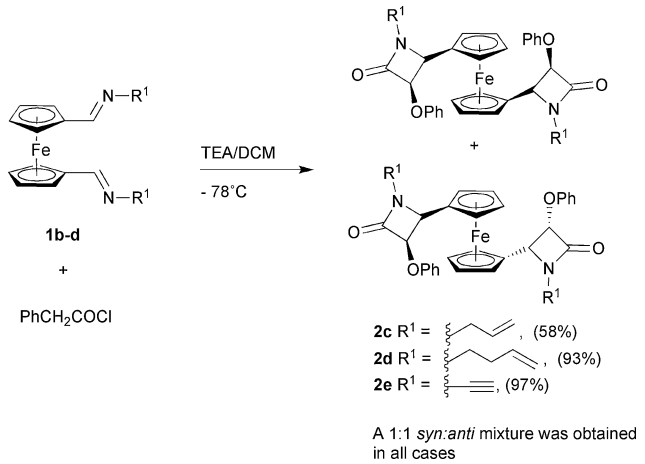
Scheme 3

Results and discussion

1,1′-ferrocenedicarbaldehyde was reacted with different substituted amines in the presence of $MgSO_4$ to obtain diimines **1** in good yields (Scheme 2). Diimine **1a** was reacted with phenoxyacetyl chloride at −78 °C in dichloromethane (DCM) and in the presence of triethylamine (TEA) yielding a mixture of *cis*-*cis*-2-azetidinones **2a** as 2:1 *syn*/*anti* mixture of diastereomers in 76% yield.

Subsequently, the reaction of diimine **1a** and phenoxyacetyl chloride in the presence of TEA, in boiling toluene, yielded a mixture of *syn*/*anti trans*-*trans*-2-azetidinones **2b** in 34% yield (Scheme 3).[8] The mixture of *syn*/*anti* diastereomers was inseparable in both cases. The structures and relative stereochemistries of bis-β-lactams **2** were established based on their spectroscopic data.[9] Thus, the two azetidinone rings in bis-β-lactams **2a** have a *cis* relative stereochemistry with a coupling constant of $J = 5.1$ Hz for the lactamic protons ($\delta = 5.40$–5.17 ppm). However, bis-β-lactams **2b** showed a characteristic *trans*-coupling constant ($J = 2.1$ Hz) for the C3–C4 hydrogens ($\delta = 5.46$-4.77 ppm). ^{13}C-NMR spectra of the diastereomeric mixtures clearly showed the azetidinone C3 and C4 signals for each isomer (**2a**: 80.6, 80.4 ppm (C3), 58.6, 58.4 ppm (C4) and **2b**: 86.8, 86.7 ppm (C3), 59.6, 59.4 ppm (C4)).

Since the reaction at low temperature gave better yields, these conditions were followed to prepare bis-β-lactams **2c–e**. The reaction between imines **1b–d** and phenoxyacetyl chloride gave the expected *cis*,*cis*-isomers of bis-β-lactams **2c–d** in all cases as 1:1 *syn*/*anti* mixtures and in good to excellent yields. The *syn*/*anti* isomers of **2c** were efficiently separated and isolated by trituration with Et_2O and sonication (29% isolated yield for each isomer) while mixtures of **2d** and **2e** were inseparable (Scheme 4). The structure of compounds **2c–e** was established on the basis of their spectroscopic data. In all cases, the characteristic signals for the 2-azetidinone ring C3–C4 hydrogens were observed



Scheme 4

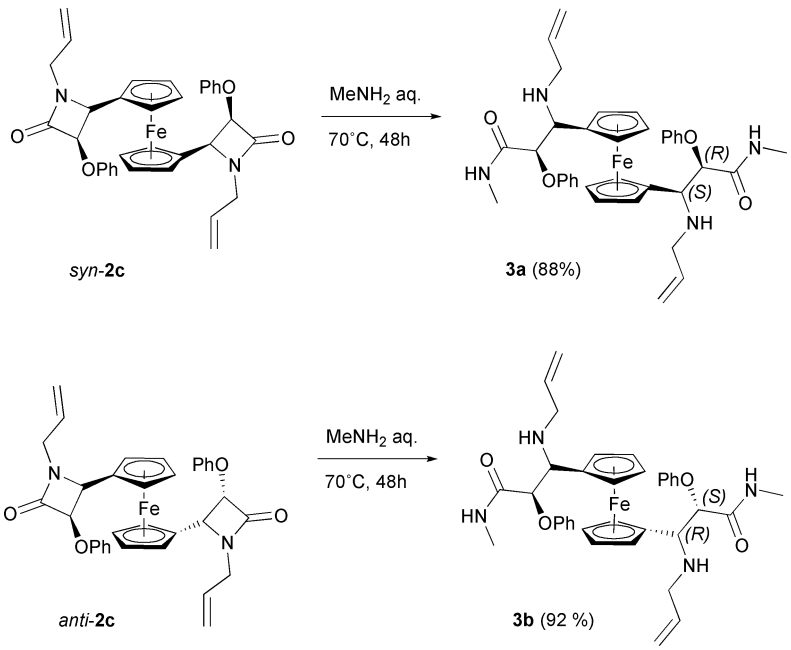
(5.42–5.33 ppm for H3, 4.96–4.74 ppm for H4) with clear H3–H4 *cis* coupling constants ($J = 4.6$–4.8 Hz).

