CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200902685

The Sequential Building of Chiral Macrocyclic Bis-β-Lactams by Double Staudinger–Cu-Catalyzed Azide–Alkyne Cycloadditions

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Abstract: A novel approach for the synthesis of macrocyclic bis-β-lactams based on the Cu-catalyzed alkyne–azide cycloaddition (CuAAC) is reported. The procedure is general and allows access to a full range of diastereomerically or enantiomerically pure macrocyclic cavities in good yields. The incorporation of chiral oxazolidinone fragments at C3 in the β-lactam rings allows the total enantiocontrol of the process.

Keywords: azides · copper · cycloaddition · lactams · macrocycles

Introduction

The synthesis of different types of macrocyclic entities has been frequently achieved during the last two decades. Today, different synthetic methodologies that allow an efficient access to this class of compounds are available.[1,2] Nevertheless, the development of approaches for the synthesis of macrocycles containing β-lactam moieties has been somewhat neglected. This fact is appealing since 2-azetidinones are highly relevant organic molecules, not only for their role as structural components of the β-lactam antibacterial agents,[3,4] but also as intermediates in the preparation of many other compounds, such as β-aminoacids and azetidines.[5] Therefore, the design of new molecules framing β-lactams in a macrocyclic structure could, at the same time, lead to new types of potentially biologically active molecules[6] and to highly versatile synthetic intermediates for the preparation of diversely functionalized macrocycles.

The synthetic approaches to building macrocyclic structures that embed 2-azetidinone rings are summarized in Scheme 1.[7] The first approach relies on the construction of the β-lactam rings on a preformed macrocycle.[8] Thus, we reported the synthesis of a series of macrocyclic β-lactams **2** starting from macrocyclic diimines **1** through a double Staudinger ketene–imine cycloaddition reaction. These compounds have been further used to obtain macrocyclic bis-β-aminoacids, bis-azetidines, and bis-amides with defined stereochemistry within the diversity-oriented synthesis (DOS) concept.[8c] Our methodology has been useful for the preparation of other structurally related macrocyclic bis-β-lactams,[8b,9] and has also been applied to acyclic diimines in combination with ring-closing metathesis (RCM) for the closure of the cycle in the last step.[9]

The second approach employs the multiple multicomponent macrocyclization (MiB) strategy. This approach requires starting from precursors that have the right geometry to warrant further macrocyclic assembly.[10] Thus, the Staudinger reaction of mixtures of dialdehydes **3** and diamines **4** affords macrocyclic tetra-β-lactams **5** in a one-pot process (Scheme 1).[11] In this case, the reaction products are obtained as inseparable mixtures of all the possible diastereoisomers. Finally, we have recently reported a different methodology that relies on the assembling of the macrocyclic β-lactam structure by means of M–C and M–N (M = Pd, Pt) bonds. The structures **6** and **7** obtained through this proce-

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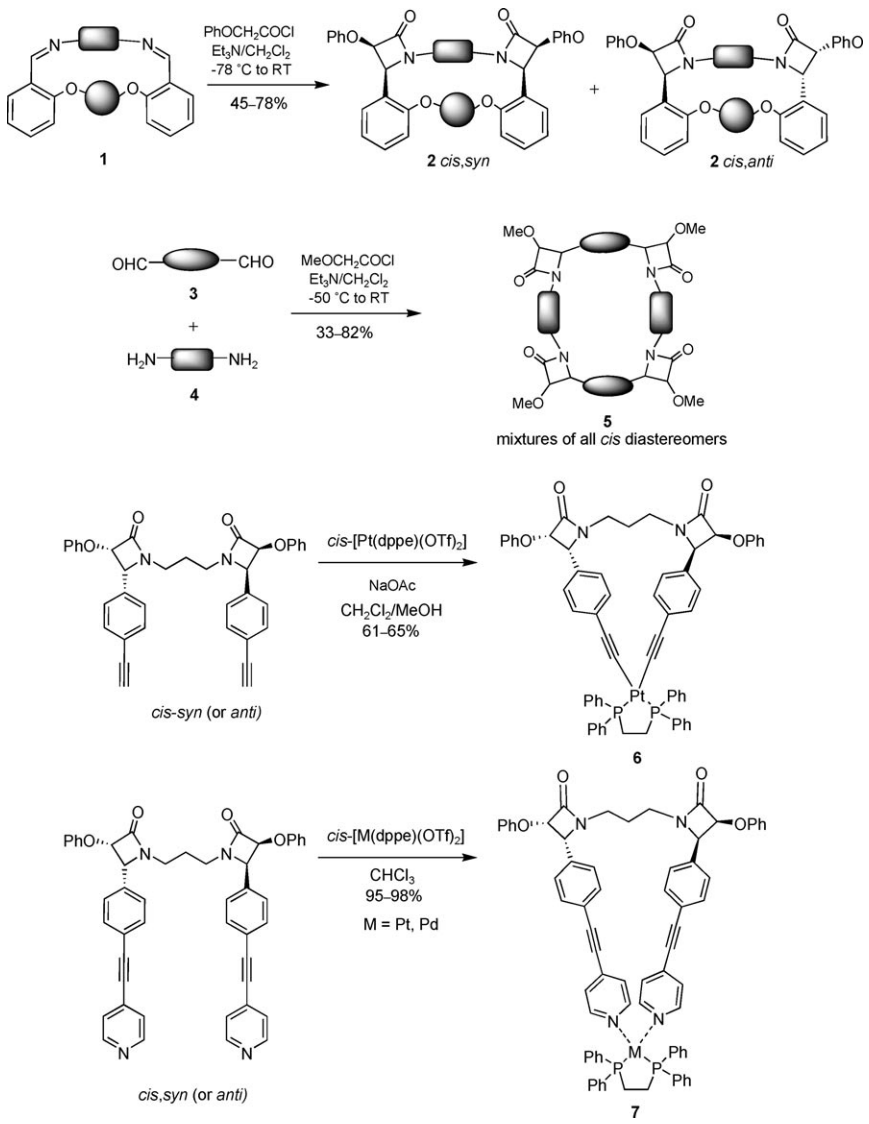
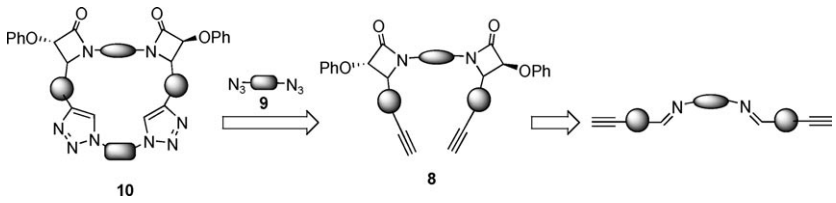
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200902685.



