C4,C4′-Bis-β-lactam to Fused Bis-γ-lactam Rearrangement

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Optically pure *cis*,*cis*-C4,C4′-bis-β-lactams **1a**−**d** are obtained in good to excellent yields, in a single step, following two different approaches. Staüdinger reaction of (*S*)-(4-phenyl-2-oxooxazolidinyl)-acetyl chloride (**2a**) and *p*-anisyldiimine gave the corresponding bis-β-lactam **1a** as a single enantiomer. The reaction of glyoxal diimine derived from (*S*)-α-phenylethylamine and different alkoxy-substituted acid chlorides gave diastereomeric mixtures of *cis*,*cis*-bis-β-lactams **1b**−**d**, enantiomers at the bicyclic skeleton. The configuration of all compounds has been determined by X-ray diffraction analysis of enantiomerically pure aldehyde **4a** and bis-β-lactam **1b**-α. The remaining bicyclic lactams have been chemically correlated to compound **1b**-α and their configurations assigned. Starting from enantiomerically pure 4-formyl-2-azetidinone **4b**, sequential imine formation and ketene cycloaddition allowed the synthesis of differently substituted, optically pure *cis*,*cis*-C4,C4′-bis-β-lactams **1f**−**i** in good overall yields. C4,C4′-Bis-β-lactams smoothly rearranged to fused *trans*,*trans*-bis-γ-lactams **7** upon basic treatment (NaOMe/MeOH) in a totally stereoselective process. The presence of alkyl groups attached to the lactam nitrogen inhibits the rearrangement. Differently substituted (aryl and alkyl substituents in either rings) bicyclic β-lactam systems gave the selective opening of the ring with the aromatic substituent attached to the lactam nitrogen. Monocyclic 2-azetidinones **8** with an amino ester side chain at C4 are then obtained. The synthesis of *trans*,*cis*-C4,C4′-bis-β-lactam **1j** and *trans*,*trans*-C4,C4′-bis-β-lactam **1l** has also been effected in the racemic form. Compound **1j** with a *trans*,*cis* stereochemistry rearranged to *cis*,*trans*-bis-γ-lactam **7d** in the presence of base while the *trans*,*trans*-bicycle **1l** gave monocyclic 2-azetidinone **8c** with an amino ester side chain. Finally, *trans*,*trans*-bis-γ-lactam **1l** can be synthesized in a single step from glyoxal diimine **3a** employing an excess of lithium isovalerate. A reaction pathway to account for all the observed data is proposed.

Introduction

The use of 2-azetidinones as starting materials in organic synthesis is based on the impressive variety of transformations which can be derived from this system.[1] The application of β-lactams in stereoselective synthesis may be divided into two groups, namely, those processes based on transformation of the 2-azetidinone by external reagents and those based on rearrangements of the 2-azetidinone ring. The first type of reactivity is exemplified by the "β-lactam synthon method" developed by Ojima and others[2] and has become an exceptionally efficient entry to enantiomerically pure nonproteinogenic amino acids and peptides.[3] The second group of reactions is based on the building of a four-membered ring with the needed functionality to produce different types of, usually cyclic, compounds by selective bond breakage and rearrangement.[4] Thus, compounds such as alkaloids,[5] carbohydrates,[6] or different kinds of heterocycles[7] have been produced from β-lactams. Ojima has reported the preparation of enantiomerically pure C3,N1-bis-β-lactams and their transformation to tripeptides with nearly total selectivity.[8]

In our ongoing project directed to the development of new methodologies based on novel fragmentations and rearrangements of the 2-azetidinone ring,[9] we recently reported our preliminary results on the previously unknown C4,C4′-bis-β-lactam to fused bis-γ-lactam transformation.[10] This process is a simple and highly efficient

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(1) See, for example: Ojima, I. *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH Publishers: New York, 1993; pp 197.

(2) See, for example: Ojima, I. *Adv. Asym. Synth.* **1995**, *1*, 95.

(3) Some recent references: (a) Ojima, I.; Ng, E. W.; Sun, C. M. *Tetrahedron Lett.* **1995**, *36*, 4547. (b) Palomo, C.; Aizpurua, J. M.; Urchegui, R.; García, J, M. *J. Chem. Soc., Chem. Commun.* **1995**, 2327. (c) Abouabdellah, A.; Welch, J. T. *Tetrahedron: Asymmetry* **1994**, *5*, 1005. (d) Palomo, C.; Aizpurua, J. M.; Gamboa, I.; Maneiro, E.; Odriozola, B. *J. Chem. Soc., Chem. Commun.* **1994**, 1505. (e) Palomo, C.; Aizpurua, J. M.; Gamboa, I.; Carreux, F.; Cuevas, C.; Maneiro, E.; Ontoria, J. M. *J. Org. Chem.* **1994**, *59*, 3123.

(4) For a review, see: Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755.

(5) Some examples: (a) Parsons, P. J.; Camp, N. P.; Underwood, J. M.; Harvey, D. M. *J. Chem. Soc., Chem. Commun.* **1995**, 1461. (b) Wasserman, H. H.; Matsuyama, H. *J. Am. Chem. Soc.* **1981**, *103*, 461.

(6) (a) Banik, B.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1994**, *59*, 4714. (b) Manhas, M. S.; Hedge, V. R.; Wagle, D. R.; Bose, A. K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2045 and references therein.

(7) Some selected references: (a) Thomas, E. J.; Williams, A. S. *J. Chem. Soc, Perkin Trans. 1* **1995**, 351. (b) Baldwin, J. E.; Adlington, R. M.; Gollins, D. W. *Tetrahedron* **1995**, *51*, 5169. (c) Van Hove, F.; Vanwetswinkel, S.; Marchand-Brynaert, J.; Fastrez, J. *Tetrahedron Lett.* **1995**, *36*, 9313. (d) Baldwin, J. E.; Adlington, R. M.; Elend, A. S.; Smith, M. L. *Tetrahedron* **1995**, *51*, 11581. (e) Li, X.; Niu, C.; Miller, M. J. *Tetrahedron Lett.* **1995**, *36*, 1617.

(8) (a) Hatanaka, N.; Ojima, I. *J. Chem. Soc., Chem. Commun.* **1981**, 344. (b) Ojima, I.; Nakahashi, K.; Brandstadter, S. M.; Hatanaka, N. *J. Am. Chem. Soc.* **1987**, *109*, 1798. (c) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K.;Yamashita, M.; Abe, R. *J. Org. Chem.* **1991**, *56*, 5263.

(9) (a) Alcaide, B.; Pérez-Castells, J.; Polanco, C.; Sierra, M. A. *J. Org. Chem.* **1995**, *60*, 6012. (b) Alcaide, B.; Martín-Cantalejo, Y.; Rodríguez-López, J.; Sierra, M. A. *J. Org. Chem.* **1993**, *58*, 4767.

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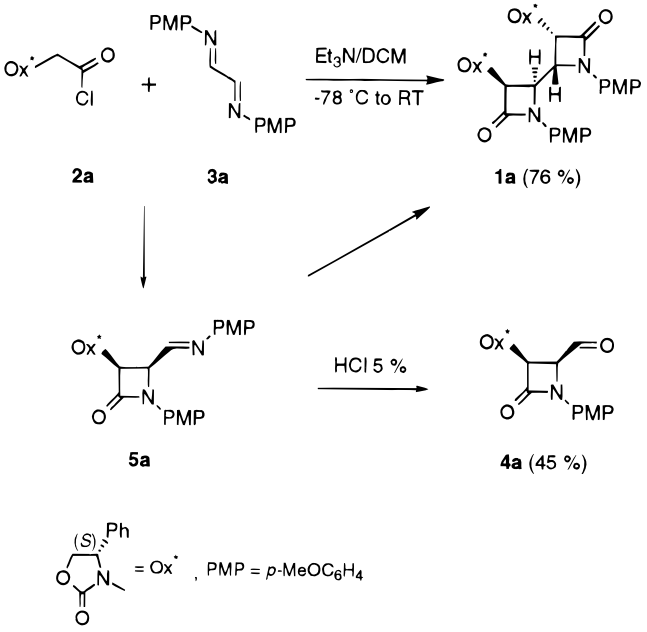
Scheme 1



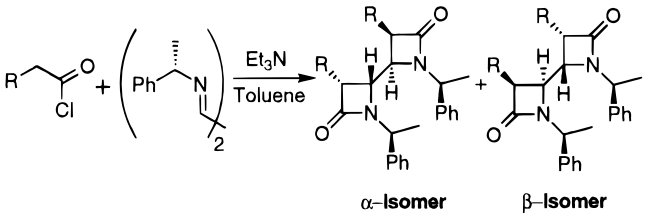
entry to the pyrrolo[3,2-*b*]pyrrole system (bis-γ-lactam or 2,6-diazabicyclo[3.3.0]octane). In fact, synthetic approaches to these compounds are scarce. To date only two other approaches to these systems have been reported.[11] The interest in this bicyclic heterocycle resides in its cage-shaped structure which makes these compounds emerging receptors to, for example, metal cations.[11a] In this paper we report the synthesis of enantiomerically pure C4,C4′-bis-β-lactams and their stereospecific rearrangement to bis-γ-lactam products. The stereochemical requisites of this rearrangement will also be discussed.

Results and Discussion

The starting C4,C4′-bis-β-lactam systems **1** were prepared in optically pure form following two different routes. The first approach allows the synthesis of the bicyclic systems in a single step. Thus, cycloaddition of the acid chloride derived from Evans oxazolidinone, **2a**, and glyoxal diimine **3a** gave C4,C4′-bis-β-lactam **1a** as a single diastereomer (Scheme 1). Alternatively, chiral diimine **3b** derived from (*S*)-α-phenylethylamine and α-alkoxy-substituted acid chlorides **2b**−**d** gave compounds **1b**−**d** as diastereomeric mixtures which are enantiomers at the bicyclic system (Scheme 2). These diastereomeric mixtures were easily separated by flash chromatography.