The use of ferrocene bis-β-lactams **2** as precursors of ferrocene-linked bis-β-amino acids was pursued next. Heating separately the *syn* and *anti* diasteromers **2c** with aqueous $MeNH_2$ in a sealed tube at 70 °C yielded ferrocene linked *bis*-β-aminoacid derivatives **3a–b** in excellent yields. Compounds **3** are C–C ferrocene tethered dipeptides and it is worth mentioning that no isomerization of the four preexisting chiral centers was observed during this process (Scheme 5).

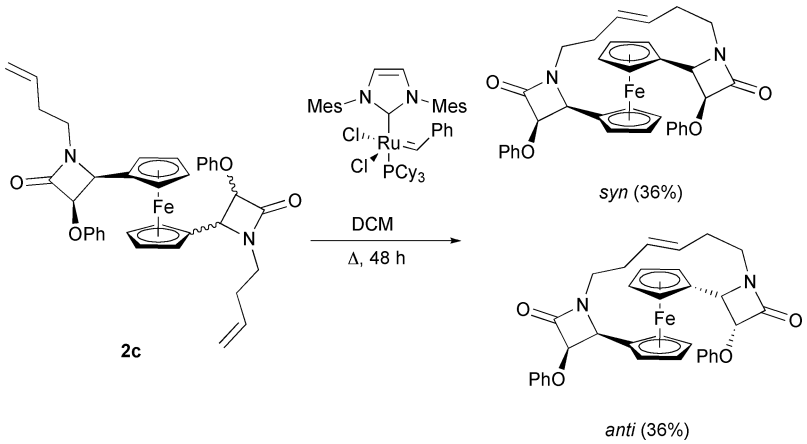
Characteristic signals for the newly developed stereogenic centers (CH hydrogens) were observed in all cases (4.94, 4.12 ppm for **3a**, 4.11, 3.86 ppm for **3b**) together with the signals corresponding to the N–Me groups (2.70 and 2.78 ppm respectively). Signal broadening precluded the measurement of coupling constants. The amide C=O group appeared at 170.8 and 171.8 ppm in the ^{13}C-NMR spectra of compounds **3**, which confirmed the open amide structure of these compounds (the corresponding azetidinone CO appeared at 165.9 and 165.8 ppm, respectively).

Formation of macrocyclic ferrocene-linked β-lactam structures by either metathesis or diyne coupling of compounds **2** was next pursued. The ring closing metathesis (RCM) reaction was effected by using the diastereomeric mixture of the *cis*,*cis*-β-lactam **2c**. The best conditions implied the reaction of **2c** with a second generation Grubbs' catalyst (10 mol%) in anhydrous DCM (1 mM) under reflux for 48 h to quantitatively yield macrocycles **4**. The crude macrocyclic *cis*,*cis*-*bis*-β-lactams **4** were isolated as 1:1 mixtures of *syn*/*anti* diastereomers that were separated by SiO_2 chromatography (Scheme 6). To unambiguously determine whether the metathesis reaction was an intra- or intermolecular reaction, FAB experiments were performed for each isomer. A detected $[M + H]^+$ ion of 589 amu clearly discarded the formation of open dimers and confirmed the formation of the macrocycle **4**. NMR signals were again in good agreement with the expected structure, showing the characteristic signals for the lactamic protons at 4.75, 3.70 ppm and 4.89, 4.14 ppm respectively with coupling constants of 4.5 and 4.7 Hz, which clearly indicated a *cis* relationship. *E* stereochemistry for the newly formed double bond was assigned according to the observed coupling constants ($J = 17.2$ and 17.8 Hz, respectively) of the olefinic protons, whose signals were found between 5.55 and 5.86 ppm for both isomers.