Scheme 1. A summary of the synthetic approaches used to build macrocyclic structures embedding 2-azetidinone rings (OTf = trifluoromethanesulfonate, dppe = 1,2-bis(diphenylphosphino)ethane).

dure combine the rigid 2-azetidinone rings with ligand-tunable metal centers that have *cis*-square-planar geometry.[12]

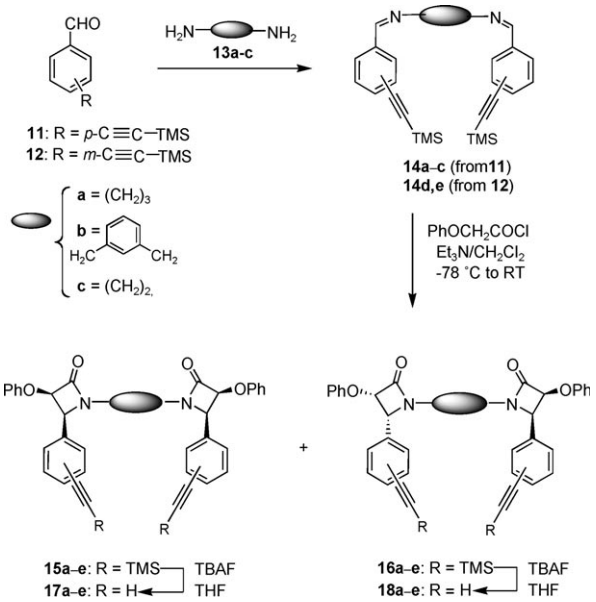
In the present work we develop an alternative approach to the synthesis of macrocyclic bis-β-lactams that relies on the sequential double Staudinger–Cu^{I}-catalyzed 1,3-dipolar cycloaddition reaction (CuAAC).[13,14] The double cycloaddition ring closure was carried out on a bis-β-lactam that has the appropriate alkynes tethered to the C4 positions of the 2-azetidinone rings. The success of the proposed methodology requires overcoming the problem of ring closure versus oligomerization (or cyclo-oligomerization). This is a key point, as kinetically controlled cyclization processes frequently lead (irreversibly) to the kinetic and statistic distribution of products, including a collection of linear/cyclic oligomers and polymers of different chain length, thus inevitably resulting in poor yields of the desired macrocycles. In these processes, taking advantage of the geometry and preorganization of the precursors is essential for the successful outcome of the reaction.[15] Here we benefit from the rigid 2-azetidinone templates embedded in the starting bis-alkynyl fragment to effect the double CuAAC. Therefore, our approach starts from a series of bis-alkynes **8** that already hold the preformed β-lactam moieties. The subsequent reaction with different bis-azides **9** allows the obtention of the ring-closure products **10** (Scheme 2). Reported herein is the successful implementation of this methodology to prepare either racemic or enantiopure bis-β-lactam cavities.



Scheme 2. Synthetic planning for **10**.

Results and Discussion

The synthesis of the starting bis-alkynyl-β-lactams follows our previous reported method (Scheme 3).[12] Thus, diimines **14a–e** were prepared in quantitative yields from diamines **13** and *p*-trimethylsilylethynylbenzaldehyde **11** or *m*-trimethylsilylethynylbenzaldehyde **12**, respectively.[16] Diimines **14** were then reacted with phenoxyacetyl chloride in the presence of NEt_3[17] to yield 1:1 mixtures of diastereomeric bis-β-lactams **15** and **16** (61–66%



Scheme 3. Synthesis of the starting bis-alkynyl–β-lactams.

average yield) that were separated by chromatography on silica gel (Table 1). The isomers were reacted independently with tetrabutylammonium fluoride (TBAF) to remove quantitatively the trimethylsilyl (TMS) groups, thereby affording pure bis-alkynyl–bis-β-lactams **17** and **18**. In all cases the *cis*-stereochemistry of the β-lactam rings was ensured by the coupling constants of H3,H4 protons (average J(H3,H4) = 4.4 Hz for compounds **17** and **18**).[18]

The *syn*/*anti* (meso/racemic) stereochemistry of the bis-alkynyl–bis-β-lactams in Table 1 was determined by means of X-ray analysis and/or spectroscopic methods. The geometry of **16a** had been already established by X-ray diffraction.[8a] The study of the ^{1}H NMR spectrum of this compound showed the signals of the diastereotopic NCH_2 protons as two doublet of triplets, dt, at $\delta = 3.39$ and 3.05 ppm, respectively ($\Delta\delta = 0.34$ ppm). This multiplicity pattern is also observed in the corresponding *syn* (meso) isomer **15a**, although the signals of the dt are now clearly far apart ($\delta =$ 3.46 and 2.98 ppm; $\Delta\delta = 0.48$ ppm) (Figure 1A). The same pattern for the NCH_2 protons was observed in the ^{1}H NMR spectra of the structurally related *syn*/*anti* couple of bis-β-lactams **15d** and **16d**, and their respective configurations were assigned in consequence. Thus, the *anti* isomer **16d** showed the NCH_2 signals at $\delta = 3.42$ and 3.07 ppm, respectively ($\Delta\delta =$ 0.35 ppm), whereas these protons in the *syn* isomer appeared at $\delta = 3.52$ and 2.96 ppm ($\Delta\delta =$ 0.56 ppm) (Figure 1B). These characteristic changes in the ^{1}H NMR spectra of *syn*/*anti* isomers have been also observed in other structurally related macrocyclic bis-β-lactams.[8a]

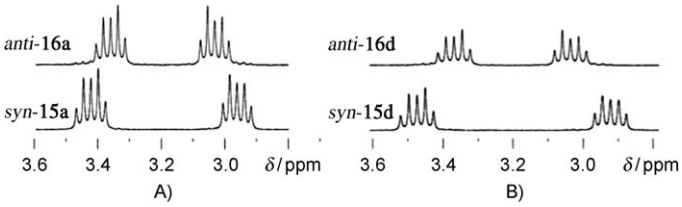
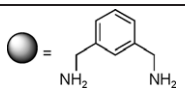
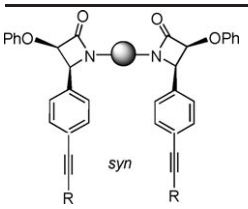
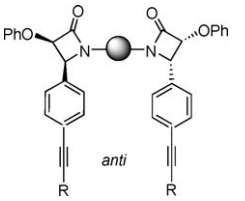
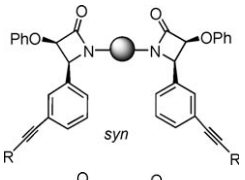
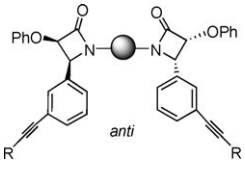


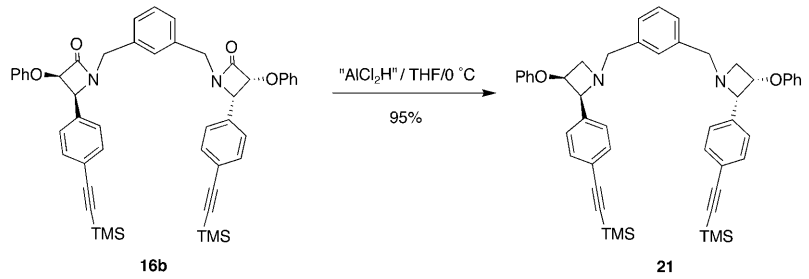
Figure 1. ^{1}H NMR spectra for compounds A) *anti*-**16a** and *syn*-**15a**, and B) *anti*-**16d** and *syn*-**15d**.

Table 1. Bis-β-lactams **15** (R = TMS), **16** (R = TMS), **17** (R = H), and **18** (R = H) and the yields in which they were produced (in parentheses).