To assign the absolute stereochemistry of compound **1a**, 2-azetidinone aldehyde **4a** was prepared in 40% yield from diimine **3a** and acid chloride **2a**. The structure and stereochemistry of the 2-azetidinone nucleus of aldehyde **4a** was resolved by X-ray difraction as 3*S*,4*S*.[24] Aldehyde **4a** is formed by *in situ* hydrolysis of 4-imino-2-azetidinone **5a**, which is an intermediate[10] in the formation of **1a**. Therefore, the stereochemistry of **1a** was assigned as 3*S*,4*R*,4′*R*,3′*S* from the stereochemical model accepted

Scheme 2



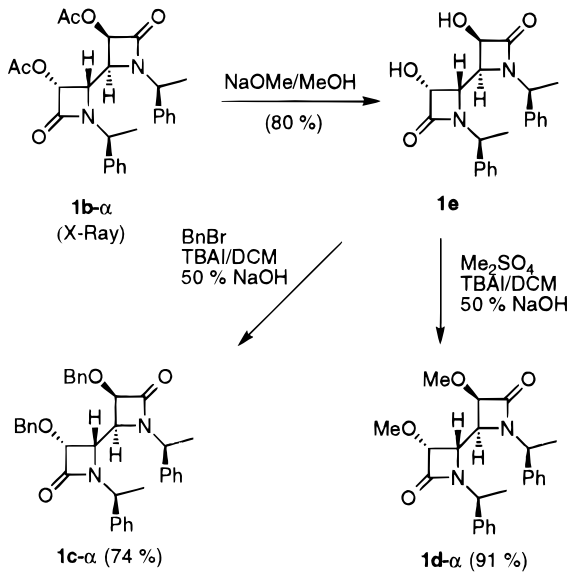
2b R = AcO **3b**
2c R = BnO
2d R = MeO

Yield α/β (%)*
1b R = AcO (35 / 30)
1c R = BnO (33 / 29)
1d R = MeO (40 / 36)

* In pure, isolated isomer

for the Staüdinger reaction.[12] Configuration of compounds **1b** was assigned by X-ray difraction analysis of the α-isomer.[24] This analysis resulted in a 3*R*,4*S*,4′*S*,3′*R* configuration in the ring stereocenters for this isomer, and hence, the configuration for the β-isomer was 3*S*,4*R*,4′*R*,3′*S*. Assignment of the stereochemistry of compounds **1c**,**d** was done by chemical correlation with compounds **1b**. Hydrolysis of the acetate group in **1b**-α (NaOMe/MeOH) yields dihydroxy-2-azetidinone **1e**, which was used as the pivotal compound for the correlation. Treatment of **1e** with benzyl bromide in the presence of base and under phase transfer conditions using tetrabutylammonium iodide (TBAI)[13] gave a compound which was physically and spectroscopically, including its $[\alpha]_D$, indistinguishable from **1c**-α. Analogously, when **1e** was methylated (Me_2SO_4) the compound formed was identical to **1d**-α (Scheme 3).

Scheme 3



The second approach to enantiomerically pure C4,C4′-bis-β-lactams was developed through a stepwise sequence from 2-azetidinone aldehyde **4b**. This compound was prepared from optically pure 2-azetidinone **6**, obtained as a single *cis* enantiomer by cycloaddition of (benzyloxy)-acetyl chloride and D-glyceraldehyde acetonide *p*-anisylimine.[14] Condensation of aldehyde **4b** with *p*-anisidine or benzylamine yields imino β-lactams **5b**,**c**. Cycloaddi-

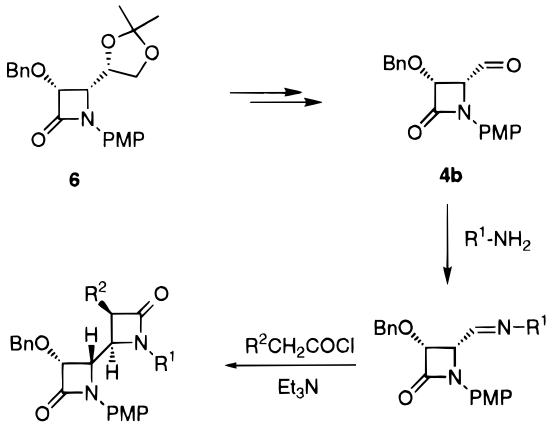
(10) Alcaide, B.; Martín-Cantalejo, Y.; Pérez-Castells, J.; Rodríguez-López, J.; Sierra, M. A.; Monge, A.; Pérez-García, V. *J. Org. Chem.* **1992**, *57*, 5921.

(11) (a) Lin, G.-q.; Shi, Z.-c. *Tetrahedron Lett.* **1995**, *36*, 9537. (b) Klaus, R.; Wolfhard, E.; Wolfgang, E.; Guenter, T.; Gerhard, M.; Heri, D.; Norbert, M. Ger. Offen. DE 3930266; *Chem. Abstr.* **1991**, *115*, 71659a.

(12) (a) Cossio, F. P.; Arrieta, A.; Lecea, B.; Ugalde, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 2085. The chiral outcome of the model proposed has been applied succesfully to our systems in this paper. (b) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *116*, 5784.

(13) Merz, A. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 846.

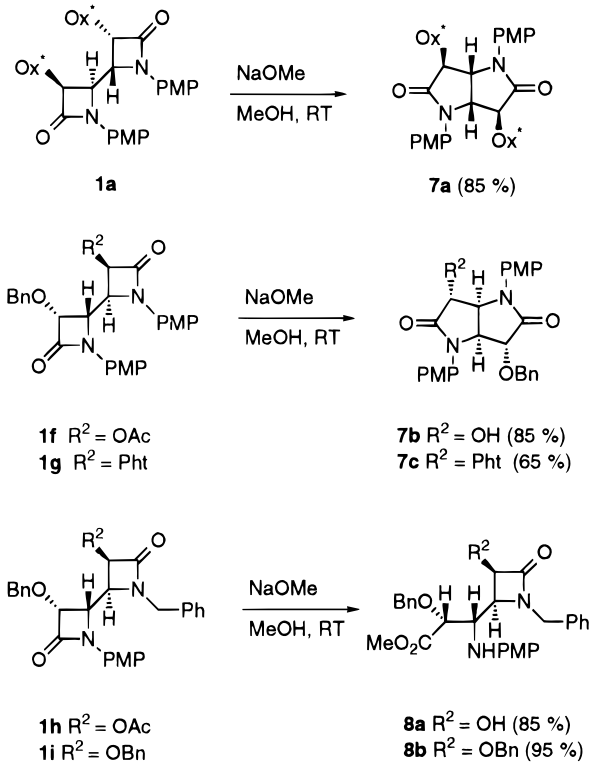
Scheme 4



tion with a new acid chloride yields the C3,C3′-differently substituted compounds **1f**−**i**. A single diastereomer of the bis-β-lactam was obtained in all cases (Scheme 4).[15] Configuration of compounds **1f**−**i** was again derived from the stereochemical model accepted for the Staüdinger reaction.[12]

With enantiopure C4,C4′-bis-β-lactams **1a**−**i** in hand, their rearrangement to bis-γ-lactams was studied next. It soon became evident that the group attached to the lactam nitrogen plays a crucial role in this reaction. Thus, compounds **1a**, **1f**, and **1g** rearranged smoothly to *trans*,*trans*-bis-γ-lactams **7a**−**c**[16] in high yields and with total retention of the starting stereochemistry by treatment with NaOMe/MeOH. However, compounds **1h**,**i** having a benzyl group at the N1 nitrogen gave monocyclic 2-azetidinones **8a**,**b** again as single enantiomers (Scheme 5). Furthermore, both diastereomers of C4,C4′-bis-β-lactams **1b**,**d** were unreactive. The sole product different from starting material was compound **1e**, formed by hydrolysis of the ester groups on **1b**. Clearly, the lability of the amide bond, which is dependent on the group attached to it,[17] is decreased by alkyl groups, and the rearrangement to compounds **7** is inhibited. Furthermore, cleavage of both rings is needed for the rearrangement to occur (see below). The influence of the groups attached to C3,C3′ is, however, less crucial.

Scheme 5



The second aspect studied was the influence of the stereochemistry of the C4,C4′-bis-β-lactam systems in their rearrangement to bis-γ-lactams. Previously compounds **1** have always had a *cis* stereochemistry in both rings. Racemic *trans*-4-imino 2-azetidinone **5d** was prepared together with its *cis* isomer **5e** by condensation of the lithium enolate derived from ethyl isovalerate and glyoxal diimine **3a** (diimine/enolate 1:2)[18] following our reported method (Scheme 6).[19] The second ring was then built from pure **5d** by cycloaddition with (benzyloxy)-acetyl chloride to form *trans*,*cis*-C4,C4′-bis-β-lactam **1j**. The relative stereochemistry of both rings was deduced immediately from the H3H4 and H3′H4′ coupling constants ($J_1 = 2.1$ Hz, $J_2 = 6.0$ Hz) as *trans*,*cis*. Standard treatment of **1j** with NaOMe/MeOH yielded a bicyclic compound with bis-γ-lactam structure **7d** having a *trans*, *cis* stereochemistry. To exclude the possibility of isomerization during the rearrangement process, *cis*,*cis*-C4,C4′-bis-β-lactam **1k** was prepared from *cis*-4-imino 2-azetidinone **5e** and (benzyloxy)acetyl chloride. Reaction of compound **5e** with NaOMe/MeOH yielded the corresponding bis-γ-lactam **7e** which was spectroscopically and physically different from **7d** (Scheme 7). Clearly, the bis-γ-lactam **7d** has a relative *trans*,*cis* stereochemistry, while **7e** is a *trans*,*trans* system. The rearrangement is thus stereoespecific and tolerates both *trans*,*trans* and *trans*,*cis* stereochemistry in the rearranged product.

An enlightening result was obtained when the reaction between the lithium enolate derived from ethyl isovalerate and glyoxal diimine **3a** was carried out in a great excess of enolate (Scheme 6). In these conditions two reaction products were isolated in variable proportion (ranging from 15:85 to the exclusive formation of compound **7f**). The minor product was identified as the

(14) The stereochemical outcome of β-lactams derived from D-glyceraldehyde acetonide has been determined both experimental and theoretically. For the experimental approach, see: (a) Hubschwerelen, C.; Schmid, G. *Helv. Chim. Acta* **1983**, *66*, 2206. (b) Welch, J. T.; Araki, K.; Kawecki, R.; Wichtowski, J. A. *J. Org. Chem.* **1993**, *58*, 2454. (c) Wagle, D. R.; Garai, C.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hedge, V. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1988**, *53*, 4227 and references therein. For the theoretical approach see, ref 12a.

(15) This sequential approach was initially reported by Bose to prepare racemic C4,C4′-bis-β-lactams starting from racemic aldehydes analogous to **4** . However, the overall yields reported in Bose's work are very low. See: Bose, A. K.; Womelsdorf, J. F.; Krishnan, L.; Urbanczyk-Lipkowska, Z.; Shelly, D. C.; Manhas, M. *Tetrahedron* **1991**, *47*, 5379.