Finally, the preparation of strained macrocycles **5** was achieved by the intramolecular Cu-catalyzed oxidative alkyne coupling in compounds **2e**. We first tested the standard Hay's[10] coupling conditions (TMEDA–$CuCl/O_2$). The procedure is a modification of the original Glaser's[11] that increases the solubility of the reactive species. However, none of them afforded positive results. Other methods like Eglinton–Galbraith[12] (Cu(II) salts in py/MeOH solution), or Eglington[13] modified methods ($Cu(AcO)_2$/DMF or $CuCl/Cu(AcO)_2$/py) were also unsuccessful. Macrocyclization was finally achieved by using $Cu(AcO)_2 \cdot H_2O$ (20 mmol) in the presence of MeCN at 50 °C for 16 h. The highly strained



Scheme 5



Scheme 6

macrocycle **5** was isolated as an inseparable 1:1 mixture of *syn*/*anti* diastereomers in 30% yield (Scheme 7). Analysis of the NMR spectra showed absence of the terminal ≡CH signal in the ^{1}H-NMR. ^{13}C-NMR C≡C signals of **5** were also compared with those of the open chain precursor **2e**. A displacement to higher field (**2e**: 73.5, 73.4 ppm and **5**: 72.5, 72.2, 60.3) indicates a higher degree of conjugation due to the coupling of the two triple bonds. FABMS experiments ([M + H]$^{+}$, 583 amu) unambiguously confirmed the intramolecular oxidative coupling. To the best of our knowledge, examples of macrocyles having embedded bis-β-lactam rings are scarce,[6] the first example of these kinds of compounds was reported from our laboratories a few years ago.[6c] Furthermore, macrocylic embedded bis-β-lactams having a ferrocene moiety are unknown. The preparation of these compounds is a straight entry to a new family of bio-organometallic compounds.[14,15]

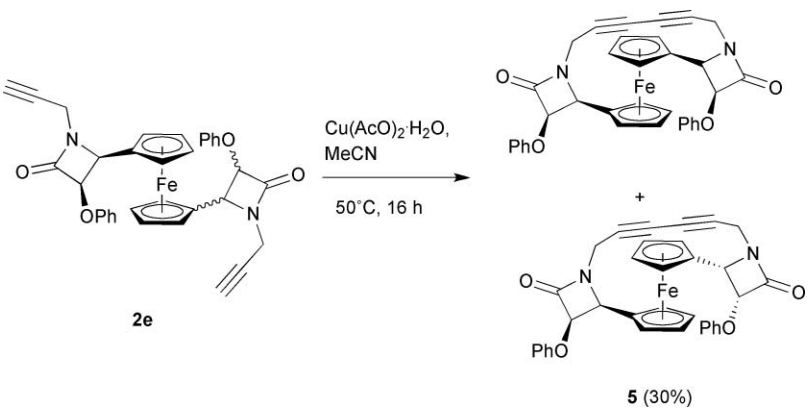
Experimental

General

NMR experiments were performed at 22 °C on Bruker Avance 300 (300.1 and 75.4 MHz), Bruker 200-AC (200.1 and 50 MHz), Bruker Avance AV-500 (500.1330 and 125.7722 MHz), or Bruker Avance AVIII-700 (1H: 700.1733 MHz) spectrometers. Chemical shifts are given in parts per million relative to TMS (1H, 0.0 ppm) or the specified solvent. IR spectra were taken on a Perkin-Elmer 781 or a Bruker Tensor 27 spectrometer. Anhydrous solvents were obtained by distillation over adequate drying agents. Flame-dried glassware and standard Schlenk techniques were used for moisture sensitive reactions. Merck silica gel (230–400 mesh) was used as the stationary phase for purification of crude reaction mixtures by flash column chromatography. Identification of products was made by TLC (kiesegel 60F254). UV light (λ = 254 nm) and 5% phosphomolybdic acid solution in 95% EtOH were used to develop the plates. All commercially available compounds were used without further purification. 1,1′-ferrocenedicarbaldehyde[16] was prepared according to literature procedures.

General method for the synthesis of diimines 1

A solution of 1,1′-ferrocenedicarbaldehyde (1.00 mmol) in anhydrous DCM (6 mL) was treated with (2.01 mmol) of *p*-anisidine in the presence of anhydrous $MgSO_4$ (2.0 g) and under Ar atmosphere. The reaction was stirred at r.t. for 48 h, filtered through Celite® and the solvent eliminated under vacuum to



Scheme 7

obtain crude imines **1** which were purified by Et_2O trituration or used without further purification.