	= $NH_2(CH_2)_3NH_2$	= 	= $NH_2(CH_2)_2NH_2$
	**15a** (30%) **17a** (97%)[a]	**15b** (31%) **17b** (98%)	**15c** (26%) **17c** (98%)
	**16a** (32%) **18a** (96%)[a]	**16b** (33%) **18b** (97%)	**16c** (31%) **18c** (98%)
	**15d** (29%) **17d** (98%)	**15e** (35%) **17e** (97%)	– –
	**16d** (33%) **18d** (98%)	**16e** (33%) **18e** (96%)	– –

[a] See ref. [12].

The stereochemistry of the bis-β-lactams having a 1,3-*m*-diaminobenzene bridge **15b**/**16b** was determined by X-ray diffraction analysis of a single crystal of the azetidine derivative **21**, which was obtained by reduction of bis-β-lactam **16b** with chloralane ($AlCl_2H$; Scheme 4). The structure of **21** showed a C_2 axis (Figure 2), as expected for the *anti* (racemic)



Scheme 4. Synthesis of azetidine derivative **21**.

Treatment of either *syn* or *anti* bis-alkynyl–bis-β-lactams **17** and **18** with a range of bis-azides having different tethers **9a–d**[19] in DMF in the presence of Cu^{I} at room temperature afforded macrocycles **19a–n** and **20a–n** in yields ranging from 14 to 64% (Table 2, Scheme 5). In all cases the reaction yielded the expected macrocycles as the

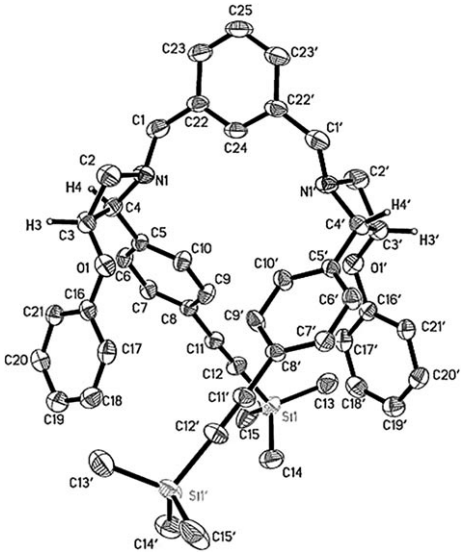


Figure 2. ORTEP plot of **21** with 25% probability. Hydrogen atoms are omitted for clarity, with an exception made for H3, H4, H3′, and H4′ bonded to the chiral carbon atoms. The asymmetric unit is one half of the molecule.

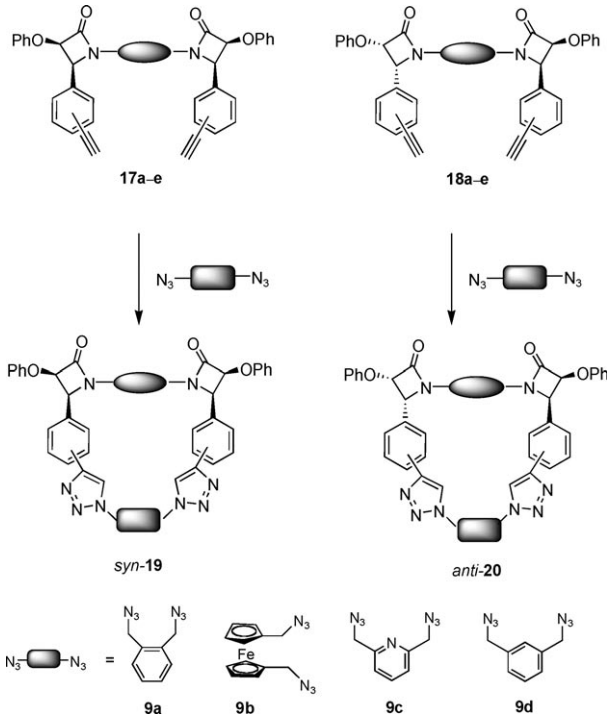
Table 2. Macrocyclic bis-β-lactams **19** and **20** and the yields in which they were produced (in parentheses).

	9a	**9b**	**9c**	**9d**
syn-**17a**	**19a** (22%)	**19b** (40%)	**19c** (60%)	**19d** (59%)
syn-**17b**	**19e** (30%)	**19f** (35%)	**19g** (55%)	**19h** (50%)
syn-**17c**	[a]	[a]	[b]	**19i** (15%)
syn-**17d**	**19j** (24%)	**19k** (37%)	**19l** (62%)	–
syn-**17e**	–	**19m** (41%)	**19n** (61%)	–
anti-**18a**	**20a** (23%)	**20b** (38%)	**20c** (60%)	**20d** (55%)
anti-**18b**	**20e** (25%)	**20f** (39%)	**20g** (57%)	**20h** (64%)
anti-**18c**	[a]	[a]	[b]	**20i** (14%)
anti-**18d**	**20j** (19%)	**20k** (35%)	**20l** (52%)	–
anti-**18e**	–	**20m** (47%)	**20n** (51%)	–

[a] No signals of the macrocyclic ring were observed in the ^{1}H NMR spectra of the crude reaction mixtures. [b] <10% determined from ^{1}H NMR spectra of the crude reaction mixtures.

diastereoisomer, which unequivocally established the stereochemistry of the precursor **16b**. In the case of the couple (**15e**)**17e**/(**16e**)**18e**, the *syn*/*anti* stereochemistry was established by X-ray diffraction analysis of the macrocyclic bis-β-lactam **19n**, derived from the CuAAC reaction of *syn*-**17e** (Figure 3, see below).

Finally, for bis-β-lactams (**15c**)**17c**/(**16c**)**18c** that have an ethylenediamine bridge, the *syn*/*anti* stereochemistry was established by a ^{1}H NMR spectroscopic study of the signals of the H3,H4 β-lactam protons in the presence of [Eu(hfc)$_3$] (hfc = [(tris(3-(heptafluoropropylhydroxymethylene)-D-camphorate)]). After the addition of the chiral shift reagent to **18c** ($CDCl_3$), the signals of the former CH duplets clearly split, in accordance with a racemic (*anti*) diastereoisomer. In a similar experiment carried out with **17c**, the CH signals did not separate, as expected for the meso (*syn*) isomer. The stereochemical assignment is in full agreement with the data reported for other structurally related compounds.[9]



Scheme 5. Synthesis of macrocycles **19** and **20**.

sole reaction products (together with polymeric material of unknown composition). No traces of other macrocyclic structures were detected in the crude reaction mixtures. The structural characterization of the products was based on analytical and spectroscopic data (see the Experimental Section and the Supporting Information). In the case of **19n**, a single crystal obtained by slow evaporation in $CHCl_3$ allowed the structural X-ray diffraction analysis (Figure 3) that unequivocally confirmed the *syn* arrangement of the precursor bis-β-lactam **17e** (see above).