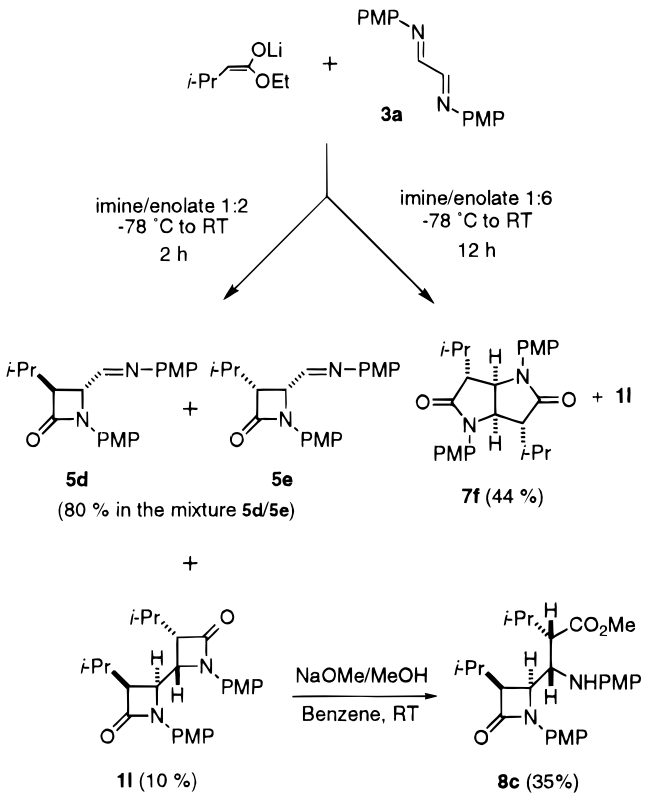
(16) In this work *trans*,*trans* and *trans*,*cis* notation in γ-lactams will refer to the relative orientation of the hydrogens attached to positions C1−C8 and C4−C5, with the hydrogens of the fusion (C1−C5) always having a *cis* orientation.

(17) This influence of the group attached to the lactam nitrogen on the reactivity of the four-membered ring is well-known in β-lactam chemistry. Thus, groups inhibitors of the amide resonance render the 2-azetidinone prone to ring opening and make the carbonyl group proclive to nucleophile addition. See, among others: (a) Baldwin, J. E.; Edwards, J. E.; Farthing, C. N.; Russell, A. T. *Synlett* **1993**, 49. (b) Kawamura, Y.; Sanemitsu, Y. *J. Org. Chem.* **1993**, *58*, 414.

(18) In these reaction conditions a 10% of *trans*,*trans*-C4,C4′-bis-β-lactam **1l** was obtained. See Experimental Section.

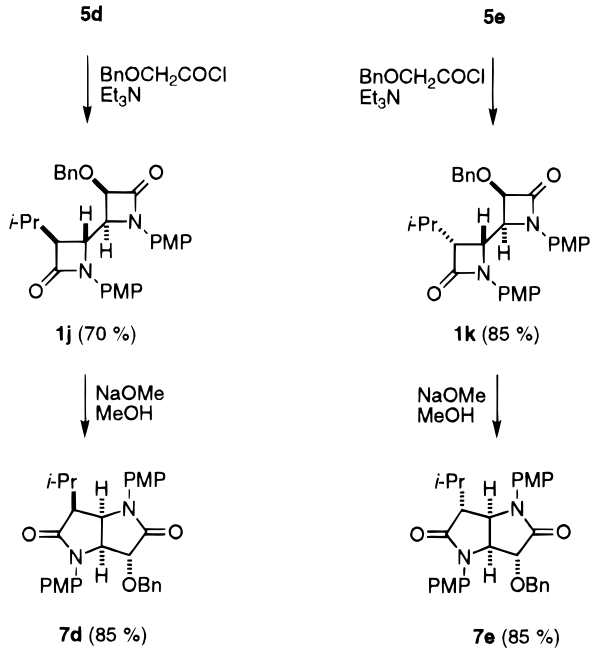
(19) Alcaide, B; Esteban, G.; Martín-Cantalejo, Y.; Plumet, J.; Rodríguez-López, J.; Monge, A.; Pérez-García, V. *J. Org. Chem.* **1994**, *59*, 7994.

Scheme 6

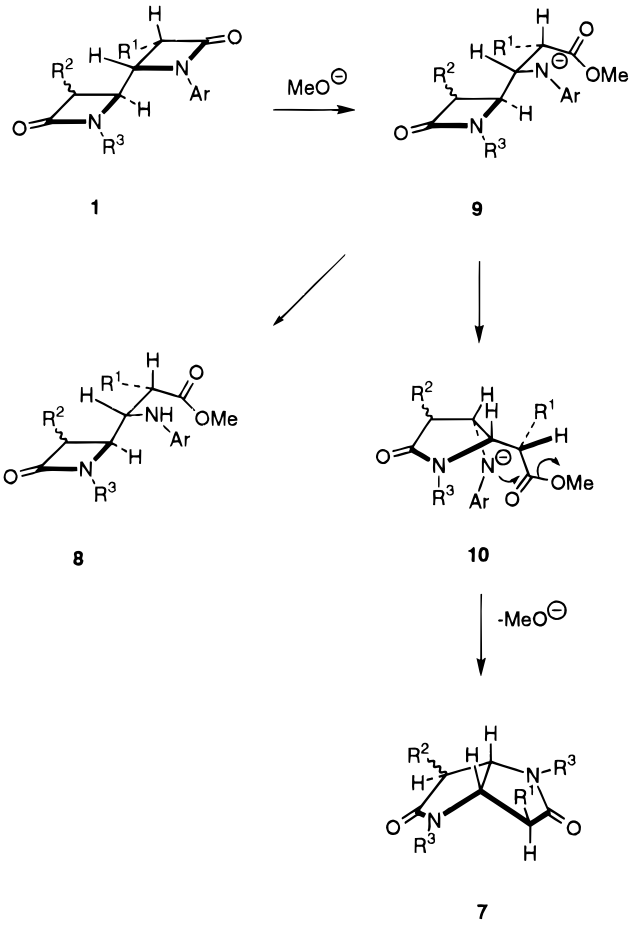


trans,trans-bis-β-lactam **1l** while the major product showed the spectroscopic data characteristic for bis-γ-lactam **7f**. The coupling constants for the last compound were in good agreement with a stereochemistry analogous to compounds **7a**−**c**. X-ray analysis of a single crystal of compound **7f** showed that the compound has in fact the configuration of *trans,trans*-bis-γ-lactam (Scheme 6).[24] However, standard base treatment of **1l** resulted in the recovery of unreacted material. To exclude the insolubility of compound **1l** in the reaction medium as responsible for its inertness, benzene was used as cosolvent to obtain an homogeneous solution. After 6 days a new product was formed in 30% yield, recovering the remaining unreacted starting material. The structure of monolactam **8c** was assigned to this new compound (Scheme 6). It is clear that placing two bulky groups in the concave face of the bis-γ-lactam system is not favored, hence the inability to obtain these systems with a *cis,cis* stereochemistry. Furthermore, compound **7f** must be formed from a different precursor than **1k**. As discussed above, the reaction of imine **3a** and lithium isovalerate yields in standard conditions a mixture of *trans*-4-imino 2-azetidinone **5d** and *cis*-4-imino 2-azetidinone **5e**. It could be thought that 2-azetidinone **5e** is the immediate precursor of **7f** while the bis-β-lactam **1k** is formed from the *trans* isomer **5d**. However, both **5d** and **5e** gave extensive decomposition to a complex mixture of uncharacterized products upon treatment with an excess of enolate.

Scheme 7

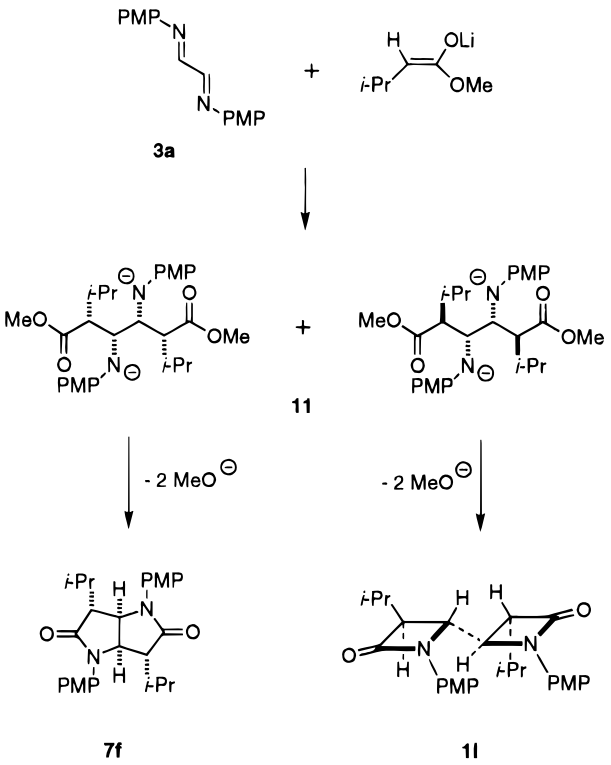


Scheme 8



The results above suggest that there are two different reaction pathways for the formation of bis-γ-lactams. Ring opening of bis-β-lactams **1** by MeO^- would form the monocyclic 2-azetidinone anion **9**. Intermediate **9** would then either cyclize to the final products **7** by intramolecular ring opening to monocyclic γ-lactams **10** followed by ring closure to **7** or end up as monolactams **8**. This is the case when alkyl groups are attached to one of the lactam nitrogens in the starting material (Scheme 8). An alternative path to γ-lactams **7** would be the double addition of a lithium enolate to the glyoxal diimine to yield the open-chain diamino acid dianion isomers **11**. Dianions **11** would evolve to final bicycles by intramolecular double aminolysis. This is the case for the formation of compound **7f**. If the stereochemistry of intermediate **11** is *anti,syn,anti*, the intramolecular aminolysis would render *trans,trans*-C4,C4′-bis-β-lactams

Scheme 9



(Scheme 9). Aromatic groups decreasing the amide resonance in the β-lactam ring are needed for intermediate **9** to be produced. Only C4,C4′-bis-β-lactams having *cis*,*cis* stereochemistry or *trans*,*cis* stereochemistry show a bias for this rearrangement. Placing two bulky groups on the concave face of the bis-γ-lactam molecule (the stereochemistry resulting from the rearrangement of a *trans*,*trans*-C4,C4′-bis-β-lactam) seems unfeasible.

