protons), 7.97 (1 H, d, J = 8 Hz, C_5-H); mass spectrum m/z 197 (M^+). Anal. Calcd for CH_3COOH: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.13; H, 5.71; N, 16.25.

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The Stereoselective Preparation of Mono- and Bis-β-lactams by the 1,4-Diaza 1,3-Diene–Acid Chloride Condensation: Scope and Synthetic Applications[1]

Benito Alcaide,* Yolanda Martín-Cantalejo, Javier Pérez-Castells, Julián Rodríguez-López, and Miguel A. Sierra

Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense, 28040-Madrid, Spain

Angeles Monge[2] and Virginia Pérez-Garcia

Laboratorio de Difracción de Rayos-X, Facultad de Química, Universidad Complutense, 28040-Madrid, Spain

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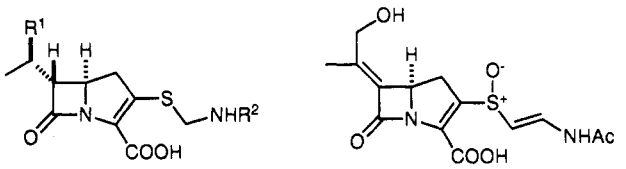
The dehydrochlorination of a variety of acid chlorides with triethylamine in the presence of 1,4-diaza 1,3-dienes gives in fair to excellent yields, with total stereoselectivity, *cis*-4-imino β-lactams **2**, *cis*-4-formyl β-lactams **3**, or C4,C4′-bis-β-lactams **4**, depending on the reaction conditions. The reaction tolerates a wide variety of substituents, including alkoxy, thiophenoxy, amino, aryl, alkyl, alkylidene, and halogen groups, at the ketene moiety. The synthetic versatility of compounds **3** has been demonstrated by their conversion to intermediates in the synthesis of carbapenems PS-5 and PS-6. Base-induced isomerization of compounds **4** to novel bis-γ-lactams **5**, which in turn are aza analogs of glycaric acids, occurred with total retention of the configuration. This process is formally the elongation of glyoxal in four carbons bearing four contiguous stereocenters with total stereoselectivity in only three or four synthetic steps.

Introduction

In spite of the fact that relatively few basic structures are to be found among the clinically important β-lactam antibiotics,[3] there is an upgrowing interest in the chemical synthesis of these compounds. Extensive efforts during recent years have led to many methods to prepare the 2-azetidinone ring, a structural feature which is characteristic of this family of antibiotics.[13] The main approaches to the β-lactam system imply cyclization of β-functionalized acids and their derivatives;[4] cyclization of ester enolates and imines[5] (which strictly speaking could be included in the first route since usually a β-amino ester is formed as the first reaction intermediate); and, finally, the ketene imine synthetic pathway[6] to β-lactams, the venerable Staüdinger reaction.[7] The above approaches have several advantages and some shortcomings, the ketene imine route being the most general when versatility and stereocontrol are taken into account.[8] Furthermore, the introduction of chromium carbene (Fischer) complexes, which upon irradiation act as ketene precursors, has widened the scope of those routes to the 2-azetidinone ring.[9]

Chart I



PS-5 R^1 = H, R^2 = Ac
PS-6 R^1 = Me, R^2 = Ac
Thienamycin R^1 = OH, R^2 = H

Asparenomycin A

(1) For a preliminary communication of a part of this work see: Alcaide, B.; Martín-Cantalejo, Y.; Plumet, J.; Rodríguez-López, J.; Sierra, M. A. *Tetrahedron Lett.* **1991**, *32*, 803.

(2) To whom inquires regarding X-ray structural determination should be addressed.

(3) For general reviews in synthesis and biology of β-lactam antibiotics, see: (a) Dürckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180. (b) *Chemistry and Biology of β-lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vols 1–3. (c) *Recent Progress in the Chemical Synthesis of Antibiotics*; Lucas, G., Ohno, M., Eds.; Springer-Verlag: Berlin-Heidelberg, 1990. (d) Hungerbühler, E.; Biollaz, M.; Ernest, I.; Kalvoda, J.; Lang, M.; Schneider, P.; Sedelmeier, G. In *New Aspects of Organic Chemistry I*; Yoshida, Z., Shiba, T., Ohshiro, Y., Eds.; VCH; Tokyo, 1989, p 419.