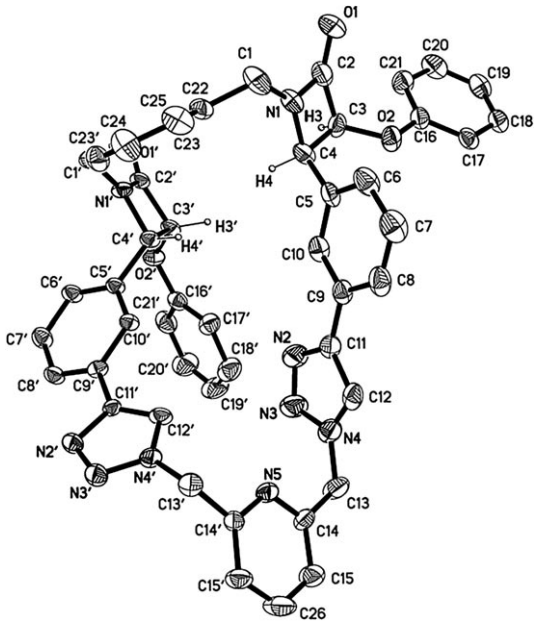
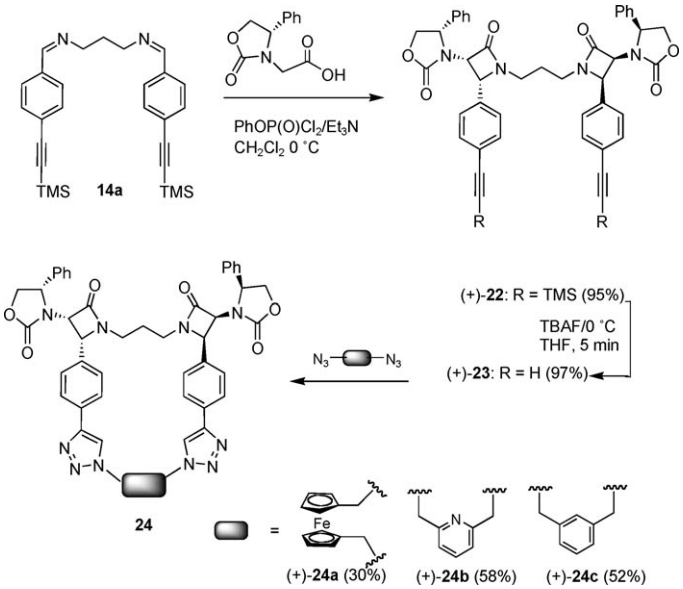


Figure 3. ORTEP plot of **19n** with 25% probability. Hydrogen atoms are omitted for clarity, with an exception made for H3, H4, H3′, and H4′ bonded to the chiral carbon atoms.

From the results in Table 2, it can be concluded that the formation of the macrocycles **19** and **20** is not influenced by the *syn*/*anti* stereochemistry of the starting bis-alkynyl ligands. Thus, for a given bis-azide **9** the yields of the cyclization products are similar with both isomers. The position *para* (**17a–c**/**18a–c**) or *meta* (**17d,e**/**18d,e**) of the alkynyl groups in the aromatic rings of the precursor bis-alkynyl–β-lactams has also little influence on the progression of the cyclization. However, the length of the tether between the nitrogen atoms in the starting bis-alkynyl ligands **17** and **18** has more effect on the outcome of the process. Oligomerization is the main reaction with bis-β-lactams (**17c** and **18c**), which have the short $(CH_2)_2$ chain as a tether, whereas for a given bis-azide, there is hardly any difference in yields when the tether is a flexible $(CH_2)_3$ chain or a more rigid 1,3-*m*-diaminobenzene bridge. Finally, the structure of the bis-azides **9** has also to be considered. The best yields (50–64%) were obtained with the structurally related and more preorganized *meta*-bis-azides **9c** and **9d**, whereas the results are poorer with ferrocenyl bis-azide **9b** (35–47%). In all cases, the lowest yields were observed when *ortho*-bis-azide **9a** (with the shortest tether) was used (19–30%).

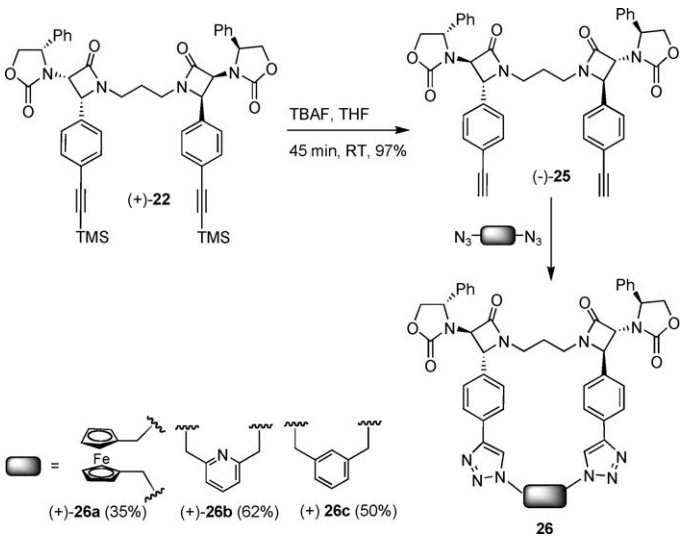
Compounds **19**/**20** in Scheme 5 constitute a range of diastereomerically pure macrocyclic cavities containing 2-azetidinones as motifs of biological relevance. To go further, the synthesis of enantiomerically pure macrocyclic cavities was pursued next. The sequence of reactions followed is shown in Scheme 6. Thus, enantiomerically pure bis-β-lactam (+)-



Scheme 6. Synthesis of enantiomerically pure macrocyclic bis-β-lactams (+)-**24a–c**.

22 was prepared in 95% yield by the reaction of imine **14a** with (*S*)-(+)-(2-oxo-4-phenyloxazolydin-3-yl)acetic acid and phenyldichlorophosphate in NEt_3.[20] Compound (+)-**22** was obtained as a single product, thereby demonstrating that the reaction occurs with total enantio- and diastereoselectivity. The *cis* stereochemistry of the β-lactam rings was established by the H3,H4 coupling constants (J(H3,H4) = 4.5 Hz), and the *anti* stereochemistry of (+)-**22** was unambiguously established by X-ray diffraction analysis of a macrocyclic derivative ((+)-**26a**; Figure 4, see below). After removal of the TMS groups (TBAF, 0 °C, 5 min, (+)-**23**, 97%) and reaction with the most efficient bis-azides **9b–d**, enantiomerically pure macrocyclic bis-β-lactams (+)-**24a–c** were obtained in 30–58% yields (Scheme 6).

The experimental conditions used in the removal of the TMS group in (+)-**22** are critical. The reaction is very fast (TBAF, 0 °C, THF, 5 min), and bis-alkynyl–bis β-lactam (+)-**23** is obtained quantitatively after workup. However, if the reaction is carried out at room temperature for 45 min, the complete *cis*/*trans* isomerization of the β-lactam rings smoothly occurs and the *anti*,*trans* bis-alkynyl–bis-β-lactam (−)-**25** is obtained in 97% isolated yield (Scheme 7). The *trans* stereochemistry of (−)-**25** was established by the new H3,H4 coupling constants (J(H3,H4) = 2.3 Hz).[18] The clean *cis*/*trans* isomerization of the β-lactam rings under the mild



Scheme 7. Synthesis of enantiopure macrocyclic β-lactam cavities (+)-**26**.