Diimine 1a. Following the general procedure, from 4.00 g (16.52 mmol) of 1,1′-ferrocenedicarbaldehyde, 4.17 g (33.87 mmol) of *p*-anisidine and after trituration with Et_2O, 5.50 g (75%) of pure **1a** were obtained as a red solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 2H), 7.09 (d, J = 8.7 Hz, 4H), 6.85 (d, J = 8.7 Hz, 4H), 4.86 (t, J = 1.9 Hz, 4H), 4.51 (t, J = 1.9 Hz, 4H), 3.83 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 157.8, 145.3, 121.8, 114.8, 82.0, 71.8, 69.8, 55.3. IR ($CHCl_3$) ν 1622, 1578, 1470, 1244, 1032 cm^{-1}. $C_{26}H_{24}FeN_2O_2$ (452.33): calcd. C, 69.04; H, 5.35; found C, 69.21; H, 5.39. MS (ESI): 453 [M + H].$^+$

Diimine 1b. Following the general procedure, from 4.00 g (16.52 mmol) of 1,1′-ferrocenedicarbaldehyde and 3.70 g (64.48 mmol) of allylamine, 4.66 g (90%) of pure **1b** were obtained as a red oil. The product was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (s, 2H), 6.03 (ddt, J = 17.1, 10.3, 5.6 Hz, 2H), 5.22 (dq, J = 17.1, 1.7 Hz, 2H), 5.15 (dq, J = 10.3, 1.7 Hz, 2H), 4.68 (t, J = 1.9 Hz, 4H), 4.38 (t, J = 1.9 Hz, 4H), 4.09 (dq, J = 5.6, 1.5 Hz, 4H).^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 136.1, 115.8, 81.5, 74.0, 71.6, 71.4, 70.5, 69.7, 69.3, 63.8. IR ($CHCl_3$) ν 3077, 2927, 2831, 1643, 1435, 1368, 1327, 1243, 1019 cm^{-1}.

Diimine 1c. Following the general procedure, from 1.45 g (5.99 mmol) of 1,1′-ferrocenedicarbaldehyde, 1.12 mL (12.28 mmol) of 3-buten-1-amine and after trituration with Et_2O, 2.07 g, (99%) of pure **1c** were obtained as a reddish solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 2H), 5.89–5.77 (m, 2H), 5.15–5.04 (m, 4H), 4.63 (t, J = 1.9 Hz, 4H), 4.36 (t, J = 1.9 Hz, 4H), 3.52 (td, J = 7.1, 1.2 Hz, 4H), 2.42 (dq, J = 7.0, 1.2 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 136.3, 116.1, 81.6, 71.4, 69.3, 61.4, 35.2. IR ($CHCl_3$) ν 3077, 2927, 2831, 1643, 1435, 1368, 1327, 1243, 1019 cm^{-1}. $C_{20}H_{24}FeN_2$ (348.26): calcd. C, 68.97; H, 6.95; found C, 69.08; H, 7.04.

Diimine 1d. Following the general procedure, from 2.00 g (8.25 mmol) of 1,1′-ferrocenedicarbaldehyde and 1.00 g (18.15 mmol) of propargylamine, 1.85 g, (71%) of pure **1d** were obtained as a red oil. The product was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.25 (s, 1H), 4.62 (s, 2H), 4.61 (s, 2H), 4.31 (s, 2H), 4.30 (s, 2H), 4.25 (s, 2H), 4.25 (s, 2H), 2.48 (t, J = 2.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 81.1, 79.2, 75.3, 71.4, 69.4, 47.2. IR ($CHCl_3$) ν 3301, 2897, 1930, 1642, 1248 cm.$^{-1}$

Synthesis of ferrocenyl bis-β-lactams 2

Method A. To a −78 °C solution of phenoxyacetyl chloride (3.00 mmol) in 5 mL of anhydrous DCM and under Ar atmosphere, TEA (6.00 mmol) was added dropwise. The mixture was stirred for 30 min and the corresponding imine **1** (1.0 mmol) in DCM (30 mL) was added slowly dropwise. The reaction temperature was raised to 0 °C and maintained for 30 min and then allowed to reach r.t. overnight. The reaction was extracted with DCM (3 × 20 mL) and the combined organics layers were washed with 10% $NaHCO_3$ (2 × 20 mL), brine (2 × 30 ml), dried over $MgSO_4$ and evaporated. Crude bis-β-lactams **2** were purified by chromatography (SiO_2, Hex/EtOAc mixtures) or Et_2O trituration.