(4) For some recent references involving cyclization of β-functionalized acids and derivatives to β-lactams see, among others: (a) Kim, C.-W.; Chunj, B. Y. *Tetrahedron Lett.* **1990**, *31*, 2905. (b) Barret, A. G. M.; Sakadarat, S. *J. Org. Chem.* **1990**, *55*, 5110. (c) Kahn, M.; Fujita, K. *Tetrahedron* **1991**, *47*, 1137. (d) Fremont, S. L.; Belletir, J. L.; Ho, D. M. *Tetrahedron Lett.* **1991**, *32*, 2335. (e) Palomo, C.; Aizpurua, J. M.; Urchegui, R.; Iturburu, M.; Ochoa de Retana, A.; Cuevas, C. *J. Org. Chem.* **1991**, *56*, 2224. (f) Williams, M. A.; Hsiao, C.-N.; Miller, M. J. *J. Org. Chem.* **1991**, *56*, 2688. (g) Miyachi, N.; Shibasaki, M. *J. Org. Chem.* **1990**, *55*, 1975. (h) Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *32*, 5287.

(5) For recent literature reviews of the ester enolate–imine condensation, see: (a) Brown, M. J. *Heterocycles* **1989**, *29*, 2225. (b) Hart, D. J.; Ha, D-C. *Chem. Rev.* **1989**, *89*, 1447. (c) van der Steen, F.; van Koten, G. *Tetrahedron* **1991**, *47*, 7503.

(6) For recent reviews on the ketene–imine approach to β-lactams, see: (a) Ghosez, L.; Marchand-Brynaert, J. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 5, p 90. (b) Govindachari, T. R.; Chinnasamy, P.; Rajewari, S.; Chandrasekaran, S.; Premila, M. S.; Nagarajan, K.; Pai, B. R. *Heterocycles* **1984**, *22*, 585. (c) Shandu, J. S.; Sain, B. *Heterocycles* **1987**, *26*, 777.

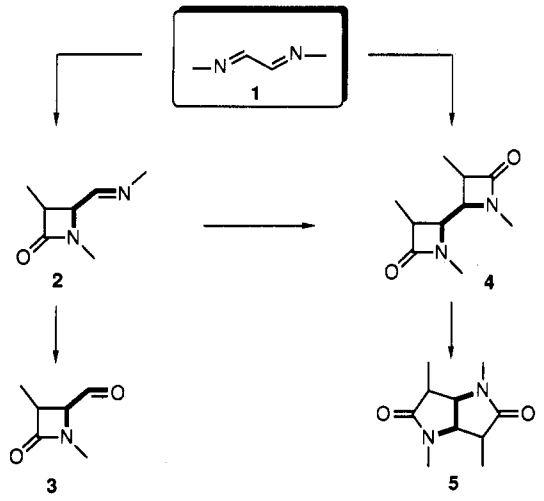
(7) Staüdinger, H. *Liebigs Ann. Chem.* **1907**, *356*, 51.

(8) For a review in the chiral control of the Staüdinger reaction, see: Cooper, R. D. G.; Daugherty, B. M.; Boyd, D. B. *Pure Appl. Chem.* **1987**, *59*, 485. See also: Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784 and pertinent references therein.

(9) (a) Schwindt, M. A.; Miller, J. R.; Hegedus, L. S. *J. Organomet. Chem.* **1991**, *413*, 143. (b) Hegedus, L. S.; Imwinkelried, R.; Alarid-Sargent, M.; Dvorak, D.; Satoh, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1109. (c) Alcaide, B.; Dominguez, G.; Plumet, J., Sierra, M. A. *J. Org. Chem.* **1992**, *57*, 447.