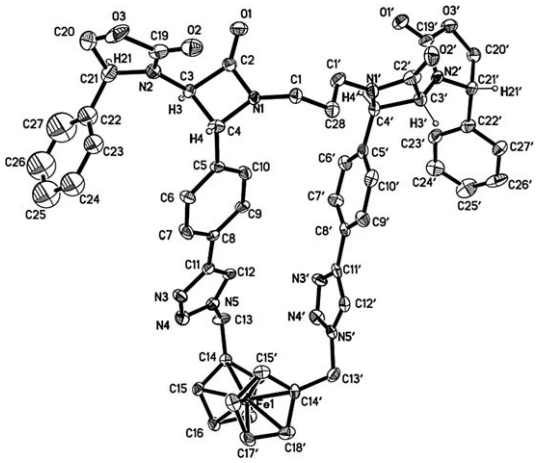


Figure 4. ORTEP plot of (+)-**26a** with 25% probability. Hydrogen atoms are omitted for clarity, with an exception made for H3, H4, H3′, and H4′ bonded to the chiral carbon atoms.

conditions used to remove the TMS groups deserves further discussion. Generally, *cis*/*trans* isomerizations in 2-azetidinones are carried out by C3 epimerization in the presence of a base.[21] The reported procedures usually require high concentrations of base, prolonged reaction times, and the yields are low due to partial destruction of the starting material during the reaction. Other methods that have been described to achieve the ring *cis*/*trans* isomerization use UV light irradiation,[22] or are restricted to 2-azetidinones that have specific structural features.[23] In contrast, if the reaction reported here would be of general applicability, it could be clearly an advantageous procedure over the known methods. Therefore, the study of the scope of this new isomerization procedure and its application to other sensitive β-lactam derivatives requires further study.

Finally, the reaction of *anti*,*trans* bis-alkynyl–bis-β-lactam (−)-**25** with azides **9b–d** under the conditions above yielded the expected enantiopure macrocyclic β-lactam cavities (+)-**26** in 35–62% yields (Scheme 7). Further structural confirmation of the products was gained by X-ray diffraction analysis of a single crystal obtained by slow evaporation of macrocyclic bis-β-lactam (+)-**26a** in MeCN (Figure 4). By means of this structure, the stereochemistry of *anti*,*trans* bis-alkynyl–bis-β-lactam precursor (−)-**25** was unequivocally established. Furthermore, and considering that (−)-**25** is very likely formed by the exclusive epimerization of the more acidic C3 positions of the β-lactam rings, the *anti*,*cis* stereochemistry of its precursor (+)-**22** could be also assigned (see above).

The structures in Figures 3 and 4 show flexible macrocyclic cavities of 10×5 and 11×5 Å, respectively, with distances of 4–5 Å between the triazole rings. Chiral cavities are of great importance in the field of molecular and anion recognition and their properties are valuable in different areas such as organic chemistry; biochemistry and molecular biology; polymer science; and supramolecular chemistry.[24] Our procedure allows easy access to enantiomerically pure cavities by just placing the right substituent (with defined stereochemistry) at C3 in the precursor bis-β-lactam fragment, and also incorporates two triazole rings into the structure that could have interesting properties for anion recognition.[25] Our method also leaves open the possibility of incorporating other chiral elements, either in the tether of the bis-alkynyl–β-lactam fragment, or in the bis-azide to build more complex chiral macrocycles.[25,26]

Conclusion

A novel approach to the synthesis of macrocyclic bis-β-lactams based on the sequential double Staudinger reaction–Cu-catalyzed alkyne–azide (CuAAC) cycloaddition has been developed. The procedure is general and allows access to a full range of diastereomerically or enantiomerically pure macrocyclic cavities in good yields. The incorporation of chiral oxazolidinone fragments at C3 in the β-lactam rings allows total enantiocontrol of the process. Eventually, we have found an efficient procedure for the *cis*/*trans* isomerization of the 2-azetidinone moieties under smooth conditions. The structures of the compounds prepared through this work have been unambiguously determined by X-ray diffraction studies and are flexible macrocyclic cavities of 10×5 and 11×5 Å, respectively, with distances of 4–5 Å between the triazole rings. The use of these chiral cavities in different molecular recognition processes will be further pursued in our laboratories.

Experimental Section

General procedures: Bis-β-lactams **15a**, **16a**, **17a**, and **18a**[12] and bis-azides **9a–d**[19] were prepared following literature procedures. Full experimental procedures for the synthesis of dimines **14**, compounds **15c–e**, **16c–e**, **17b–e**, **18b–e**, **19a–m**, and **20a–n**; crystallographic data; and

copies of NMR spectra of all new complexes discussed in the text are available in the Supporting Information. ^{1}H and ^{13}C NMR spectra were recorded at 22 °C using Bruker Avance 700 (700.1 and 176.0 MHz), 500 (500.1 and 125.7 MHz), 300 (300.1 and 75.5 MHz), or Bruker 200-AC (200.1 and 50 MHz) spectrometers. Chemical shifts are given in ppm relative to $CHCl_3$ (^{1}H, $\delta = 7.27$ ppm) and $CDCl_3$ (^{13}C, $\delta = 77.0$ ppm), DMF (^{1}H, $\delta = 8.02$ ppm) and [D$_7$]DMF (^{13}C, $\delta = 163.2$ ppm), DMSO (^{1}H, $\delta = 2.50$ ppm) and [D$_6$]DMSO (^{13}C, $\delta = 39.5$ ppm), and CD_3CN (^{1}H, $\delta = 1.95$ ppm) and CD_3CN (^{13}C, $\delta = 118.0$ ppm). IR spectra were recorded using a Bruker Tensor 27 (MIR 8000–400 cm^{-1}) spectrometer of a solid film of pure compound. Mass spectra were recorded using a QSTAR pulsar I (hybrid analyzed QTOF, applied biosystems) (ESI), or a MAT 95 XP ThermoFinnigan (FAB) apparatus. CH_2Cl_2 was distilled from calcium hydride and THF from sodium benzophenone. 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 the products was made by TLC (Kiesegel 60F-254). UV light ($\lambda = 254$ nm) was used to develop the plates.