Method B. To a solution of imine **1** (1.00 mmol) in dry toluene (19 mL), TEA (4.00 mmol) was added dropwise. The mixture was heated to reflux and the corresponding acid chloride (2.40 mmol) in dry toluene (6.0 mL) was then added dropwise. Reflux was maintained overnight and after cooling to r.t., the reaction was extracted with DCM (3 × 20 mL). The combined organic layers were washed with 10% $NaHCO_3$ (2 × 20 mL), brine (2 × 30 mL), dried over $MgSO_4$ and evaporated. Crude bis-β-lactams **2** were purified by chromatography (SiO_2, Hex/EtOAc/DCM mixtures).

Ferrocene bis-β-lactam 2a. Following method A, from 3.00 g (6.63 mmol) of imine **1a**, 3.10 g (18.20 mmol) of phenoxyacetyl chloride and 4.00 g (39.80 mmol) of TEA and after overnight Et_2O trituration, 3.70 g (76%) of pure *cis,cis*-**2a** were obtained as an inseparable 2:1 *syn*/*anti* diastereomeric mixture as a light brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.28 (m, 16H), 7.06–6.99 (m, 12H), 6.92–6.87 (m, 8H), 5.40 (d, J = 5.1 Hz, 2H), 5.31 (d, J = 5.1 Hz, 2H), 5.17 (d, J = 5.1 Hz, 4H), 4.25–4.01 (m, 16H), 3.79 (s, 12H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.6, 157.4, 157.1, 157.0, 129.8, 129.6, 122.3, 120.7, 120.5, 115.7, 115.6, 114.6, 114.4, 82.4, 82.1, 80.6, 80.4, 70.0, 69.8, 69.6, 69.0, 68.9, 58.6, 58.4, 55.5. IR (KBr) ν 2934, 1747, 1597, 1514, 1495, 1387, 1240, 1111 cm^{-1}. $C_{42}H_{36}FeN_2O_6$ (720.19): calcd. C, 70.01; H, 5.04; found C, 70.12; H, 5.10.

Ferrocene bis-β-lactam 2b. Following method B, from 1.50 g (3.31 mmol) of imine **1a**, 1.23 g (7.20 mmol) of phenoxyacetyl chloride and 1.34 g (13.26 mmol) of TEA and after purification by chromatography (SiO_2, Hex/EtOAc/DCM 10:2:3), 0.82 g (34%) of pure *trans,trans*-**2b** were obtained as an inseparable 1:1 *syn*/*anti* diastereomeric mixture as a light brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.25 (m, 16H), 7.19–6.89 (m, 12H), 6.81–6.75 (m, 8H), 5.46 (d, J = 2.1 Hz, 2H), 5.40 (d, J = 2.1 Hz, 2H), 5.00 (d, J = 2.1 Hz, 2H), 4.77 (d, J = 2.1 Hz, 2H), 4.46–4.42 (m, 4H), 4.32–4.20 (m, 12H), 3.75 (s, 6H), 3.75 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 157.3, 157.2, 156.6, 156.5, 129.9, 122.8, 122.4, 122.0, 119.2, 119.2, 116.2, 116.2, 114.8, 114.2, 86.8, 86.7, 82.6, 82.6, 71.6, 71.4, 70.7, 70.5, 69.4, 69.1, 67.5, 67.3, 59.6, 59.4, 55.4, 55.4. IR (KBr) ν 1747, 1512, 1493, 1387, 1298, 1238, 1113 cm^{-1}. $C_{42}H_{36}FeN_2O_6$ (720.19): calcd. C, 70.01; H, 5.04. found C, 70.21; H, 5.13.

Ferrocene bis-β-lactam 2c. Following method A, from 4.66 g (14.55 mmol) of imine **1b**, 6.20 g (36.40 mmol) of phenoxyacetyl chloride and 7.76 g (76.84 mmol) of TEA, 5.00 g (58%) of a 1:1 *syn*/*anti* diastereomeric mixture of *cis*,*cis*-bis-β-lactams **2c**. Both isomers were separated by Et_2O trituration. Yield: 2.50 g (29%) of *syn*-**2c** as a brown solid and 2.50 g (29%) of *anti*-**2c** as a dark brown solid. *syn*-**2c**: m. p. 198–200 °C.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.22 (m, 3H), 7.02–6.92 (m, 7H), 5.80 (ddt, J = 15.1, 10.9, 6.3 Hz, 2H), 5.38 (d, J = 4.6 Hz, 2H), 5.30–5.21 (m, 4H), 4.80 (d, J = 4.6 Hz, 2H), 4.34–4.23 (m, 2H), 4.21–4.11 (m, 8H), 3.72–3.62 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 157.2, 131.5, 129.4, 122.1, 118.2, 115.5, 81.3, 81.2, 69.9, 68.8, 68.3, 68.3, 57.8, 42.2. IR ($CHCl_3$) ν 3488, 2483, 2335, 1758, 1248 cm^{-1}. An. Calcd. for $C_{34}H_{32}FeN_2O_4$ (%): C, 69.39; H, 5.48; found: C, 69.12; H, 5.71. *anti*-**2c**: m. p. 129–131 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.23 (m, 3H), 7.02–6.94 (m, 7H), 5.84–5.72 (m, 2H), 5.42 (d, J = 4.7 Hz, 2H), 5.29–5.21 (m, 4H), 4.81 (d, J = 4.7 Hz, 2H), 4.31–4.09 (m, 10H), 3.65 (dd, J = 16.0, 6.8 Hz, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 157.2, 131.5, 129.4, 122.1, 118.2, 115.4, 81.2, 81.1,