In conclusion, the structural and stereochemical requisites for the C4,C4′-bis-β-lactam to fused bis-γ-lactam rearrangement have been studied. Routes to prepare enantiomerically pure C4,C4′-bis-β-lactams and fused bis-γ-lactam have been developed. Additionally, the preparation of bis-γ-lactams from the direct condensation of lithium enolates and glyoxal diimines is reported.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were recorded, except when otherwise stated, in $CDCl_3$. Specific rotation $[\alpha]_D$ is given in deg per dm at the specified temperature, and the concentration (*c*) is expressed in g per 100 mL in $CHCl_3$ unless otherwise stated. Elemental analyses were obtained from the UCM Microanalysis Service (Facultad de Farmacia, UCM, Madrid). All solvents used in this work were purified by distillation. Tetrahydrofuran (THF) and ethyl ether (Et_2O) were distilled from Na−benzophenone. Toluene, CH_2Cl_2 (DCM), and Et_3N were distilled from CaH_2. Flame-dried glassware and standard Schlenck techniques were used for moisture sensitive reactions. For purification of crude reaction mixtures by flash chromatography, Merck silica gel (230−400 Mesh) was used as the stationary phase. Identification of products was made by TLC (Kiesegel 60F-254). UV light (λ = 254 nm), and a vanillin solution in sulfuric acid and 95% EtOH (1 g of vanillin, 5 mL of H_2SO_4, 150 mL of EtOH) was used to develop the plates.

All commercially available compounds were used without further purification. The following chemicals were prepared according to literature procedures: *N*,*N*′-di-*p*-anisylethylenediimine,[20] *N*,*N*′-di-(*S*)-α-phenylethylethylenediimine,[21] phthalimidoacetyl chloride,[22] (3*R*,4*S*)-*cis*-1-(*p*-anisyl)-3-(benzyloxy)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-azetidinone.[14c]

Synthesis of (+)-(3*S*,4*R*,4′*R*,3′*S*)-1,1′-di-(*p*-anisyl)-3,3′-bis[(*S*)-4-phenyl-2-oxooxazolidin-3-yl)]-4,4′-bi-2-azetidinone (1a). A solution of Et_3N (0.7 mL, 5 mmol) in DCM (5 mL) was added dropwise to a solution of (*S*)-(4-phenyl-2-oxooxazolidinyl)acetyl chloride (0.71 g, 3 mmol) in DCM (10 mL) at −78 °C under argon. The mixture was stirred for 10 min, and a solution of *N*,*N*′-di-*p*-anisylethylenediimine (0.27 g, 1 mmol) in DCM (5 mL) was added. The reaction was allowed to reach room temperature and was stirred for 12 h. Then, MeOH (1 mL) and DCM (20 mL) were added succesively. The mixture was washed with water and brine. The organic layer was dried ($MgSO_4$) and the solvent eliminated under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexanes 4:1) to obtain 0.51 g (76%) of pure compound **1a** as a white crystalline solid. Mp: 204−206 °C (EtOAc/hexanes). $[\alpha]_D$: +24.76 (*c* 1.68). ^{1}H NMR (DMSO-d_6, 150 °C): δ 3.55 (s, 6H), 4.29 (dd, 2H, J_1 = 5.1 Hz, J_2 = 8.7 Hz), 4.43 (s (b), 2H), 4.84 (t, 2H, J = 8.7 Hz), 4.86 (d, 2H, J = 5.1 Hz), 5.20 (dd, 2H, J_1 = 5.1 Hz, J_2 = 8.7 Hz), 6.40 (d, 4H, J = 9.0 Hz), 6,71 (d, 4H, J = 9.0 Hz), 7.33−7.43 (m, 6H), 7.56 (d, 4H, J = 7.3 Hz). ^{13}C NMR: δ 161.3, 159.2, 155.3, 138.2, 130.0, 129.3, 127.8, 119.3, 119.0, 113.2, 71.1, 68.7, 62.1, 59.7, 55.1. IR ($CHCl_3$): ν 1770, 1740. Anal. Calcd for $C_{38}H_{34}N_4O_8$: C, 67.63; H, 5.08; N, 8.31. Found: C, 67.51; H, 5.12; N, 8.27.

General Procedures for the Synthesis of C4,C4′-bi-2-azetidinones 1b−d,f−k. Method A. A solution of acid chloride **2** (2 mmol) in anhydrous toluene (5 mL) was added dropwise via syringe to a suspension of the corresponding diimine **3** (1 mmol) in toluene (10 mL) containing Et_3N (3 mmol) at room temperature under argon. The mixture was stirred until complete disappearance of starting diimine (TLC). The reaction mixture was diluted with $CHCl_3$ and succesively washed with aqueous $NaHCO_3$ (saturated solution), water, and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, residues were purified by crystallization (EtOAc or mixtures EtOAc/hexanes) or by flash chromatography (hexanes/EtOAc mixtures) to yield analytically pure compounds. When the reaction yielded diastereomeric mixtures, chromatographic separation allowed the isolation of pure diastereomers.

Method B. Acid chloride **2** (2 mmol) in anhydrous toluene (5 mL) were added dropwise via syringe to a solution of 4-imino 2-azetidinone **5** (1 mmol) in toluene (10 mL) containing Et_3N (3 mmol) at room temperature under argon. The resulting mixture was stirred until complete disappearance of the starting material **5** (TLC). Then, the crude reaction mixture was diluted with $CHCl_3$ and washed with aqueous $NaHCO_3$ (saturated solution), water, and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, residues were purified by crystallization (EtOAc/hexanes mixtures) to yield analytically pure compounds **1**.

3,3′-Diacetoxy-1,1′-bis[(*S*)-α-phenylethyl)]-4,4′-bi-2-azetidinones 1b. Method A. Reaction time: 2 h. Compound **1b** was obtained as a 1:1 mixture of diastereomers. **(+)-(3*R*,4*S*,4′*S*,3′*R*)-3,3′-Diacetoxy-1,1′-bis[(*S*)-α-phenylethyl)]-4,4′-bi-2-azetidinone (1b−α).** Yield: 0.16 g (35%). White crystalline solid. Mp: 138−140 °C (EtOAc/hexanes). $[\alpha]_D$: +123.8 (*c* 0.1). ^{1}H NMR: δ 1.67 (s, 6H), 1.93 (d, 6H, J = 7.2 Hz), 3.74 (d, 2H, J = 4.8 Hz), 4.47 (q, 2H, J = 7.2 Hz), 5.82 (d, 2H, J = 4.8 Hz) 7.23−7.33 (m, 10H). ^{13}C NMR: δ 169.2, 165.4, 141.2, 129.0, 127.8, 125.8, 73.7, 57.6, 54.7, 22.1, 19.8. IR ($CHCl_3$): ν 1770, 1750. Anal. Calcd for $C_{26}H_{28}N_2O_6$: C, 67.24; H, 6.03; N, 6.03. Found: C, 67.36; H, 5.97; N, 6.09. **(+)-(3*S*,4*R*,4′*R*,3′*S*)-3,3′-Diacetoxy-1,1′-bis[(*S*)-α-phenylethyl)]-4,4′-bi-2-azetidinone (1b−*β*).** Yield: 0.14 g (30%). White crystalline solid. Mp: 178−180 °C (EtOAc/hexane). $[\alpha]_D$: +104.6 (*c* 0.2). ^{1}H NMR (DMSO-d_6, 150 °C): δ 1.43 (d, 6H, J = 7.2 Hz), 2.01 (s, 6H), 4.14 (d, 2H, J = 3.3 Hz), 4.33 (q, 2H,

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(21) tom Dieck, H.; Dietrich, J. *Chem. Ber.* **1984**, *117*, 694.
(22) Balenovic, K. *J. Org. Chem.* **1951**, *16*, 1308.

J = 7.2 Hz), 5.88 (d, 2H, J = 3.3 Hz), 7.22−7.30 (m, 10H). ^{13}C NMR (DMSO-d_6, 100 °C): δ 168.3, 164.3, 140.1, 128.0, 126.9, 126.1, 73.3, 56.8, 53.7, 19.6, 18.8. IR ($CHCl_3$): ν 1765, 1750. Anal. Calcd for $C_{26}H_{28}N_2O_6$: C, 67.24; H, 6.03; N, 6.03. Found: C, 67.28; H, 6.00; N, 6.07.

3,3′-Bis(benzyloxy)-1,1′-bis[(*S*)-α-phenylethyl)]-4,4′-bi-2-azetidinones 1c. Method A. Reaction time: 3 h. Compound **1c** was obtained as a 1.1:1 mixture of diastereomers. **(+)-(3*R*,4*S*,4′*S*,3′*R*)-3,3′-bis(benzyloxy)-1,1′-bis[(*S*)-α-phenylethyl)]-4,4′-bi-2-azetidinone (1c−α).** Yield: 0.18 g (33%). Yellow oil. $[\alpha]_D$: +2.4 (*c* 2.0). ^{1}H NMR: δ 1.91 (d, 6H, J = 7.2 Hz), 3.60 (d, 2H, J = 5.1 Hz), 4.47−4.49 (m, 4H), 4.54 (d, 2H, J = 11.7 Hz), 4.76 (d, 2H, J = 11.7 Hz), 7.11−7.29 (m, 20H). ^{13}C NMR: δ 168.5, 142.5, 136.4, 128.6, 128.5, 128.4, 128.2, 127.2, 126.5, 80.3, 73.6, 56.6, 55.5, 21.4. IR ($CHCl_3$): ν 1740, 1500, 1450, 1400. Anal. Calcd for $C_{36}H_{36}N_2O_4$: C, 77.14; H, 6.48; N, 4.00. Found: C, 77.26; H, 6.51; N, 4.07. **(+)-(3*S*,4*R*,4′*R*,3′*S*)-3,3′-bis(benzyloxy)-1,1′-bis[(*S*)-α-phenylethyl)]-4,4′-bi-2-azetidinone (1c−β).** Yield: 0.16 g (29%). Yellow oil. $[\alpha]_D$: +0.3 (*c* 3.4). ^{1}H NMR: δ 1.35 (d, 6H, J = 7.2 Hz), 3.91 (d, 2H, J = 5.1 Hz), 4.52 (q, 2H, J = 7.2 Hz), 4.55 (d, 2H, J = 5.1 Hz), 4.63 (d, 2H, J = 11.7 Hz), 4.88 (d, 2H, J = 11.7 Hz), 7.21−7.34 (m, 20H). ^{13}C NMR: δ 168.3, 140.2, 136.6, 128.6, 128.5, 128.4, 128.3, 127.4, 127.3, 80.7, 73.3, 56.5, 53.5, 18.4. IR ($CHCl_3$): ν 1745. Anal. Calcd for $C_{36}H_{36}N_2O_4$: C, 77.14; H, 6.48; N, 4.00. Found: C, 77.19; H, 6.44; N, 4.03.