0022-3263/92/1957-5921$03.00/0

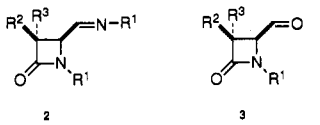
Scheme I



In our ongoing project devoted to develop easily available imine substrates for the Staüdinger reaction, recently, we introduced 1,4-diaza 1,3-dienes, **1**, as building blocks for β-lactam synthesis.[1,10] These easily available glyoxal diimines lead to 4-imino β-lactams, **2**, which yield 4-formyl β-lactams, **3**, after acid hydrolysis. Compounds **3** are interesting as starting monocyclic β-lactams in the synthesis of biologically active carbapenems such as PS-5, PS-6, asparenomycin, and thienamycin.[11] These compounds have been also used as precursors of monobactams and isocepham antibiotics.[12] Previously reported routes to **3** have involved either oxidative degradation or multistep functional group transformation from differently 4-substituted β-lactams.[13] Furthermore, adequately functionalized β-lactams are always interesting due to their role in the preparation of more complex non-β-lactam structures[14] (the β-lactam synthon method).[15]

Use of 1,4-diaza 1,3-dienes as the imine moiety in the preparation of 4-formyl-2-azetidinones from ester enolates has been reported by us[10] and others.[16] To date the scope of these reactions has been limited to α-disubstituted,[10,16a] α-amino,[16b] and simple α-alkyl enolates,[17] formation of β-lactam occurring in some cases[10,16a,17] with low cis–trans selectivities. In contrast to the extensive studies involving the reaction of ketenes with simple imines, 1-aza, and 2-aza 1,3-dienes, little attention has been paid to the related

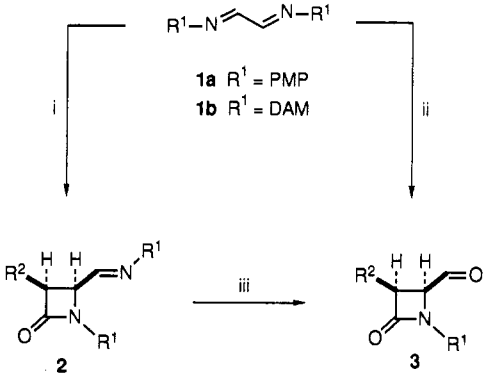
Table I. Synthesis of *cis*-4-Imino β-Lactams 2 and *cis*-4-Formyl β-Lactams 3[a]



	R^2	R^3	R^1	yield[b]	mp[c] (°C)
2a	CH_3	H	PMP	51	131–133
2b	Ph	H	PMP	82	122–124
2c	PhO	H	DAM	65	oil
2d	$PhCH_2O$	H	PMP	35	175–177
2e	PhS	H	PMP	60	65 dec
2f	Md[d]	H	PMP	77	190–191
3a[e]	Me	H	PMP	90	118–120
3b[e]	Me	H	DAM	75	oil
3c[e]	Et	H	PMP	73	90–91
3d[e]	^iPr	H	PMP	80	91–93
3e[e]	Ph	H	PMP	85	154–156
3f[e]	PhO	H	PMP	70	109–110
3g[e]	PhO	H	DAM	80	oil
3h[e]	$PhCH_2O$	H	PMP	32	99–101
3i[e]	PhS	H	PMP	80	153–154
3j[e]	PhS	H	DAM	66	oil
3k[f]	Md[d]	H	PMP	75	200–202
3l[f]	Pht[g]	H	PMP	76	246–248
3m[e]	Pht[g]	H	DAM	59	oil
3n[e]	Cl	H	PMP	57	124–126
3o[e,h]	Cl	Me	PMP	76[i]	120–121[i]
3p[e]	Cl	Cl	PMP	55	97–99
3q[e]	Br	Et	PMP	72	116–118
3r[e]	CH_2=C(Me)–	H	PMP	73	74–76
3s[e]	CH_2=CH–	H	PMP	60	107–108

[a] In all cases PMP = 4-$MeOC_6H_4$, DAM = $(4\text{-}MeOC_6H_4)_2CH$. [b] From diimine 1, in pure isolated compound with correct analytical data. [c] Recrystallized from EtOAc/hexanes mixtures. [d] Malimidyl. [e] Prepared from diimine 1 following the one-pot procedure. [f] Obtained by hydrolysis of the corresponding 4-imino β-lactam. [g] Phthalimidyl. [h] Obtained as a cis–trans (95:5) mixture of isomers. [i] Data corresponding to the cis isomer.

Scheme II[a]



[a] Key (i) R^2CH_2COCl/Et_2N/toluene; (ii) Et_3N/toluene, (2) HCl; (iii) HCl.

(10) Alcaide, B.; Gômez, A.; Plumet, J.; Rodríguez-Lôpez, J. *Tetrahedron* **1989**, *45*, 2751.