70.0, 68.8, 68.6, 68.2, 57.7, 42.1. IR ($CHCl_3$) ν 3369, 2358, 2252, 1757, 1238 cm^{-1}. $C_{34}H_{32}FeN_2O_4$ (588.17): calcd. C, 69.39; H, 5.48; found C, 69.55; H, 5.63.

Ferrocene bis-β-lactam 2d. Following method A, from 2.18 g (6.26 mmol) of imine **1c**, 2.14 g (12.52 mmol) of phenoxyacetyl chloride and 1.92 g (18.78 mmol) of TEA and after purification by chromatography (SiO_2, Hex/EtOAc 2:1), 3.60 g (93%) of pure *cis*,*cis* bis-β-lactams **2d** were obtained as an inseparable 1:1 *syn*/*anti* diastereomeric mixture as a light brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.23 (m, 8H), 7.01–6.95 (m, 12H), 5.83–5.74 (m, 4H), 5.34 (d, J = 4.7 Hz, 2H), 5.33 (d, J = 4.7 Hz, 2H), 5.18–5.10 (m, 8H), 4.77 (d, J = 4.7 Hz, 2H), 4.74 (d, J = 4.7 Hz, 2H), 4.22–4.09 (m, 16 H), 3.63 (dt, J = 14.3, 7.2 Hz, 4H), 3.20 (dt, J = 13.8, 6.8 Hz, 4H), 2.47–2.27 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 165.7, 157.0, 134.2, 129.2, 129.1, 121.8, 117.3, 117.3, 115.3, 115.2, 81.5, 81.4, 80.8, 80.8, 69.7, 69.7, 68.6, 68.5, 57.8, 57.3, 39.2, 39.1, 31.8, 31.8. IR ($CHCl_3$) ν 2924, 1754, 1641, 1598, 1494, 1235, 1048 cm^{-1}. $C_{36}H_{36}FeN_2O_4$ (616.20): calcd. C, 70.13; H, 5.89; found C, 70.35; H, 5.02.

Ferrocene bis-β-lactams 2e. Following method A, from 1.00 g (3.16 mmol) of imine **1d**, 1.08 g (6.32 mmol) of phenoxyacetyl chloride and 0.98 g (9.48 mmol) of TEA and after overnight Et_2O trituration, 1.79 g (97%) of an inseparable 1:1 *syn*/*anti* diastereomeric mixture of *cis*,*cis*-bis-β-lactams **2e** were obtained as a light brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (t, J = 7.3 Hz, 8H), 6.97 (t, J = 7.3 Hz, 4H), 6.88 (d, J = 7.8 Hz, 8H), 5.36 (d, J = 4.8 Hz, 2H), 5.34 (d, J = 4.8 Hz, 2H), 4.96–4.95 (m, 4H), 4.60 (dd, J = 17.6, 2.5 Hz, 2H), 4.59 (dd, J = 17.7, 2.9 Hz, 2H), 4.26–4.19 (m, 16H), 3.90 (d, J = 17.6 Hz, 2H), 3.89 (d, J = 17.7 Hz, 2H), 2.41 (d, J = 2.5 Hz, 2H), 2.40 (d, J = 2.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 165.2, 157.1, 129.4, 129.3, 122.2, 122.2, 115.6, 115.5, 81.6, 81.6, 81.0, 81.0, 73.5, 73.4, 69.9, 69.9, 69.1, 68.9, 68.3, 68.3, 67.7, 67.7, 57.6, 57.6, 29.5, 29.5. IR ($CHCl_3$) ν 3288, 1761, 1590, 1494, 1234, 1047 cm^{-1}. $C_{34}H_{28}FeN_2O_4$ (584.14): calcd. C, 69.87; H, 4.83; found C, 69.94; H, 4.97.