Synthesis of bis-β-lactams 15b/16b: A solution of phenoxyacetyl chloride (1.30 g, 7.2 mmol) in dry CH_2Cl_2 (20 mL) was purged with argon and cooled at −78 °C. Then a solution of triethylamine (1.40 g, 14.4 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise. The mixture was stirred for 30 min at −78 °C, and a solution of diimine **14b** (1.20 g, 2.4 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise by means of a syringe pump for 2 h, with the temperature maintained at −78 °C. The reaction was stirred at room temperature for 16 h, and then quenched with a MeOH/water/ice mixture (25 mL). The organic layer was washed with HCl (0.5 M; to remove the excess of triethylamine) and brine, and then dried with $MgSO_4$. The desiccant was removed by filtration and the solvent was evaporated at reduced pressure. The crude solid was suspended in Et_2O, filtered with cold Et_2O, and dried, thus yielding a 1:1 mixture of *syn*- and *anti*-bis-β-lactams **15b/16b** (1.46 g, 79 %) that were separated by chromatography on silica gel (hexane/AcOEt 7:3). *Syn*-bis-β-lactam **15b** was obtained as a crystalline solid (574 mg, 31 %). M.p. 228–231 °C ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.37$ (d, $J = 8.2$ Hz, 4H; ArH), 7.28 (t, $J = 7.7$ Hz, 1H; ArH), 7.21–7.07 (m, 10H; ArH), 6.90 (s, 1H; ArH), 6.87 (t, $J = 7.2$ Hz, 2H; ArH), 6.69 (d, $J = 7.8$ Hz, 4H; ArH), 5.38 (d, $J = 4.4$ Hz, 2H; CH−O), 4.73 (d, $J = 14.9$ Hz, 2H; CH_2−N), 4.69 (d, $J = 4.4$ Hz, 2H; CH−N), 3.90 (d, $J = 14.9$ Hz, 2H; CH_2−N), 0.22 ppm (s, 18H; CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 165.3$ (C=O), 156.5, 135.3, 133.0, 131.7, 129.4, 129.1, 128.5, 128.4, 128.1, 123.4, 122.0, 115.2 (ArC), 104.3 (≡C), 95.2 (≡C), 82.0 (CH−O), 61.4 (CH−N), 44.1 (CH_2−N), −0.1 ppm (CH_3); IR (film): $\tilde{\nu}_{max} = 3041$, 2959, 2157, 1762, 1703, 1598, 1494, 1397, 1234, 1084, 953, 863, 753 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{48}H_{49}N_2O_4Si_2$ $[M+H]^+$: 773.3230; found 773.3217. *Anti*-bis-β-lactam **16b** was obtained as a crystalline solid (610 mg, 33 %). M.p. 225–227 °C ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.36$ (d, $J = 8.3$ Hz, 4H; ArH), 7.27 (t, $J = 7.8$ Hz, 1H; ArH), 7.17 (d, $J = 8.3$ Hz, 4H; ArH), 7.14–7.07 (m, 6H; ArH), 6.92 (s, 1H; ArH), 6.87 (t, $J = 7.4$ Hz, 2H; ArH), 6.70 (d, $J = 8.2$ Hz, 4H; ArH), 5.44 (d, $J = 4.5$ Hz, 2H; CH−O), 4.73 (d, $J = 14.8$ Hz, 2H; CH_2−N), 4.72 (d, $J = 4.5$ Hz, 2H; CH−N), 3.91 (d, $J = 14.8$ Hz, 2H; CH_2−N), 0.21 ppm (s, 18H; CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 165.5$ (C=O), 156.6, 135.4, 133.0, 131.8, 129.2, 128.5, 128.4, 128.3, 128.1, 123.4, 122.1, 115.3 (ArC), 104.3 (≡C), 95.3 (≡C), 82.1 (CH−O), 61.6 (CH−N), 44.2 (CH_2−N), −0.1 ppm (CH_3); IR (film): $\tilde{\nu}_{max} = 3039$, 3960, 2920, 2160, 1764, 1597, 1495, 1399, 1353, 1237, 1083, 954, 844, 755 cm^{-1}. HRMS (ESI): *m/z*: calcd for $C_{48}H_{49}N_2O_4Si_2$ $[M+H]^+$: 773.3230; found: 773.3245.

Synthesis of bis-azetidine 21: A solution of $AlCl_3$ (103 mg, 0.77 mmol) in dry THF (5 mL) was added with a cannula to a stirred suspension of $LiAlH_4$ (26 mg, 0.77 mmol) in dry THF (10 mL) at 0 °C and under Ar. The mixture was stirred for 30 min at room temperature and then cooled to 0 °C before the addition (also with a cannula) of a solution of bis-β-lactam **16d** (100 mg, 0.13 mmol) in dry THF (10 mL). After 20 min at room temperature, the reaction was quenched with ice and extracted with Et_2O (3 × 20 mL). The organic phases were washed with brine and water and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (CH_2Cl_2/AcOEt 9:1). Bis-azetidine **21** (561 mg, 98 %) was obtained as a crystalline solid. M.p. 112–114 °C ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.49$ (d, $J = 8.2$ Hz, 4H; ArH), 7.41 (d, $J = 8.2$ Hz, 4H; ArH), 7.23–7.08 (m, 8H; ArH), 6.84 (t, $J = 7.3$ Hz, 2H; ArH), 6.58 (d, $J = 8.4$ Hz, 4H; ArH), 4.94 (t, $J = 5.8$ Hz, 2H; CH−O), 4.48 (d, $J = 5.8$ Hz, 2H; CH−N), 3.84 (d, $J = 13.0$ Hz, CH_2−Ar), 3.58–3.49 (m, 4H; CH_2−N + CH_2−Ar), 3.34–3.26 (m, 2H; CH_2−N), 0.27 ppm (s, 18H; TMS); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 157.3$, 137.6, 137.4, 131.9, 129.2, 129.1, 128.4, 128.0, 127.5, 121.9, 120.7, 114.9 (ArC), 105.3, 93.7 (≡C), 71.5 (CH−O), 64.3 (CH−N), 60.8 (CH_2−Ar), 57.1 ppm (CH_2−N); IR (film): $\tilde{\nu}_{max} = 3287$, 3061, 3039, 2949, 2105, 1694, 1598, 1494, 1457, 1237, 1103, 1026, 795, 753 cm^{-1}.

General procedure for the synthesis of macrocycles: The bis-azide and (+)-sodium L-ascorbate was added to a stirred solution of the corresponding bis-β-lactam in DMF. The mixture was purged with Ar for 15 min and then $CuSO_4 \cdot 5H_2O$ was added in one portion. The molar ratio of bis-β-lactam/bis-azide/L-ascorbate/$CuSO_4 \cdot 5H_2O$ was 1:1:0.4:0.2. The reaction was stirred overnight at room temperature and the solvent was removed under reduced pressure. The crude product was solved in CH_2Cl_2 (40 mL), washed with water (2 × 20 mL), the organic layer dried over $MgSO_4$, and the solvent removed under reduced pressure. The pure macrocycles were obtained after chromatography on silica gel (CH_2Cl_2/AcOEt/MeOH, 8:2:0.1).

Synthesis of 19n: From bis-β-lactam **17e** (50 mg, 79 μmol), bis-azide **9c** (15 mg, 79 μmol), (+)-sodium L-ascorbate (6 mg, 30 μmol), and $CuSO_4 \cdot 5H_2O$ (4 mg 16 μmol) in DMF (100 mL), **19n** (40 mg, 61 %) was obtained as a pale yellow crystalline solid. M.p. 176–178 °C ($CHCl_3$ + MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.26$ (s, 2H; =CH), 7.95 (t, $J = 7.7$ Hz, 1H; ArH), 7.66–7.61 (m, 4H; ArH), 7.57–7.50 (m, 2H; ArH), 7.32–7.24 (m, 1H; ArH), 7.21–7.07 (m, 10H; ArH), 6.86–6.74 (m, 7H; ArH), 5.79–5.66 (m, 6H; CH_2−Ar + CH−O), 4.92 (d, $J = 4.4$ Hz, 2H; CH−N), 4.62 (d, $J = 15.4$ Hz, 2H; CH_2−N), 4.03 ppm (d, $J = 15.4$ Hz, 2H; CH_2−N); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 165.0$ (C=O), 156.3, 154.2 (ArC), 145.9 (C), 138.7, 135.1, 134.0, 130.2, 129.2, 128.9, 128.3, 128.2, 127.4, 127.1, 125.5, 125.0, 122.9, 121.6 (ArC), 121.5 (=CH), 114.9 (ArC), 81.4 (CH−O), 61.0 (CH−N), 54.1 (CH_2−Ar), 43.6 ppm (CH_2−N); IR (film): $\tilde{\nu}_{max} = 3137$, 3062, 2926, 1757, 1597, 1493, 1457, 1352, 1231, 1077, 1047, 864, 755 cm^{-1}; FABMS: *m/z*: 818.9 $[M+H]^+$; HRMS (ESI): *m/z*: calcd for $C_{49}H_{30}N_9O_4$ $[M+H]^+$: 818.3203; found: 818.3202.