(11) For reviews on carbapenem synthesis, see: (a) Kametani, T.; Fukumoto, K.; Ihara, M. *Heterocycles* **1982**, *17*, 463. (b) Nagahara, T.; Kametani, T. *Heterocycles* **1987**, *25*, 729. (c) Georg, G. I. In *Studies in Natural Products Synthesis*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1989; Vol. 4, p 431. (d) Palomo, C. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Springer-Verlag: Berlin-Heidelberg, 1990, p 565.

(12) See, for example: (a) Huffman, W. F.; Holden, K. G.; Buckley, T. F.; Gleason, J. G.; Wu, L. *J. Am. Chem. Soc.* **1977**, *99*, 2352. (b) Hakimelahi, G. H.; Khalafi-Nezhad, A. *Helv. Chim. Acta* **1984**, *67*, 18. (c) Nitta, H.; Hatanaka, M.; Ishimaru, T. *J. Chem. Soc., Chem. Commun.* **1987**, 51. (d) Mastalerz, H.; Vinet, H. *J. Chem. Soc., Chem. Commun.* **1987**, 1283. (e) Mastalerz, H.; Menard, M.; Vinet, V.; Desidereio, J.; Fung-Tomc, T.; Kessler, R.; Tsai, Y. *J. Med. Chem.* **1988**, *31*, 1190.

(13) From 4-styryl-β-lactams, see: (a) Hart, D. J.; Ha, D.-Ch. *Tetrahedron Lett.* **1985**, *26*, 5493. (b) Cainelli, G.; Panunzio, M.; Basile, T.; Bargini, A.; Giacomini, D. *J. Chem. Soc., Perkin Trans 1* **1987**, 2637. (c) Georg, G. I.; Kant, J.; Gill, H. S. *J. Am. Chem. Soc.* **1987**, *19*, 1129. (d) Georg, G. I.; Gill, H. S. *J. Chem. Soc., Chem. Commun.* **1985**, 1433. (e) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783. (f) Thomas, R. C. *Tetrahedron Lett.* **1989**, *30*, 5239. From 4-oxyranyl, see: (g) Evans, D. A.; Williams, J. M. *Tetrahedron Lett.* **1988**, *29*, 5065. From 4-alkoxycarbonyl, see: (h) Labia, R.; Morin, C. *Chem. Lett.* **1984**, 1007. (i) Palomo, C.; Ontoria, J. M.; Odriozola, J. M.; Aizpurua, J. M.; Gamboa, I. *J. Chem. Soc., Chem. Commun.* **1990**, 503.

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

(15) See, for example: (a) Ojima, I.; Pey, Y. *Tetrahedron Lett.* **1992**, *33*, 887. (b) Ojima, I.; Habus, I.; Zhao, M.; Georg, G. I.; Jayasshinge, L. R. *J. Org. Chem.* **1991**, *56*, 1681. (c) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K.; Yamashita, M.; Abe, R. *J. Org. Chem.* **1991**, *56*, 5263. (d) Ojima, I.; Pei, Y. *Tetrahedron Lett.* **1990**, *31*, 977. (e) Ojima, I.; Komata, T.; Qiu, X. *J. Am. Chem. Soc.* **1990**, *112*, 770. (f) Ojima, I.; Chen, H.-J.; Qiu, X. *Tetrahedron* **1988**, *44*, 5307. (g) Ojima, I., Chen, H.-J.; Nakahashi, K. *J. Am. Chem. Soc.* **1988**, *110*, 278.

(16) (a) van der Steen, F. H.; Kleijn, H.; Spek, A. L.; van Koten, G. *J. Chem. Soc., Chem. Commun.* **1990**, 503. (b) van der Steen, F. H.; Kleijn, H.; Spek, A. L.; van Koten, G. *J. Org. Chem.* **1991**, *56*, 5868.

(17) Lithium enolates derived from methyl butyrate and methyl isovalerate gave the corresponding β-lactams with cis–trans selectivities of 55/45 and 35/65, respectively. Alcaide, B.; Martín-Cantalejo, Y.; Rodríguez-Lôpez, J., unpublished results.

1,4-diaza 1,3-dienes in this type of chemistry. To the best of our knowledge the only related work is by Sakamoto[18] who reported the isolation of some β-lactams in the reaction of dimethyl- and diphenylketene with *N,N*-diphenyl-1,4-diaza dienes derived from benzil and diacetyl. These aryl-substituted β-lactams are of little use as intermediates in β-lactam synthesis. Moreover, the stereochemical course of this reaction has not been investigated, since nonprochiral ketenes were taken into consideration.