Compound 3a. 0.50 g (0.85 mmol) of *syn*-**2c** were placed in a sealed tube and treated with 40% aq. $MeNH_2$ (5 mL, 57.00 mmol). The tube was sealed and the mixture was heated to 70 °C for 48 h until total disappearance of the starting material (T.L.C.). The crude was then extracted with DCM (2 × 5 mL), dried (anhyd. $MgSO_4$) and evaporated to yield, after chromatography purification (SiO_2, Hex/EtOAc 1:1), 0.48 g (88%) of **3a** as a dark brown solid. m. p. 138–140 °C.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.19 (m, 4H), 6.92–6.82 (m, 6H), 6.46 (c, J = 4.9 Hz, 2H), 5.75 (ddt, J = 14.1, 10.0, 6.8 Hz, 2H), 5.14–5.01 (m, 4H), 4.94 (bs, 2H), 4.12 (bs, 2H), 3.98–3.80 (m, 8H), 3.23–3.12 (m, 4H), 2.70 (d, J = 4.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 157.2, 136.6, 129.6, 121.8, 115.9, 114.9, 89.2, 81.8, 69.2, 68.6, 68.1, 66.8, 57.4, 49.9, 25.6. IR ($CHCl_3$) ν 3502, 2400, 1714, 1219 cm^{-1}. $C_{36}H_{42}FeN_4O_4$ (650.26): calcd. C, 66.46; H, 6.51; found C, 66.67; H, 6.73.

Compound 3b. 1.00 g (1.70 mmol) of *anti*-**2c** were placed in a sealed tube and treated with 40% aq. $MeNH_2$ (10 mL, 115.00 mmol). The tube was sealed and the mixture was heated to 70 °C for 24 h until total disappearance of the starting material (T.L.C.). The crude was then extracted with DCM (2 × 10 mL), dried over $MgSO_4$ and evaporated to yield, after chromatography purification (SiO_2, Hex/EtOAc 1:1), 1.1 g (92%) of **3b** as a dark brown solid. m. p. 160–162 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.26 (m, 4H), 7.06-6.93 (m, 6H), 6.54 (c, J = 4.9 Hz, 2H), 5.80 (ddt, J = 16.9, 10.7, 6.9 Hz, 2H), 5.18–5.02 (m, 4H), 4.11 (bs, 2H), 4.04–4.02 (m, 2H), 3.86 (bs, 2H), 3.75–3.72 (m, 2H), 3.56–3.47 (m, 4H), 3.32–3.13 (m, 4H), 2.78 (d, J = 4.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 157.3, 136.8, 129.8, 122.0, 116.0, 115.1, 89.2, 82.2, 69.4, 68.7, 68.3, 67.2, 57.5, 50.1, 25.8. IR ($CHCl_3$) ν 3498, 2400, 2385, 1716, 1512, 1225 cm^{-1}. $C_{36}H_{42}FeN_4O_4$ (650.26): calcd. C, 66.46; H, 6.51; found C, 66.63; H, 6.71.