Synthesis of (+)-24a: From bis-β-lactam (+)-**23** (50 mg, 71 μmol), bis-azide **9b** (21 mg, 71 μmol), (+)-sodium L-ascorbate (6 mg, 30 μmol), and $CuSO_4 \cdot 5H_2O$ (4 mg, 16 μmol) in DMF (100 mL), (+)-**24a** (21 mg, 30 %) was obtained as a pale yellow crystalline solid. M.p. 200 °C ($CHCl_3$ + MeOH; decomp); $[\alpha]_D^{25} = +63°$ ($c = 0.001$ in CH_2Cl_2); ^{1}H NMR (300 MHz, CD_3CN): $\delta = 8.05$ (s, 2H; =CH), 7.69 (d, $J = 8.1$ Hz, 4H; ArH), 7.43–7.32 (m, 10H; ArH), 7.30–7.19 (m, 4H; ArH), 5.23 (d, $J = 15.2$ Hz, 2H; CH_2-Cp), 5.16 (d, $J = 15.2$ Hz, 2H; CH_2-Cp), 4.85 (d, $J = 5.0$ Hz, 2H; CH−N), 4.42–4.33 (m, 4H; CH−N), 4.25–4.13 (m, 6H; CpH), 4.05 (t, $J = 8.8$ Hz, 2H; CH_2−O), 3.90 (br s, 2H; CpH), 3.88–3.79 (m, 2H; CH_2−O), 3.47 (dt, $^1J = 14.4$ Hz, $^2J = 7.0$ Hz, 2H; CH_2−N), 3.11 (dt, $^1J = 14.4$ Hz, $^2J = 7.0$ Hz, 2H; CH_2−N), 1.82 ppm (q, $J = 7.0$ Hz, 2H; CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 164.5$, 156.0 (C=O), 145.7 (C), 137.8, 134.7, 130.0, 129.0, 128.7, 128.2, 127.1, 124.8 (ArC), 121.9 (=CH), 84.3 (CpC), 69.5 (CH_2−O), 68.9, 68.6, 68.6, 68.5 (CpC), 63.2, 62.9, 58.6 (CH−N), 48.3, 40.6 (CH_2−N), 28.0 ppm (CH_2); IR (film): $\tilde{\nu}_{max} = 3132$, 2924, 1758, 1672, 1450, 1414, 1225, 1078, 1043, 881, 757 cm^{-1}; ESIMS: *m/z*: 1001.7 $[M+H]^+$; HRMS (ESI): *m/z*: calcd for $C_{55}H_{49}FeN_{10}O_6$ $[M+H]^+$: 1001.3185; found: 1001.3212.

Synthesis of (+)-24b: From bis-β-lactam (+)-**23** (50 mg, 71 μmol), bis-azide **9b** (13 mg, 71 μmol), (+)-sodium L-ascorbate (6 mg,30 μmol), and $CuSO_4 \cdot 5H_2O$ (4 mg, 16 μmol) in DMF (100 mL), (+)-**24b** (36 mg, 58 %) was obtained as a crystalline solid. M.p. 250 °C ($CHCl_3$ + MeOH; decomp); $[\alpha]_D^{25} = +76°$ ($c = 0.001$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.87$ (t, $J = 7.7$ Hz, 1H; ArH), 7.83 (s, 2H; =CH), 7.69 (d, $J = 8.1$ Hz, 4H; ArH), 7.52 (d, $J = 7.7$ Hz, 2H; ArH), 7.41–7.33 (m, 6H; ArH), 7.31 (d, $J = 8.1$ Hz, 4H; ArH), 7.23–7.13 (m, 4H; ArH), 5.73 (d, $J = 14.9$ Hz, 2H; CH_2−Ar), 5.67 (d, $J = 14.9$ Hz, 2H; CH_2−Ar), 4.72 (d, $J = 4.8$ Hz, 2H; CH−N), 4.38 (d, $J = 4.8$ Hz, 2H; CH−N), 4.16–4.04 (m,

4H; CH–N+CH_2–O), 3.87 (t, J=12.2 Hz, 2H; CH_2–O), 3.56 (dt, ^1J=14.2 Hz, ^2J=6.9 Hz, 2H; CH_2–N), 3.12 (dt, ^1J=14.2 Hz, ^2J=6.9 Hz, 2H; CH_2–N), 1.79 ppm (q, J=6.9 Hz, 2H; CH_2); ^{13}C NMR (175 MHz, [D_6]DMSO): δ=164.2, 155.9 (C=O), 154.3 (ArC), 145.9 (C), 138.7, 137.7, 134.3, 130.1, 129.0, 128.7, 128.1, 127.1, 124.8, 122.7, (ArC), 121.5 (=CH), 69.4 (CH_2–O), 63.1, 62.7, 58.7 (CH–N), 53.9 (CH_2–Ar), 40.3 (CH_2–N), 27.6 ppm (CH_2); IR (film): $\tilde{\nu}_{max}$=2924, 1757, 1458, 1418, 1368, 1226, 1120, 1044, 882, 761 cm^{-1}; ESIMS: m/z: 894.5 [M+H]$^+$; HRMS (ESI): m/z: calcd for $C_{50}H_{44}N_{11}O_6$ [M+H]$^+$: 894.3475; found: 894.3507.

Synthesis of (+)-24c: From bis-β-lactam (+)-**23** (50 mg, 71 μmol), bis-azide **9d** (13 mg, 71 μmol), (+)-sodium L-ascorbate (6 mg, 30 μmol), and $CuSO_4$·5H_2O (4 mg, 16 μmol) in DMF (100 mL), (+)-**24c** (32 mg, 52%) was obtained as a crystalline solid. M.p. 210°C ($CHCl_3$+MeOH; decomp); $[\alpha]_D^{25}$=+75° (c=0.001 in CH_2Cl_2); ^{1}H NMR (700 MHz, [D_6]DMSO) δ=8.46 (s, 2H; =CH), 7.64 (d, J=8.0 Hz, 4H; ArH), 7.53–7.46 (m, 3H; ArH), 7.42–7.33 (m, 6H; ArH), 7.31 (d, J=8.0 Hz, 4H; ArH), 7.26 (d, J=7.3 Hz, 4H; ArH), 7.01 (s, 1H; ArH), 5.67 (s, 4H; CH_2–Ar), 4.90 (d, J=5.0 Hz, 2H; CH–N), 4.43–4.40 (m, 4H; CH_2–O+CH–N), 4.03 (t, J=8.8 Hz, 2H; CH_2–O), 3.86–3.83 (m, 2H; CH–N), 3.38 (dt, ^1J=14.3 Hz, ^2J=7.3 Hz, 2H; CH_2–N), 3.12 (dt, J_1=14.3 Hz, J_2=7.3 Hz, 2H; CH_2–N), 1.70 ppm (q, J=7.3 Hz, 2H; CH_2); ^{13}C NMR (175 MHz, [D_6]DMSO): δ=164.4, 155.9 (C=O), 146.4 (C), 137.7, 136.8, 134.5, 130.1, 129.2, 129.0, 128.7, 128.1, 128.0, 127.1, 126.3, 124.8 (ArC), 121.1 (=CH), 69.5 (CH_2–O), 63.0, 62.7, 58.7 (CH–N), 52.7 (CH_2–Ar), 40.6 (CH_2–N), 27.8 ppm (CH_2); IR (film): $\tilde{\nu}_{max}$=3136, 2959, 1756, 1457, 1417, 1363, 1260, 1225, 1119, 1080, 1042, 802, 756 cm^{-1}; ESIMS: m/z: 893.8 [M+H]$^+$; HRMS (ESI): m/z: calcd for $C_{51}H_{45}N_{10}O_6$ [M+H]$^+$: 893.3523; found: 893.3556.