3,3′-Dimethoxy-1,1′-bis[(*S*)-α-phenylethyl)]-4,4′-2-azetidinones 1d. Method A. Reaction time: 3 h. Compound **1d** was obtained as a 1.1:1 mixture of diastereomers. **(+)-(3*R*,4*S*,4′*S*,3′*R*)-3,3′-Dimethoxy-1,1′-bis[(*S*)-α-phenylethyl)]-4,4′-2-azetidinone (1d−α).** Yield: 0.16 g (40%). Yellow oil. $[\alpha]_D$: +2.4 (*c* 2.0). ^{1}H NMR: δ 1.94 (d, 6H, J = 7.2 Hz), 3.47 (s, 6H), 3.75 (d, 2H, J = 5.1 Hz), 4.38 (d, 2H, J = 5.1 Hz), 4.51 (q, 2H, J = 7.2 Hz), 7.32 (m, 10H). ^{13}C NMR: δ 168.2, 142.5, 128.5, 127.4, 126.4, 82.4, 59.1, 56.8, 55.1, 21.3. IR ($CHCl_3$): ν 1740. Anal. Calcd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86. Found: C, 70.61; H, 6.95; N, 6.84. **(+)-(3*S*,4*R*,4′*R*,3′*S*)-3,3′-Dimethoxy-1,1′-bis[(*S*)-α-phenylethyl)]-4,4′-bi-2-azetidinone (1d−β).** Yield: 0.14 g (36%). White crystalline solid. Mp: 155−156 °C. $[\alpha]_D$: +72.9 (*c* 2.51). ^{1}H NMR: δ 1.41 (d, 6H, J = 6.9 Hz), 3.52 (s, 6H), 3.88 (d, 2H, J = 4.8 Hz), 4.40 (d, 2H, J = 4.8 Hz), 4.51 (q, 2H, J = 7.2 Hz), 7.29 (m, 10H). ^{13}C NMR: δ 168.1, 140.1, 128.2, 127.3, 127.1, 82.7, 58.9, 56.6, 53.2, 18.3. IR ($CHCl_3$): ν 1740. Anal. Calcd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86. Found: C, 70.66; H, 6.94; N, 6.88.

(+)-(3*R*,4*S*,4′*S*,3′*R*)-1-(*p*-Anisyl)-4-[3-acetoxy-1-(*p*-anisyl)-2-oxoazetidin-4-yl]-3-(benzyloxy)-2-azetidinone (1f). Method B. Reaction time: 3 h. Yield: 0.39 g (80%). Colorless oil. $[\alpha]_D$: +10.74 (*c* 4.70). ^{1}H NMR: δ 2.09 (s, 3H), 3.64 (s, 6H), 4.53 (dd, 1H, J_1 = 5.4 Hz, J_2 = 8.1 Hz), 4.77−4.81 (m, 2H), 4.85 (d, 1H, J = 5.4 Hz), 4.93 (d, 1H, J = 12.0 Hz), 6.21 (d, 1H, J = 5.4 Hz), 6.47 (m, 4H), 6.95 (m, 4H), 7.39 (m, 5H). ^{13}C NMR: δ 168.6, 164.5, 162.1, 156.6, 156.5, 136.2, 129.9, 129.8, 128.8, 128.7, 128.6, 119.4, 119.3, 113.9, 113.8, 80.1, 73.9, 73.3, 56.9, 55.5, 55.4, 20.7. IR ($CHCl_3$): ν 1750, 1680. Anal. Calcd for $C_{29}H_{28}N_2O_7$: C, 67.43; H, 5.46; N, 5.42. Found: C, 67.55; H, 5.52; N, 5.49.

(+)-(3*R*,4*S*,4′*S*,3′*R*)-1-(*p*-Anisyl)-4-[1-(*p*-anisyl)-2-oxo-3-phthalimidoazetidin-4-yl]-3-(benzyloxy)-2-azetidinone (1g). Method B. Reaction time: 15 h. Yield: 80%. White solid. Mp: 130−132 °C (EtOAc). $[\alpha]_D$: +2.13 (*c* 0.77) ^{1}H NMR: δ 3.61 (s, 6H), 4.52 (d, 1H, J = 5.4 Hz), 4.69 (d, 1H, J = 11.4 Hz), 4.76 (d, 1H, J = 11.4 Hz), 4.77 (dd, 1H, J_1 = 5.4 Hz, J_2 = 9.3 Hz), 4.90 (dd, 1H, J_1 = 5.4 Hz, J_2 = 9.3 Hz), 5.76 (d, 1H, J = 5.4 Hz), 6.43 (m, 4H), 6.95−7.91 (m, 13H). ^{13}C NMR: δ 164.4, 161.5, 156.4, 156.3, 135.7, 134.7, 131.3, 129.7, 129.6, 128.8, 128.3, 128.2, 122.3, 119.6, 119.3, 113.5, 78.9, 72.7, 59.5, 56.7, 55.4, 55.2. IR (KBr): ν 1755, 1720. MS: *m/e* 546, 512, 456, 411, 335, 293, 214, 160, 134, 91 (parent). Anal. Calcd for $C_{35}H_{29}N_3O_7$: C, 69.64; H, 4.84; N, 6.96. Found: C, 69.73; H, 4.98; N, 6.81.

(+)-(3*R*,4*S*,4′*S*,3′*R*)-1-(*p*-Anisyl)-4-[3-acetoxy-1-benzyl-2-oxoazetidin-4-yl]-3-(benzyloxy)-2-azetidinone (1h). Method B. Reaction time: 3 h. Yield: 0.38 g (75%). Colorless oil. $[\alpha]_D$: +10.74 (*c* 4.70) ^{1}H NMR: δ 2.01 (s, 3H), 3.33 (d, 1H, J = 15.0 Hz), 3.80 (d, 1H, J = 15.0 Hz), 3.82 (s, 3H), 3.97 (dd, 1H, J_1 = 5.4 Hz, J_2 = 7.5 Hz), 4.45−4.51 (m, 2H), 4.63 (d, 1H, J = 12.0 Hz), 4.70 (d, 1H, J = 6.9 Hz), 4.76−4.81 (m, 2H), 5.99 (d, 1H, J = 4.8 Hz), 6.78 (m, 2H), 6.96 (d, 2H, J = 8.7 Hz), 7.23−7.35 (m, 10H). ^{13}C NMR: δ 168.4, 165.7, 164.9, 157.4, 140.7, 135.9, 134.2, 129.4, 128.8, 128.7, 128.5, 128.3, 127.6, 120.8, 114.5, 79.8, 74.3, 73.1, 57.6, 56.3, 55.5, 45.9, 20.5. IR ($CHCl_3$): ν 1755, 1680. Anal. Calcd for $C_{29}H_{28}N_2O_6$: C, 69.59; H, 5.64; N, 5.60. Found: C, 69.70; H, 5.77; N, 5.58.

(+)-(3*R*,4*S*,4′*S*,3′*R*)-1-(*p*-Anisyl)-4-[1-benzyl-3-(benzyloxy)-2-oxoazetidin-4-yl]-3-(benzyloxy)-2-azetidinone (1i). Method B. Reaction time: 3 h. Yield: 0.46 g (85%). Colorless oil. $[\alpha]_D$: +35.92 (*c* 1.35). ^{1}H NMR: δ 3.25 (d, 1H, J = 14.7 Hz), 3.78 (d, 1H, J = 14.7 Hz), 3.79 (s, 3H), 3.90 (dd, 1H, J_1 = 5.4 Hz, J_2 = 7.5 Hz), 4.61−4.69 (m, 4H), 4.80 (d, 1H, J = 5.4 Hz), 4.80 (d, 1H, J = 12.0 Hz), 4.89 (d, 1H, J = 12.0 Hz), 6.79−6.83 (m, 2H), 6.90 (d, 2H, J = 8.7 Hz), 7.18-7.39 (m, 15H). ^{13}C NMR: δ 168.2, 165.0, 157.0, 136.7, 136.5, 134.6, 130.0, 128.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 121.5, 120.2, 114.5, 81.6, 80.9, 73.2, 73.1, 57.3, 56.2, 55.4, 45.5. IR ($CHCl_3$): ν 1750. Anal. Calcd for $C_{34}H_{32}N_2O_5$: C, 74.43; H, 5.88; N, 5.11. Found: C, 74.58; H, 5.92; N, 5.19.

(3*S,4*R**,4′*S**,3′*R**)-1-(*p*-Anisyl)-4-[1-(*p*-anisyl)-3-(benzyloxy)-2-oxoazetidin-4-yl]-3-isopropyl-2-azetidinone (1j). Method B.** Reaction time: 2 h. Yield: 0.35 g (70%). White solid. Mp: 143−145 °C (EtOAc/hexanes). ^{1}H NMR: δ 0.90 (d, 3H, J = 6.6 Hz), 0.93 (d, 3H, J = 6.6 Hz), 2.00−2.15 (m, 1H), 3.22 (dd, 1H, J_1 = 2.1 Hz, J_2 = 6.0 Hz), 3.70 (s, 6H), 4.35 (dd, 1H, J_1 = 2.1 Hz, J_2 = 6.0 Hz), 4.57 (t, 1H, J = 6.0 Hz), 4.76 (d, 1H, J = 11.7 Hz), 4.83 (d, 1H, J = 11.7 Hz), 4.85 (d, 1H, J = 5.7 Hz), 6.65 (d, 2H, J = 9.0 Hz), 7.06−7.37 (m, 9H). ^{13}C NMR: δ 166.4, 164.7, 156.3, 155.9, 136.2, 130.4, 129.9, 128.4, 128.2, 128.0, 118.9, 118.7, 114.1, 114.0, 80.7, 73.5, 59.9, 57.9, 55.3, 55.2, 54.7, 27.8, 20.6, 18.8. IR (KBr): ν 1745. MS: *m/e* 500 ($M^{\bullet+}$), 351, 309, 244, 190, 149, 134, 91 (parent). Anal. Calcd for $C_{30}H_{32}N_2O_5$: C, 71.98; H, 6.44; N, 5.60. Found: C, 72.15; H, 6.55; N, 5.55.

(3*R,4*R**,4′*S**,3′*R**)-1-(*p*-Anisyl)-4-[1-(*p*-anisyl)-3-(benzyloxy)-2-oxoazetidin-4-yl]-3-isopropyl-2-azetidinone (1k). Method B.** Reaction time: 2 h. Yield: 0.42 g (85%). White solid. Mp: 151−152 °C (EtOAc/hexanes). ^{1}H NMR: δ 0.97 (d, 3H, J = 6.6 Hz), 1.25 (d, 3H, J = 6.6 Hz), 2.21 (m, 1H), 3.14 (dd, 1H, J_1 = 5.7 Hz, J_2 = 8.7 Hz), 3.57 (s, 3H), 3.58 (s, 3H), 4.53 (dd, 1H, J_1 = 5.7 Hz, J_2 = 9.0 Hz), 4.67 (dd, 1H, J_1 = 5.7 Hz, J_2 = 9.0 Hz), 4.75 (d, 1H, J = 11.4 Hz), 4.81 (d, 1H, J = 5.4 Hz), 4.99 (d, 1H, J = 11.4 Hz), 6.39−6.42 (m, 4H), 6.85−7.34 (m, 9H). ^{13}C NMR: δ 167.5, 165.0, 156.4, 156.1, 136.5, 130.6, 130.3, 128.5, 128.3, 128.2, 119.6, 119.0, 113.8, 113.7, 80.7, 73.4, 66.9, 59.2, 56.3, 55.4, 53.3, 25.7, 22.9, 21.0. IR (KBr): ν 1745. Anal. Calcd for $C_{30}H_{32}N_2O_5$: C, 71.98; H, 6.44; N, 5.60. Found: C, 71.78; H, 6.45; N, 5.70.