Here, we report in full[1] a general, totally stereoselective synthesis of 4-formyl-2-azetidinones, **3**, and the one-pot, highly efficient, totally stereoselective synthesis of the, at the beginning of this work unknown,[19] C4,C4′-bis-β-lactam system, **4**. The versatility of compounds **3** in β-lactam synthesis is illustrated by their transformation to intermediates of the synthesis of PS-5 and PS-6 carbapenems. Furthermore, a novel totally stereoselective transformation of compounds **4** in fused bis-γ-lactams which may be envisaged as aza analogues of glycaric acids, namely idaric acid, has also been achieved. The last process is formally the elongation of glyoxal in four carbons bearing four contiguous stereocenters with total stereocontrol in only three synthetic steps (Scheme I).

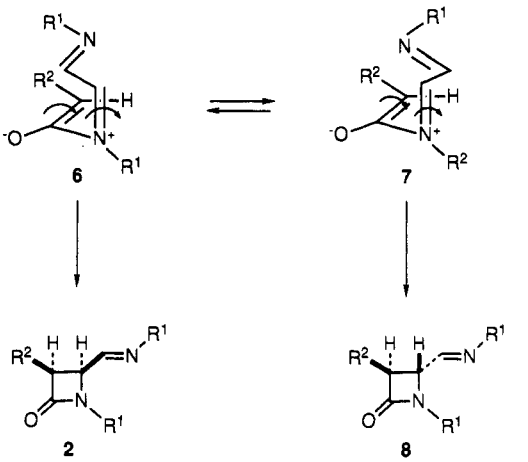
Results and Discussion

Synthesis of *cis*-4-Formyl-3-functionalized-2-azetidinones. In order to develop a general route which would allow for the introduction of several groups in position 3 of the 4-formyl-2-azetidinone system, we tested the reaction of several acid chlorides and glyoxal diimines **1a** and **1b** (Scheme II). As listed in Table I substituted acetic acid chlorides bearing amino, alkoxy, thiophenoxy, alkyl, and unsaturated radicals were converted smoothly into the desired β-lactams. Both aromatic and aliphatic diimines are suitable substrates for this reaction, although imines bearing the DAM [(*p,p*′-dimethoxybenzhydryl)amino] moiety gave somewhat lower yields of β-lactam. The reactions were performed in one-pot fashion, in toluene at room temperature, and occur through the intermediate 4-imino β-lactams, **2**, which are hydrolized in situ by adding aqueous hydrochloric acid to the reaction mixture. Pure β-lactams **3** were obtained by flash chromatography in good to excellent yields. Additionally, compounds **3** can be prepared in multigram scale with analogous yields. On the other hand, 4-imino β-lactams could be obtained if acidic treatment is avoided, in fair to good yields. Some examples are listed in Table I. Compounds **2** yielded 4-formyl β-lactams **3** upon acidic hydrolysis in essentially quantitative yields. However, compounds **2** were relatively unstable, and extensive decomposition was observed in some cases after chromatography. This unstability accounts for the lower yields in 4-imino β-lactams when compared with the one-pot yields in 4-formyl β-lactams, and hence the one pot procedure is preferred for the synthesis of the latter compounds (an exception is compound **3h** for which better yields were obtained by using the two-step procedure).

It is noteworthy that the above reaction tolerates a wide variety of groups attached to the acid chloride moiety. For example, alkyl-substituted acid chlorides gave good yields of the corresponding β-lactam **3** as one sole stereoisomer (see above).[20] Other synthetically versatile groups such as amino, alkenyl, thiophenyl, and alkoxy groups may be efficiently located at the 3-position of the β-lactam ring. Regarding the stereochemical outcome of the above reaction, it is outstanding that only the cis-isomer was detected for both 4-imino- and 4-formyl-2-azetidinones, an exception was compound **3o** derived from 2-chloropropionyl chloride for which a 95/5 cis–trans mixture was observed.[21] The stereochemical assignment was based on the observed H3–H4 proton coupling (4.8–6.3 Hz) which is in agreement with previously reported coupling values in cis-β-lactams.[22] The stereochemistry of compound **3o** was determined by NOE measurements. Thus, an enhancement of 4.8% was observed in the signal corresponding to H4 upon irradiation of the methyl group attached at C3 of the four-membered ring, for the major isomer. In contrast, an enhancement of 4% was observed in the CHO proton upon irradiation of the CH_3 at C3 for the minor isomer, enhancement on H4 being less than 0.5%. Therefore, cis-stereochemistry should be assigned for the major isomer.