Synthesis of ferrocenic macrocycles

Lactamic ferrocenic macrocycle 4. A solution of **2c** (0.11 g, 0.18 mmol) in 20 mL of anhydrous DCM was added over a 2 h period using a syringe pump to a refluxing deoxygenated solution of Grubbs 2nd Gen. catalyst (10 mol%) in 180 mL of anhyd. DCM. The reaction was monitored by T.L.C. until total disappearance of the starting material (48 h), filtered through a short pad of SiO_2 and evaporated. The crude thus obtained was purified by flash chromatography (SiO_2, Hex/EtOAc 1:1) to obtain 40 mg (36%) of isomer *syn*-*E*-**4**, 40 mg (36%) of isomer *anti*-*E*-**4** as orange solids. *Syn*-*E*-**4**. m. p. 219–221 °C (dec). ^{1}H NMR (500 MHz, C_6D_6) δ 6.99 (dd, J = 8.5, 7.4 Hz, 4H), 6.81 (d, J = 8.5 Hz, 4H), 6.75 (t, J = 7.4 Hz, 2H), 5.86 (m, 1H), 5.83 (m, 1H), 4.75 (d, J = 4.5 Hz, 2H), 4.18 (s, 2H), 3.76 (td, J = 2.4, 1.3 Hz, 2H), 3.70 (d, J = 4.5 Hz, 2H), 3.67 (s, 2H), 3.56 (s, 2H), 3.21 (t, J = 12.5 Hz, 2H), 3.06–3.01 (m, 2H), 2.99 (qd, J = 12.5, 3.9 Hz, 2H), 1.85–1.79 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 157.0, 131.1, 129.1, 121.9, 115.4, 82.0, 80.9, 69.2, 68.9, 68.5, 68.2, 59.4, 43.2, 30.2. IR (KBr) ν 2924, 1755, 1599, 1496, 1358, 1237, 1145, 1030, 804, 755 cm^{-1}. $C_{34}H_{32}FeN_2O_4$ (588.17): calcd. C, 69.39; H, 5.48; found C, 69.54; H, 5.63. MS (FAB) m/z 589 $[M + H]^+$ (12). *anti*-*E*-**4**. m.p. 213–215 °C (dec). ^{1}H NMR (500 MHz, C_6D_6) δ 7.04–6.97 (m, 4H), 6.87 (dd, J = 8.7, 0.9 Hz, 4H), 6.76 (t, J = 7.3 Hz, 2H), 5.60 (m, 1H), 5.55 (m, 1H), 4.89 (d, J = 4.7 Hz, 2H), 4.14 (d, J = 4.7 Hz, 2H), 4.13 (s, 2H), 3.80–3.76 (m,4H), 3.55-3.53 (m, 2H), 3.39–3.30 (m, 2H), 3.14 (ddd, J = 13.3, 8.2, 3.7 Hz, 2H), 2.60–2.50 (m, 2H, 2.17–2.07 (m, 2H). ^{13}C NMR (75 MHz, C_6D_6) δ 166.0, 158.2, 131.9, 129.6, 122.3, 116.2, 82.7, 82.5, 69.0, 68.7, 67.7, 67.6, 58.1, 40.5, 25.9. IR (KBr) ν 2924, 1753, 1598, 1494, 1415, 1236, 754 cm^{-1}. MS (FAB) m/z 589 $[M + H]^+$ (43). $C_{34}H_{32}FeN_2O_4$ (588.17): calcd. C, 69.39; H, 5.48; found C, 69.48; H, 5.54

Lactamic ferrocenic macrocycle 5. A solution of **2e** (0.10 g, 0.17 mmol) in 36 mL of anhyd. MeCN was treated with 0.68 g (3.42 mmol) of $Cu(OAc)_2$ monohydrate. The mixture was heated to 50 °C for 16 h. The reaction was filtrated through Celite®, evaporated and purified by flash chromatography (SiO_2, DCM/EtOAc 10:1) to obtain 30.00 mg (30%) of **5** as a 1:1 inseparable mixture of *syn*/*anti* diastereomers as a dark red solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.23 (m, 10H), 7.05–6.97 (m, 6H), 6.91 (d, J = 8.0, Hz, 4H), 5.39 (bs, 2H), 5.32 (d, J = 4.2 Hz, 2H), 5.17 (bs, 2H), 5.02 (bs, 2H), 4.68 (d, J = 18.6 Hz, 2H), 4.64 (d, J = 18.2, Hz, 2H), 4.44–4.34 (m, 6H), 4.19–4.11 (m, 10H), 4.04 (d, J = 18.2 Hz, 2H), 3.98 (d, J = 18.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 166.0, 157.5, 157.3, 129.6, 129.4, 122.3, 122.2, 115.8, 115.7, 83.2, 83.0, 81.7, 81.5, 72.5, 72.2, 69.4, 69.1, 68.8, 68.7, 62.5, 61.2, 60.3, 32.6, 32.4. IR (KBr) ν 2926, 1759, 1596, 1493, 1415, 1234, 1174,

1094, 828, 752 cm^{-1}. $C_{34}H_{26}FeN_2O_4$ (582.12): calcd. C, 70.11; H, 4.50; found C, 70.24; H, 4.72. MS (FAB) *m/z* 583 $[M + H]^+$ (12).

Conclusions

This study has demonstrated the possibility of obtaining new ferrocenyl derivatives using azetidinone rings as versatile synthons. New ferrocenyl bis-β-lactams, peptides and macrocyclic derivatives can be easily obtained and these molecules are a new group of bio-organometallic derivatives with potential bioactivity.

Acknowledgements

Support for this work under grants CTQ2007-67730-C02-01/BQU and CSD2007-0006 (Programa Consolider-Ingenio 2010) from the MEC (Spain) and CCG07-UCM/PPQ-2596 CAM, is gratefully acknowledged. M. Rodríguez-Fernández was a FPU-MEC fellow.

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