Synthesis of (+)-(3*R*,4*S*,4′*S*,3′*R*)-3,3′-Dihydroxy-1,1′-bis[(*S*)-α-phenyl-ethyl)]-4,4′-bi-2-azetidinone (1e). To a solution of biazetidinone **1b**-α (1.0 g, 2.1 mmol) in absolute MeOH (25 mL) was added NaOMe (0.24 g, 4.3 mmol). The mixture was stirred under argon for 2 h. Then, the excess NaOMe was hydrolyzed with water (2 drops), the solvent was partially evaporated under reduced pressure, and 10 mL of water was added. The product was extracted with EtOAc and dried ($MgSO_4$). After filtration and evaporation of the solvent, the residue was purified by crystalization (EtOAc) to yield 0.65 g (81%) of compound **1e**. White solid. Mp: 155−157 °C. $[\alpha]_D$: +62.7 (*c* 1.13, EtOH). ^{1}H NMR: δ 1.71 (d, 6H, J = 7.2 Hz), 3.67 (d, 2H, J = 4.5 Hz), 4.53 (q, 2H, J = 7.2 Hz), 4.73 (s (b), 2H), 6.37 (s (b), 2H), 7.19−7.34 (m, 10H). ^{13}C NMR: δ 169.7, 142.7, 133.7, 128.5, 126.3, 74.2, 57.2, 54.4, 20.6. IR (KBr): ν 3500, 1725. Anal. Calcd for $C_{22}H_{23}N_2O_4$: C, 69.64; H, 6.11; N, 7.38. Found: C, 69.61; H, 6.33; N, 7.48.

Synthesis of (3*S,4*R**,4′*R**,3′*S**)-1-(*p*-Anisyl)-4-[1-(*p*-anisyl)-3-isopropyl-2-oxoazetidin-4-yl]-3-isopropyl-2-azetidinone (1l) and 1-(*p*-Anisyl)-4-(*N*-(*p*-anisyl)azomethinyl)-3-isopropyl-2-azetidinones 5d,e.** Ethyl isovaleriate (1.83 mL, 17.6 mmol) was added dropwise to a solution of LDA (17.6 mmol) in THF−hexanes cooled to −78 °C. After 15 min at this temperature, a solution of diimine **3a** (1.72 g, 8 mmol) in THF (60 mL) was added, the bath was removed, and the mixture was stirred for 2 h. The reaction was quenched with H_2O and diluted with Et_2O (two or three times its original

volume). The organic layer was successively washed with H_2O, brine, and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, a mixture containing compounds **1l** and **5d**,**e** (1:6) was obtained. Separation by flash chromatography (hexanes/EtOAc) gave 2.2 g (80%) of compounds **5d**,**e** (*trans*/*cis* 75:35) and 0.35 g (10%) of pure compound **1l**. White solid. Mp: 182−184 °C. ^{1}H NMR: δ 0.73 (d, 6H, J = 6.7 Hz), 0.96 (d, 6H, J = 6.7 Hz), 1.93 (m, 2H), 2.93 (d, 2H, J = 8.1 Hz), 3.79 (s, 6H), 4.35 (s, 2H), 6.86 (d, 2H, J = 8.9 Hz), 7.29 (d, 2H, J = 8.9 Hz). ^{13}C NMR: δ 166.2, 156.2, 130.6, 118.4, 114.6, 57.6, 55.5, 54.2, 28.3, 20.6, 20.2. IR (KBr): ν 1735. MS: *m*/*e* 436, 394, 351, 309, 245, 244 (parent), 188, 134, 123, 77. Anal. Calcd for $C_{26}H_{32}N_2O_4$: C, 71.52; H, 7.39; N, 6.42. Found: C, 71.38; H, 7.26; N, 6.35.

Synthesis of (−)-(3*S*,4*S*)-1-(*p*-Anisyl)-4-formyl-3-[(*S*)-4-phenyl-2-oxooxazolidin-3-yl)]-2-azetidinone (4a). A solution of Et_3N (0.16 g, 1.5 mmol) in DCM (10 mL) was added dropwise to a solution of (*S*)-(4-phenyl-2-oxooxazolidinyl)acetyl chloride (0.17 g, 0.7 mmol) in DCM (10 mL) at −78 °C under argon. The mixture was stirred for 30 min, and a solution of *N*,*N*′-di(*p*-anisyl)ethylenediimine (0.27 g, 1 mmol) in DCM (10 mL) was added. The reaction was allowed to warm to room temperature followed by stirring for 12 h. Then, MeOH (1 mL) and DCM (20 mL) were added succesively. The mixture was washed with water and brine. The organic layer was dried ($MgSO_4$) and the solvent eliminated under reduced presure. The crude product was purified by column chromatography (EtOAc/hexanes) to obtain 0.31 g (45%) of imino β-lactam **5a** along with 5% of its *trans* diastereomer as a pale yellow oil. This mixture of 4-imino β-lactams was disolved in $CHCl_3$ (15 mL) and vigorously stirred with 5% aqueous HCl (10 mL) for 2 h. The organic layer was successively washed with water and brine and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, residues were purified by column chromatography (hexanes/EtOAc) to yield 0.15 g (44%) of pure compound **4a**. White solid. Mp: 182−184 °C (EtOAc/hexanes). $[\alpha]_D$: −65.4 (*c* 0.11). ^{1}H NMR: δ 3.77 (s, 3H), 4.19 (t, 1H, J = 9.0 Hz), 4.53 (dd, 1H, J_1= 2.4 Hz, J_2 = 6.3 Hz), 4.57 (d, 1H, J = 6.3 Hz), 4.70 (t, 1H, J = 9.0 Hz), 4.98 (t, 1H, J = 9.0 Hz), 6.86 (d, 2H, J = 9.0 Hz), 7.25 (d, 2H, J = 9.0 Hz), 7.43 (m, 5H), 9.77 (d, 1H, J = 2.4 Hz). ^{13}C NMR: δ 198.1, 160.7, 157.3, 156.8, 135.8, 130.4, 129.7, 129.5, 127.4, 117.9, 114.5, 71.3, 63.2, 61.2, 60.5, 55.5. IR ($CHCl_3$): ν 1755, 1720. Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.56; H, 4.96; N, 7.65. Found: C, 65.43; H, 5.01; N, 7.92.

Synthesis of (+)-(3*R*,4*R*)-1-(*p*-Anisyl)-4-formyl-3-(benzyloxy)-2-azetidinone (4b). To a solution of β-lactam **6** (6.5 g, 17 mmol) in 200 mL of THF−water (1:1), was added *p*-toluenesulfonic acid was added (3.55 g, 18.7 mmol), and the mixture was refluxed for 12 h. The organic solvent was removed *in vacuo*, and $NaHCO_3$ (saturated solution) was added until pH = 7. The aqueous phase was extracted with DCM (3 × 40 mL), and the organics were washed with water and brine and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the resulting oil was disolved in 180 mL of MeOH−water (5:1). Sodium periodate was added, and the mixture was stirred at room temperature for 14 h. The organic solvent was removed *in vacuo*, the aqueous phase was extracted with DCM (3 × 40 mL), and the organics were washed with water and brine and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the resulting oil was purified by flash chromatography to obtain 4.54 g (86%) of pure compound **4b**. White crystalline solid. Mp: 99−101 °C (EtOAc/hexanes) (lit.[23] mp 154−155 °C). $[\alpha]_D$: +176.6 (*c* 1, CH_2Cl_2).

Synthesis of 1-(*p*-Anisyl)-4-formyl-3-isopropyl-2-azetidinones 4c,d. A mixture of imino β-lactams **5d**,**e** (0.35 g, 1 mmol), obtained as described in the synthesis of compound **3l**, was disolved in $CHCl_3$ (15 mL) and vigorously stirred with 5% aqueous HCl (10 mL) for 2 h. The organic layer was successively washed with water and brine and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, residues were purified by column chromatography (DCM) to yield pure compounds **4c**,**d**. **(3*S**,4*R**)-1-(*p*-Anisyl)-4-formyl-3-isopropylazetidin-2-one (4c).** Yield: 0.12 g (50%). White crystalline solid. Mp: 126−128 °C (EtOAc/hexanes).^{1}H NMR: δ 0.96 (d, 3H, J = 6.6 Hz), 1.04 (d, 3H, J = 6.6 Hz), 2.0−2.2 (m, 1H), 3.34 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.0 Hz), 3.76 (s, 3H), 4.13 (dd, 1H, J_1 = 2.4 Hz, J_2 = 4.2 Hz), 6.84 (d, 2H, J = 9.3 Hz), 7.21 (d, 2H, J = 9.3 Hz), 9.64 (d, 1H, J = 4.2 Hz). ^{13}C NMR: δ 199.9, 165.1, 156.3, 131.0, 117.4, 114.4, 61.5, 60.3, 55.3, 25.7, 21.4, 20.5. IR (KBr): ν 1755, 1735. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.13; H, 6.83; N, 5.76. **(3*R**,4*R**)-1-(*p*-Anisyl)-4-formyl-3-isopropylazetidin-2-one (4d).** Yield: 0.06 g (24%). White crystalline solid. Mp: 91−93 °C (EtOAc/hexanes). ^{1}H NMR: δ 0.94 (d, 3H, J = 6.6 Hz), 1.19 (d, 3H, J = 6.6 Hz), 2.0−2.2 (m, 1H), 3.34 (dd, 1H, J_1 = 6.0 Hz, J_2 = 8.0 Hz), 3.76 (s, 3H), 4.43 (dd, 1H, J_1 = 4.2 Hz, J_2 = 6.0 Hz), 6.84 (d, 2H, J = 9.3 Hz), 7.21 (d, 2H, J = 9.3 Hz), 9.88 (d, 1H, J = 4.2 Hz). ^{13}C NMR: δ 199.9, 165.1, 156.3, 131.0, 117.4, 114.4, 61.5, 60.3, 55.3 , 25.7, 21.4, 20.5. IR (KBr): ν 1755, 1735 . MS: *m*/*e* 247 ($M^{\bullet+}$), 218, 190, 163, 149, 134 (parent), 107, 92, 77. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.05; H, 6.98; N, 5.53.