It is known that the stereochemical outcome of the Staüdinger reaction is hardly predictable, but it can be controlled by reaction conditions and the substituents attached both at the acid chloride and the imine.[6b,c,8] In our case, the observed bias for the cis-isomer may be accounted as depicted in Scheme III. Assuming that the reaction between acid chlorides and imines occurs through previous formation of the ketene by action of the tertiary amine,[23] and that nucleophiles attack the LUMO of the

Scheme III



(18) Sakamoto, M.; Miyazawa, K.; Ishihara, Y.; Yomimatsu, Y. *Chem. Pharm. Bull. Tokyo* **1974**, *22*, 1419.

(19) Before the completion of this work the synthesis of some C4,C4′-bis-β-lactams by using a related methodology has been reported; see: Bose, A. K.; Womelsdorf, J. F.; Krishnan, L.; Urbanczyk-Lipkowska, Z.; Shelly, D. C.; Manhas, M. *Tetrahedron* **1991**, *47*, 5379. See text for a detailed discussion.

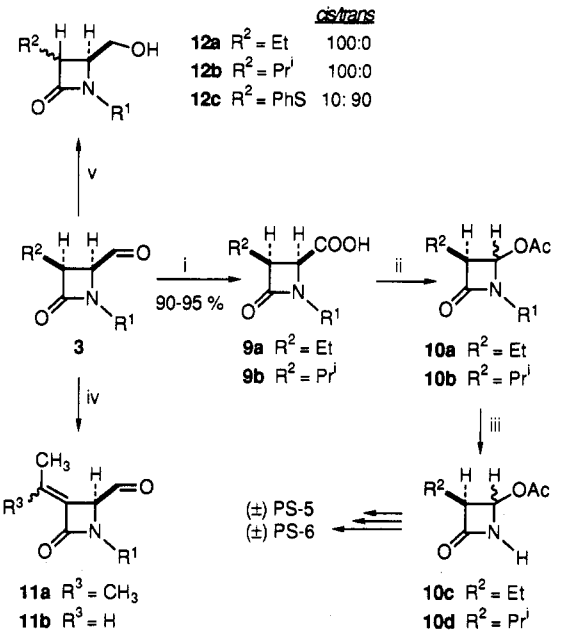
(20) The acid chloride–imine route to β-lactams having alkyl groups at the 3-position gave usually low yields or poor selectivities. See: (a) Alcaide, B.; Escobar, G.; Parreño, U.; Plumet, J. *Heterocycles*, **1986**, *24*, 1579. (b) Tschaen, D. M. Fuentes, L. M.; Lynch, J. E.; Laswell, W. L.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 2779. For an indirect route to these compounds see: (c) Palomo, C.; Cossio, F. P.; Odriozola, J. M.; Oiarbide, M. *Tetrahedron Lett.* **1989**, *29*, 2409. For 3-alkylidene β-lactams see: (d) Manhas, M. S.; Ghosh, M.; Bose, A. K. *J. Org. Chem.* **1990**, *55*, 575.

(21) In all cases ^{1}H NMR analysis (300 MHz) of the crude reaction mixtures showed formation of the cis isomer. For compound **3o** the ratio of cis–trans isomers was determined by integration of well-resolved signals in the ^{1}H NMR (signals corresponding to CH_3 and CHO protons) of the crude reaction mixture.

(22) See, for example: Descases, J.; Luche, J. L.; Kagan, H. B. *Tetrahedron Lett.* **1975**, 3661.