Synthesis of (+)-26a: From bis-β-lactam (−)-**25** (50 mg, 71 μmol), bis-azide **9a** (21 mg, 71 μmol), (+)-sodium L-ascorbate (6 mg, 30 μmol), and $CuSO_4$·5H_2O (4 mg, 16 μmol) in DMF (100 mL), (+)-**26a** (25 mg, 35%) was obtained as a pale yellow crystalline solid. M.p. 195°C ($CHCl_3$+MeOH; decomp); $[\alpha]_D^{25}$=+30° (c=0.001 in CH_2Cl_2); ^{1}H NMR (300 MHz, CD_3CN): δ=8.03 (s, 2H; =CH), 7.57 (d, J=8.2 Hz, 4H; ArH), 7.32–7.24 (m, 4H; ArH), 7.22–7.14 (m, 6H; ArH), 7.07 (d, J=8.2 Hz, 4H; ArH), 5.22 (d, J=15.2 Hz, 2H; CH_2-Cp), 5.15 (d, J=15.2 Hz, 2H; CH_2-Cp), 4.98–4.89 (m, 2H; CH_2–O), 4.77–4.67 (m, 4H; CH–N), 4.25–4.15 (m, 6H; CH_2–O+CpH), 4.10 (d, J=2.3 Hz, 2H; CH–N), 4.04 (brs, 2H; CpH), 3.99 (brs, 2H; CpH), 3.04–2.83 (m, 4H; CH_2–N), 1.53 ppm (q, J=7.2 Hz, 2H; CH_2); ^{13}C NMR (175 MHz, [D_6]DMSO): δ=165.0, 156.2 (C=O), 145.7 (C), 138.2, 136.0, 130.2, 128.7, 128.5, 127.3, 127.1, 125.1 (ArC), 121.9 (=CH), 84.3 (CpC), 70.1 (CH_2–O), 68.8, 68.7, 68.6 (CpC), 67.1, 59.8, 59.7 (CH–N), 48.2 (CH_2-Cp), 38.9 (CH_2–N), 26.1 ppm (CH_2); IR (film): $\tilde{\nu}_{max}$=2925, 2854, 1754, 1496, 1457, 1418, 1109, 1081, 1042, 830, 757 cm^{-1}; FABMS: m/z: 1001.6 [M+H]$^+$; HRMS (ESI): m/z: calcd for $C_{55}H_{49}FeN_{10}O_6$ [M+H]$^+$: 1001.3185; found: 1001.3195.

Synthesis of (+)-26b: From bis-β-lactam (−)-**25** (50 mg, 71 μmol), bis-azide **9b** (13 mg, 71 μmol), (+)-sodium L-ascorbate (6 mg, 30 μmol), and $CuSO_4$·5H_2O (4 mg, 16 μmol) in DMF (100 mL), (+)-**26b** (39 mg, 62%) was obtained as a crystalline solid. M.p. 220°C ($CHCl_3$+MeOH; decomp); $[\alpha]_D^{25}$=+29° (c=0.001 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.87 (t, J=7.6 Hz, 1H; ArH), 7.78 (s, 2H; =CH), 7.53 (d, J=7.6 Hz, 2H; ArH), 7.45 (d, J=7.5 Hz, 4H; ArH), 7.15 (brs, 10H; ArH), 6.81 (d, J=7.5 Hz, 4H; ArH), 5.74 (d, J=14.4 Hz, 2H; CH_2–Ar), 5.63 (d, J=14.4 Hz, 2H; CH_2–Ar), 4.90–4.79 (m, 2H; CH–N), 4.75–4.61 (m, 4H; CH–N+CH_2–O), 4.28–4.14 (m, 2H; CH_2–O), 3.96 (brs, 2H; CH–N), 3.13–2.90 (m, 4H; CH_2–N), 1.57–1.44 ppm (m, 2H; CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=165.7, 156.6 (C=O), 153.9 (ArC), 147.1 (C), 139.0, 137.1, 135.7, 130.5, 129.3, 129.2, 126.8, 126.7, 125.8, 123.3 (ArC), 120.0 (=CH), 70.4 (CH_2–O), 68.1, 61.1, 60.8 (CH–N), 55.0 (CH_2–Ar), 39.5 (CH_2–N), 26.4 ppm (CH_2); IR (film): $\tilde{\nu}_{max}$=3451, 3010, 1756, 1674, 1597, 1458, 1417, 1224, 1045, 756 cm^{-1}; FABMS: m/z: 894.5 [M+H]$^+$; HRMS (ESI): m/z: calcd for $C_{50}H_{44}N_{11}O_6$ [M+H]$^+$: 894.3475; found: 894.3473.

Synthesis of (+)-26c: From bis-β-lactam (−)-**25** (50 mg, 71 μmol), bis-azide **9c** (13 mg, 71 μmol), (+)-sodium L-ascorbate (6 mg, 30 μmol), and $CuSO_4$·5H_2O (4 mg, 16 μmol) in DMF (100 mL), (+)-**26c** (32 mg, 50%) was obtained as a crystalline solid. M.p. 200°C ($CHCl_3$+MeOH; decomp); $[\alpha]_D^{25}$=+81° (c=0.001 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD): δ=8.32 (s, 2H; =CH), 7.60–7.38 (m, 7H; ArH), 7.36–7.12 (m, 11H; ArH), 7.06 (d, J=8.1 Hz, 4H; ArH), 5.62 (s, 4H; CH_2–Ar), 5.12–4.97 (m, 2H; CH_2–O), 4.80–4.67 (m, 4H; CH–N), 4.28–4.10 (m, 4H; CH_2–O+CH–N), 3.09 (dt, ^1J=14.1 Hz, ^2J=7.2 Hz, 2H; CH_2–N), 2.70 (dt, J_1=14.1 Hz, J_2=7.2 Hz, 2H; CH_2–N), 1.37 ppm (q, J=7.2 Hz, 2H; CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$+CD_3OD): δ=169.3, 163.0 (C=O), 154.3 (ArC), 144.5 (C), 136.1, 134.6, 133.8, 128.5, 127.3, 126.8, 126.7, 125.6, 125.2, 125.1, 123.2 (ArC), 118.8 (=CH), 68.2 (CH_2–O), 65.5, 58.0, 57.9 (CH–N), 51.1 (CH_2–Ar), 40.2 (CH_2–N), 29.4 ppm (CH_2); IR (film): $\tilde{\nu}_{max}$=3011, 2957, 1755, 1667, 1457, 1417, 1222, 1187, 1044, 754 cm^{-1}; FABMS: m/z: 893.5 [M+H]$^+$; HRMS (ESI): m/z: calcd for $C_{51}H_{44}N_{10}O_6$ [M+H]$^+$: 893.3523; found: 893.3542.

Acknowledgements

Support for this work under grants CTQ2007-67730-C02-01/BQU and CSD2007-00006 (Programa Consolider-Ingenio 2010) from the MEC (Spain) and CCG07-UCM/PPQ-2596 from the Comunidad de Madrid is gratefully acknowledged. P. Ramírez-López is a Juan de la Cierva Fellow.

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Received: September 29, 2009
Published online: December 18, 2009