General Procedure for the Synthesis of Compounds 5. A suspension of 4-formyl-β-lactam **4** (1 mmol), the appropriate amine (1 mmol), and $MgSO_4$ (1 mmol) in DCM (10 mL) was stirred at room temperature overnight. Then, the mixture was filtered, the solvent was removed *in vacuo*, and the resulting imino β-lactams **5** were used as such (oils) or recrystallized (solids, EtOAc/hexanes).

(+)-(3*S*,4*R*)-1-(*p*-Anisyl)-4-(*N*-(*p*-anisyl)azomethinyl)-3-[(*S*)-4-phenyl-2-oxooxazolidin-3-yl)]-2-azetidinone (5a). Yield 0.45 g (95%). Colorless oil. $[\alpha]_D$: +180 (*c* 12.0). ^{1}H NMR: δ 3.76 (s, 3H), 3.81 (s, 3H), 4.14 (t, 1H, J = 8.1 Hz), 4.58 (m, 2H), 4.92 (t, 1H, J = 5.4 Hz), 4.98 (t, 1H, J = 8.1 Hz), 6.83 (d, 2H, J = 9.0 Hz), 7.42 (m, 13H), 8.04 (d, 1H, J = 5.4 Hz). ^{13}C NMR: δ 160.6, 158.8, 158.6, 157.3, 156.4, 143.0, 136.7, 130.8, 129.6, 127.7, 122.1, 117.9, 116.2, 114.4, 114.2, 113.3, 70.9, 61.7, 61.2, 60.5, 55.6, 55.4. IR (KBr): ν 1770, 1740, 1630. Anal. Calcd for $C_{27}H_{25}N_3O_5$: C, 68.78; H, 5.34; N, 8.91. Found: C, 68.63; H, 5.27; N, 9.02.

(+)-(3*R*,4*S*)-1-(*p*-Anisyl)-4-(*N*-(*p*-anisyl)azomethinyl)-3-(benzyloxy)-2-azetidinone (5b). Yield: 0.38 g (93%). White solid. Mp: 121−123 °C. $[\alpha]_D$: +23.69 (*c* 1.03). ^{1}H NMR: δ 3.75 (s, 3H), 3.80 (s, 3H), 4.70 (d, 1H, J = 11.7 Hz), 4.83 (d, 1H, J = 5.1 Hz), 5.03 (d, 2H, J = 3.9 Hz), 6.82−7.41 (m, 8H), 7.96 (d, 1H, J = 7.2 Hz). ^{13}C NMR: δ 163.1, 158.7, 158.6, 142.9, 136.1, 135.2, 130.8, 128.3, 128.1, 127.9, 122.2, 118.1, 114.1, 82.7, 73.0, 61.2, 55.2. IR (KBr): ν 1755, 1620. MS: *m*/*e* 416 ($M^{\bullet+}$), 309, 281, 238, 189, 134, 91 (parent), 77. Anal. Calcd for $C_{25}H_{24}N_4O_2$: C, 72.80; H, 5.86; N, 13.58. Found: C, 72.93; H, 5.79; N, 13.67.

(+)-(3*R*,4*S*)-1-(*p*-Anisyl)-4-(*N*-benzylazomethinyl)-3-(benzyloxy)-2-azetidinone (5c). Yield: 0.38 g (95%). White solid. Mp: 106−108 °C. $[\alpha]_D$: +58.3 (*c* 2.0). ^{1}H NMR: δ 3.73 (s, 3H), 4.56−4.75 (m, 5H), 4.91 (d, 1H, J = 5.1 Hz), 6.80 (d, 2H, J = 9.1 Hz), 7.24−7.34 (m, 7H), 7.82 (d, 1H, J = 6.9 Hz). ^{13}C NMR: δ 163.3, 161.9, 156.5, 137.8, 136.3, 130.9, 128.5, 128.4, 128.0, 127.2, 126.9, 126.7, 118.3, 114.3, 82.3, 73.0, 65.1, 55.4. IR (KBr): ν 1750, 1670. MS: *m*/*e* 416 ($M^{\bullet+}$), 309, 281, 238, 189, 134, 91 (parent), 77. Anal. Calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 13.58. Found: C, 75.02; H, 6.15; N, 6.83.

(3*S,4*R**)-1-(*p*-Anisyl)-4-(*N*-(*p*-anisyl)azomethinyl)-3-isopropyl-2-azetidinone (5d).** Yield: 0.35 g (97%). Pale yellow oil. ^{1}H NMR: 1.09 (d, 3H, J = 6.6 Hz), 1.16 (d, 3H, J = 6.6 Hz), 2.18 (m, 1H), 3.12 (dd, 1H, J_1 = 2.4 Hz, J_2 = 7.2 Hz), 3.76 (s, 3H), 3.80 (s, 3H), 4.46 (dd, 1H, J_1 = 2.4 Hz, J_2 = 7.8 Hz), 6.62−7.41 (m, 8H), 7.90 (d, 1H, J = 7.8 Hz). IR ($CHCl_3$): ν 1745, 1640. Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.66; H, 6.74; N, 8.04.

(3*R,4*R**)-1-(*p*-Anisyl)-4-(*N*-(*p*-anisyl)azomethinyl)-3-isopropyl-2-azetidinone (5e).** Yield: 0.34 g (95%). White solid. Mp: 115−116 °C. ^{1}H NMR: 1.09 (d, 3H, J = 6.6 Hz), 1.16 (d, 3H, J = 6.6 Hz), 2.18 (m, 1H), 3.12 (dd, 1H, J_1 = 6.0 Hz, J_2 = 7.4 Hz), 3.76 (s, 3H), 3.80 (s, 3H), 4.75 (dd, 1H, J_1 = 6.0 Hz, J_2 = 7.8 Hz), 6.62−7.41 (m, 8H), 7.95 (d, 1H, J = 7.8

(23) Jarayaman, M.; Deshmukh, A. R.-A. S.; Bhawal, B. M. *J. Org. Chem.* **1994**, *59*, 5921.

(24) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Hz). ^{13}C NMR: δ 166.1, 159.8, 158.8, 156.0, 143.3, 131.6, 121.9, 117.7, 114.4, 114.3, 61.3, 58.0, 55.4, 55.4, 26.0, 21.3, 20.8. IR (KBr): ν 1750, 1640. Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.66; H, 6.74; N, 8.04.

General Procedure for the Synthesis of Compounds 7, 8, and 9. A solution of NaOMe (4 mmol) in absolute MeOH (10 mL) was added dropwise via syringe to a solution of biazetidinone **1** (1 mmol) in MeOH (10 mL). The mixture was stirred under argon until complete disappearance of the starting biazetidinone (TLC). Then, the excess NaOMe was hydrolyzed with water (2 drops), the solvent was partially evaporated under reduced pressure, and 10 mL of water was added. The product was extracted with EtOAc and dried ($MgSO_4$). After filtration and evaporation of the solvent, residues were purified by flash chromatography to yield compounds **7**, **8**, or **9**.

(+)-(1*R*,4*S*,5*R*,8*S*)-2,6-Di(*p*-anisyl)-4,8-bis[(*S*)-4-phenyl-2-oxooxazolidin-3-yl)]-2,6-diazabicyclo[3.3.0]octane-3,7-dione (7a). Reaction time: 12 h. Yield: 0.57 g (85%). White solid. Mp: 212−214 °C. $[\alpha]_D$: +5.8 (*c* 0.9). ^{1}H NMR: δ 3.70 (s (b), 2H), 3.85 (s, 6H), 4.05 (t, 2H, *J* = 9.0 Hz), 4.31 (t, 2H, *J* = 9.0 Hz), 4.54 (t, 2H, *J* = 8.4 Hz), 4.62 (s (b), 2H), 6.93 (d, 4H, *J* = 8.7 Hz), 7.10 (m, 4H), 7.14 (d, 4H, *J* = 8.7 Hz), 7.26−7.29 (m, 6H). ^{13}C NMR: δ 167.4, 158.9, 157.3, 135.3, 129.5, 129.1, 128.7, 127.7, 126.9, 114.8, 71.0, 61.8, 60.5, 57.9, 57.8, 57.8, 55.5. IR ($CHCl_3$): ν 1755, 1720. Anal. Calcd for $C_{38}H_{34}N_4O_8$: C, 67.63; H, 5.08; N, 8.31. Found: C, 67.59; H, 5.06; N, 8.33.

(−)-(1*S*,4*R*,5*S*,8*R*)-2,6-Di(*p*-anisyl)-4-(benzyloxy)-8-hydroxy-2,6-diazabicyclo[3.3.0]octane-3,7-dione (7b). Reaction time: 12 h. Yield: 0.40 g (85%). White solid. Mp: 126−128 °C. $[\alpha]_D$: −38.36 (*c* 0.49). ^{1}H NMR: δ 3.70 (s (b), 2H), 3.85 (s, 6H), 4.05 (t, 2H, *J* = 9.0 Hz), 4.31 (t, 2H, *J* = 9.0 Hz), 4.54 (t, 2H, *J* = 8.4 Hz), 4.62 (s (b), 2H), 6.93 (d, 4H, *J* = 8.7 Hz), 7.10 (m, 4H), 7.14 (d, 4H, *J* = 8.7 Hz), 7.26−7.29 (m, 6H). ^{13}C NMR: δ 167.4, 158.9, 157.3, 135.3, 129.5, 129.1, 128.7, 127.7, 126.9, 114.8, 71.0, 61.8, 60.5, 57.9, 57.8, 57.8, 55.5. IR ($CHCl_3$): ν 1755, 1720, 1610, 1510. Anal. Calcd for $C_{27}H_{26}N_2O_6$: C, 68.33; H, 5.33; N, 5.91. Found: C, 68.49; H, 5.36; N, 5.89.

(+)-(1*S*,4*R*,5*S*,8*R*)-2,6-Di(*p*-anisyl)-4-(benzyloxy)-8-phtalimido-2,6-diazabicyclo[3.3.0]octane-3,7-dione (7c). Reaction time: 4 h. Yield: 0.41 g (68%). Yellow solid. Mp: 170 °C dec. $[\alpha]_D$: +20.65 (*c* 0.49). ^{1}H NMR (100 °C): δ 3.72 (s, 3H), 3.77 (s, 3H), 4.11 (s (a), 1H), 4.20 (d, 1H, *J* = 2.4 Hz), 4.60 (d, 1H, *J* = 11.7 Hz), 4.74 (d, 1H, *J* = 11.7 Hz), 4.84 (dd, 1H, J_1 = 1.8 Hz, J_2 = 7.8 Hz), 5.18 (dd, 1H, J_1 = 1.8 Hz, J_2 = 7.8 Hz), 6.91−7.78 (m, 17H). ^{13}C NMR: δ 169.8, 169.2, 157.3, 156.7, 137.2, 130.4, 129.8, 128.6, 128.3, 127.9, 127.8, 124.9, 124.1, 114.2, 78.8, 71.6, 60.9, 56.7, 55.3, 55.2. IR (KBr): ν 1740, 1720. MS: *m/e* 497, 456, 347, 333, 243, 201, 149, 108, 79 (parent). Anal. Calcd for $C_{35}H_{29}N_3O_7$: C, 69.63; H, 4.85; N, 6.96. Found: C, 69.58; H, 4.77; N, 7.07.