(23) A revent low-temperature FTIR study of the reaction of acid chlorides with imines in the presence of base to form β-lactams was rationalized to show that β-lactam formation occurs exclusively through a ketene intermediate. See: Lynch, J. E.; Riseman, S. M.; Laswell, W. L.; Tschaen, D. M.; Volante, R. P.; Smith, G. B.; Shinkai, I. *J. Org. Chem.* **1989**, *54*, 3792. Nevertheless, it has been shown that β-lactam formation occurs, in some cases, even in the absence of tertiary base, in conditions for what previous ketene formation seemed to be unlikely; see: Alcaide, B.; Dominguez, G.; Plumet, J.; Sierra, M. A. *Heterocycles* **1988**, *27*, 1317. Therefore, at least in some cases, alternative reaction pathways to form the zwitterionic intermediate may be operative.

Scheme IV[a]

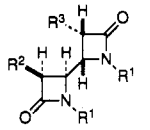


[a] Key: (i) Jones' reagent/0 °C; (ii) $Pb(OAc)_4/Cu(OAc)_2$/MeCN/80 °C; (iii) CAN/MeCN–H_2O/0 °C; (iv) DBU/C_6H_4/Δ; (v) $NaBH_4$/MeOH/rt.

ketene carbonyl group which is coplanar to the ketene substituents,[24] then the zwitterionic intermediate may be similar to **6** according to the currently accepted reaction pathway for the reaction of acid chlorides and imines, the more voluminous R group placed away from the imine moiety. Conrotatory ring closure of **6** would yield the observed cis isomer **2**. However, the total cis-selectivity observed in most cases excludes isomerization of intermediate **6** to **7**. In fact, the latter intermediate would yield the *trans*-β-lactam, **8**, after ring closure.

In order to ensure the feasibility of compounds **3** in the preparation of more elaborate β-lactams, we undertook their conversion to previously reported intermediates in the synthesis of carbapenems (Scheme IV). Thus, Jones' oxidation of compounds **3c** and **3d** gave acids **9a** and **9b**, respectively, in excellent yields. Compounds **9a** and **9b** were converted into 4-acetoxy β-lactams **10a** and **10b** by standard $Pb(OAc)_4$ decarboxylation–acetoxylation[20d] and subsequently N-dearylated by Kronenthal's cerium ammonium nitrate (CAN) oxidation[25] to yield compounds **10c–d**. Compounds **10a** and **10b** were obtained as a trans–cis (90/10) mixture of isomers. Since *trans*-**10c** and **10d** have been converted into (±)-PS-5 and (±)-PS-6 carbapenems,[20d,26,27] the process described above is a short, stereoselective formal synthesis of these carbapenem antibiotics. On the other hand, isomerization of compounds **3r** and **3s** to 3-alkylidene β-lactams **11a** and **11b** promoted by base (DBU) was also achieved in high yields, the latter compound being obtained as a 40/60 mixture of *Z*/*E* isomers. Compound **11a** is related to intermediates used

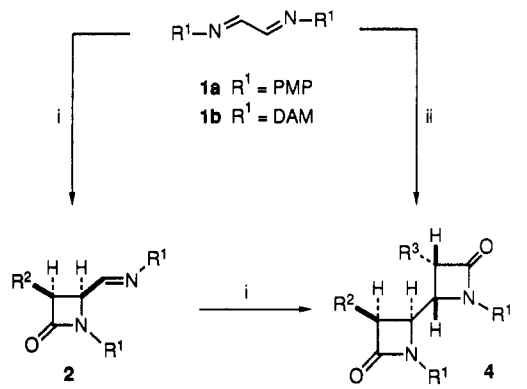
Table II. Synthesis of 4,4'-Bis(2-azetidinone)s 4[a]



	R^2	R^3	R^1	yield[b] (%)	mp[c] (°C)
4a[d]	Me	PhO	PMP	90	239–241
4b[d]	Me	PhO	DAM	40	oil
4c[d]	Ph	PhO	PMP	76	188–190
4d[e]	MeO	MeO	PMP	85	177–178
4e[e]	PhO	PhO	PMP	90	>250
4f[e]	PhO	PhO	DAM	64	159–161
4g[d]	PhO	PhS	PMP	70	206–208
4h[d]	PhO	Md[f]	PMP	70	210 dec
4i[d]	PhO	Cl	PMP	85	229–231
4j[e]	$PhCH_2O$	$PhCH_2O$	PMP	80	166–168
4k[e]	$PhCH_2O$	$PhCH_2O$	DAM	56	oil
4l[d]	PhS	Pht[g]	PMP	62	229–231
4m[e]	Md[f]	Md[f]	PMP	82	>250
4n[e]	Pht[g]	Pht[g]	PMP	89	>250
4o[e]	Pht[g]	Pht[g]	DAM	44	>250

[a] In all cases PMP = 4-$MeOC_6H_4$ and DAM = $(4\text{-}MeOC_6H_4)_2CH$. [b] In pure isolated compound with correct analytical data. [c] Recrystallized from EtOAc/hexanes mixtures. [d] Prepared from 4-imino β-lactams **2**. [e] Prepared from diimine **1**. [f] Malimidyl. [g] Phthalimidyl.