(1*R,4*R**,5*S**,8*S**)-2,6-Di(*p*-anisyl)-8-(benzyloxy)-4-isopropyl-2,6-diazabicyclo[3.3.0]octane-3,7-dione (7d).** Reaction time: 4 h. Yield: 0.43 g (86%). White solid. Mp: 140 °C dec. ^{1}H NMR (DMSO-d_6, 100 °C): δ 0.86 (d, 6H, *J* = 6.6 Hz), 0.88 (d, 6H, *J* = 6.6 Hz), 1.92 (m, 2H), 3.27 (dd, 1H, J_1 = 1.8 Hz, J_2 = 6.6 Hz), 3.59 (s, 3H), 3.68 (s, 3H), 3.65 (d, 1H, *J* = 3.0 Hz), 4.03 (dd, 1H, J_1 = 3.0 Hz, J_2 = 6.3 Hz), 4.09 (dd, 1H, J_1 = 1.8 Hz, J_2 = 6.3 Hz), 4.26 (d, 1H, *J* = 11.7 Hz), 4.84 (d, 1H, *J* = 11.7 Hz), 6.45 (d, 2H, *J* = 9.0 Hz), 6.60 (d, 2H, *J* = 9.0 Hz), 6.77 (d, 2H, *J* = 9.0 Hz), 7.18−7.39 (m, 7H). ^{13}C NMR: δ 177.3, 167.6, 156.1, 152.6, 140.5, 136.9, 131.0, 128.7, 128.6, 128.1, 119.0, 115.5, 114.8, 114.4, 78.9, 72.8, 58.4, 56.8, 55.4, 54.4, 50.3, 28.2, 20.6, 19.6. IR (KBr): ν 1740. MS: *m/e* 353 (M − 149), 318, 282, 246, 207, 149 (parent), 108, 77. Anal. Calcd for $C_{30}H_{32}N_2O_5$: C, 71.98; H, 6.44; N, 5.60. Found: C, 71.75; H, 6.54; N, 5.77.

(1*R,4*R**,5*S**,8*R**)-2,6-Di(*p*-anisyl)-8-(benzyloxy)-4-isopropyl-2,6-diazabicyclo[3.3.0]octane-3,7-dione (7e).** Reaction time: 4 h. Yield: 0.37 g (75%). Colorless oil. ^{1}H NMR (DMSO-d_6, 80 °C): δ 0.89 (d, 6H, *J* = 6.6 Hz), 0.92 (d, 6H, *J* = 6.6 Hz), 2.02 (m, 2H), 3.25 (dd, 1H, J_1 = 6.0 Hz, J_2 = 7.5 Hz), 3.62 (s, 3H), 3.71 (s, 3H), 3.64 (dd, 1H, J_1 = 2.4 Hz, J_2 = 6.0 Hz), 4.11 (d, 1H, *J* = 7.5 Hz), 4.20 (d, 1H, *J* = 12.2 Hz), 4.50 (dd, 1H, J_1 = 2.4 Hz, J_2 = 7.5 Hz), 4.70 (d, 1H, *J* = 12.2 Hz), 6.55−7.44 (m, 8H). The product was unstable, and ^{13}C and analytical data could not be obtained.

Methyl (−)-(2*R*,3*S*)-3-[(*p*-Anisyl)amino]-3-[(3*R*,4*S*)-3-hydroxy-1-benzyl-2-oxoazetidin-4-yl]-2-(benzyloxy)propanoate (8a). Reaction time: 3 h. Yield: 0.44 g (90%). Colorless oil. $[\alpha]_D$: −1.39 (*c* 4.29) ^{1}H NMR: δ 3.35 (s, 3H), 3.69 (s, 3H), 3.71 (m, 1H), 4.01 (d, 1H, *J* = 15.0 Hz), 4.25 (m, 2H), 4.32 (d, 1H, *J* = 11.4 Hz), 4.52 (d, 1H, *J* = 5.2 Hz), 4.69 (d, 1H, *J* = 15.0 Hz), 4.78 (d, 1H, *J* = 11.4 Hz), 6.60 (d, 2H, *J* = 9.0 Hz), 6.71 (d, 2H, *J* = 9.0 Hz), 7.11 (m, 2H), 7.26−7.32 (m, 6H). ^{13}C NMR: δ 170.8, 170.0, 152.7, 140.0, 136.5, 135.4, 128.8, 128.7, 128.5, 128.3, 127.7, 121.8, 115.6, 114.7, 76.4, 75.8, 72.8, 58.4, 57.3, 55.6, 51.8, 44.9. IR ($CHCl_3$): ν 3400, 3300, 1740, 1645. Anal. Calcd for $C_{28}H_{30}N_2O_6$: C, 68.54; H, 6.17; N, 5.71. Found: C, 68.67; H, 6.21; N, 5.77.

Methyl (+)-(2*R*,3*S*)-3-[(*p*-Anisyl)amino]-3-[(3*R*,4*S*)-1-benzyl-3-(benzyloxy)-2-oxoazetidin-4-yl]-2-(benzyloxy)-propanoate (8b). Reaction time: 1 h. Yield: 0.55 g (95%). Colorless oil. $[\alpha]_D$: +4.8 (*c* 3.22) ^{1}H NMR: δ 3.33 (s, 3H), 3.61 (dd, 1H, J_1 = 5.1 Hz, J_2 = 10.2 Hz), 3.72 (s, 3H), 3.88 (d, 1H, *J* = 14.7 Hz), 4.11 (d, 1H, *J* = 5.1 Hz), 4.20 (d, *J* = 13.5 Hz), 4.21 (s, 2H), 4.40 (d, 1H, *J* = 11.7 Hz), 4.72 (d, 1H, *J* = 14.7 Hz), 4.77 (d, 1H, *J* = 13.5 Hz), 4.86 (d, 1H, *J* = 11.7 Hz), 6.57 (d, 2H, *J* = 9.0 Hz), 6.72 (d, 2H, *J* = 9.0 Hz), 7.07 (m, 2H), 7.13 (m, 2H), 7.22−7.32 (m, 11H). ^{13}C NMR: δ 170.8, 168.0, 152.3, 140.8, 140.4, 137.1, 136.8, 135.6, 128.6, 128.6, 128.4, 128.4, 128.3, 127.7, 127.5, 127.4, 115.1, 114.7, 80.3, 75.5, 72.6, 72.4, 57.8, 56.5, 55.6, 51.6, 44.7. IR ($CHCl_3$): ν 3410, 1740, 1670. Anal. Calcd for $C_{35}H_{36}N_2O_6$: C, 72.38; H, 6.25; N, 4.83. Found: C, 72.28; H, 6.38; N, 4.85.

Methyl (2*S,3*R**)-3-[(*p*-Anisyl)amino]-3-[(3*S**,4*R**)-1-(*p*-Anisyl)-3-isopropyl-2-oxoazetidin-4-yl]-2-isopropylpropanoate (8c).** For this compound a mixture of benzene (6 mL) and MeOH (3 mL) was used as solvent. Reaction time: 6 days. Yield: 0.16 g (35%). Colorless oil. ^{1}H NMR: δ 0.75 (d, 3H, *J* = 6.6 Hz), 0.81 (d, 3H, *J* = 6.6 Hz), 0.93 (d, 3H, *J* = 6.6 Hz), 0.99 (d, 3H, *J* = 6.6 Hz), 1.95 (m, 1H), 2.03 (m, 1H), 2.25 (dd, 1H, J_1 = 3.6 Hz, J_2 = 9.0 Hz), 2.68 (dd, 1H, J_1 = 2.1 Hz, J_2 = 7.5 Hz), 3.69 (s, 3H), 3.71 (s, 3H), 3.74 (s, 3H), 4.06 (m, 1H), 6.47 (d, 2H, *J* = 9.0 Hz), 6.67 (d, 2H, *J* = 9.0 Hz), 6.78 (d, 2H, *J* = 9.0 Hz), 7.29 (d, 2H, *J* = 9.0 Hz). ^{13}C NMR: δ 175.8, 166.9, 156.1, 151.7, 141.4, 130.9, 119.2, 119.1, 115.3, 114.4, 59.0, 58.9, 58.8, 58.7, 57.9, 55.7, 55.4, 28.5, 28.4, 20.8, 20.4, 20.2, 19.9. IR ($CHCl_3$): ν 3410, 1740. Anal. Calcd for $C_{27}H_{35}N_2O_5$: C, 69.36; H, 7.54; N, 5.95. Found: C, 69.44; H, 7.38; N, 5.85.

Synthesis of (1*R,4*R**,5*R**,8*R**)-2,6-Di(*p*-anisyl)-4,8-diisopropyl-2,6-diazabicyclo[3.3.0]octane-3,7-dione (7f).** Ethyl isovaleriate (2.35 g, 18 mmol) was added dropwise to a solution of LDA (18 mmol) in THF−hexanes cooled to −78 °C. After 15 min at this temperature, a solution of diimine **3a** (0.80 g, 3 mmol) in THF (40 mL) was added, and the mixture was allowed to warm to room temperature followed by stirring for 12 h. The reaction was quenched with H_2O and diluted with Et_2O (two or three times its original volume). The organic layer was successively washed with H_2O and brine and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the crude was purified by flash chromatography (hexanes/EtOAc). Yield: 0.56 g (44%). White solid. Mp: 181−183 °C. ^{1}H NMR: δ 0.89 (d, 6H, *J* = 6.9 Hz), 0.96 (d, 6H, *J* = 6.9 Hz), 2.21 (m, 2H), 2.47 (d, 2H, *J* = 3.9 Hz), 3.80 (s, 6H), 4.44 (s, 2H), 6.92 (d, 2H, *J* = 9.0 Hz), 7.22 (d, 2H, *J* = 9.0 Hz). ^{13}C NMR: δ 173.2, 158.2, 128.3, 126.0, 114.4, 59.5, 55.3, 52.5, 29.3, 19.9, 18.5. IR (KBr): ν 1740, 1700. MS: *m/e* 436 ($M^{\bullet+}$), 394, 351, 309, 245, 244 (parent), 134, 77. Anal. Calcd for $C_{26}H_{32}N_2O_4$: C, 71.52; H, 7.39; N, 6.42. Found: C, 71.65; H, 7.49; N, 6.31.

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