Scheme V[a]

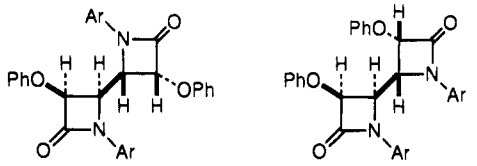


[a] Key: (i) R^2CH_2COCl/Et_3N/toluene, rt; (iii) R^3CH_2COCl/Et_3N/toluene, rt.

in the synthesis of asparenomycin antibiotics.[20d,28] The above transformations show the versatility of 4-formyl β-lactams in the synthesis of valuable β-lactam intermediates. Additionally, $NaBH_4$ reduction of the aldehyde group yielded cleanly 4-hydroxymethyl derivatives **12** in high yields. This transformation deserves some comments. When compound **3i** was reduced with $NaBH_4$ the corresponding alcohol was obtained, but instead of a single cis-isomer, the sole reaction product for reduction of compounds **3c** and **3d**, a mixture of cis- and trans-β-lactams was isolated. Furthermore, the trans-isomer was the main reaction product (cis/trans 10/90). Clearly, base-promoted epimerization at C-3 is ocurring before or after the reduction takes place. Independent treatment of compound **3i** with KOH/MeOH gave cis to trans isomerization after a few minutes.[29] The ability of the PhS group to stabilize a carbanion accounts for the observed isomerization to the thermodynamically more stable trans-isomer.[30]

(24) Seikaly, H. R.; Tidwell, T. T. *Tetrahedron* **1986**, *42*, 2587.
(25) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.
(26) (a) Kametani, T.; Honda, T.; Nakayama, A.; Fukumoto, K. *Heterocycles* **1980**, *14*, 1967. (b) Kametani, T.; Fukumoto, K.; Ihara, M. *Heterocycles* **1982**, *17*, 496.
(27) Recently, Palomo, et al. have described the synthesis of the trans-β-lactam **10d**, via Reformatsky reaction between methyl α-bromoisovalerate and *N*-(4-methoxyphenyl)-α-methylcinnamylidenamine in five steps with lower overall yields. Palomo, C.; Cossio, F. P.; Arrieta, A.; Odriozola, J. M.; Oiarbide, M.; Ontoria, J. M. *J. Org. Chem.* **1989**, *54*, 5736.
(28) Buynak, J. D.; Rao, M. N.; Pajouhesh, H.; Chandrasekaran, R. Y.; Finn, K.; deMeester, P.; Chu, S. C. *J. Org. Chem.* **1985**, *50*, 4245.
(29) ^1H NMR (300-MHz) analysis of crude reaction mixture showed almost complete isomerization together with variable amounts of unidentified compounds.

Chart II

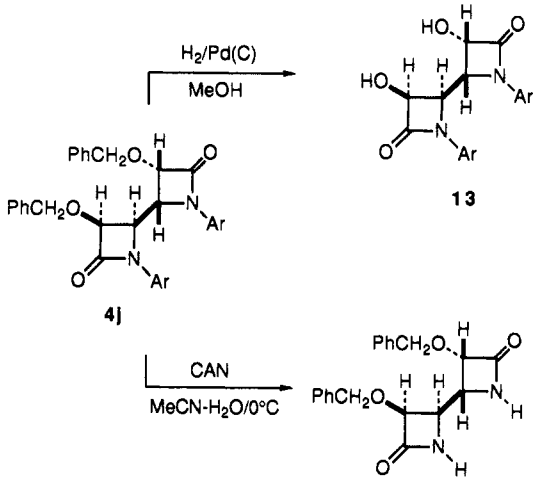


4A (3S*,4R*,3'S*,4'R*) **4B** (3S*,4R*,3'R*,4'S*)

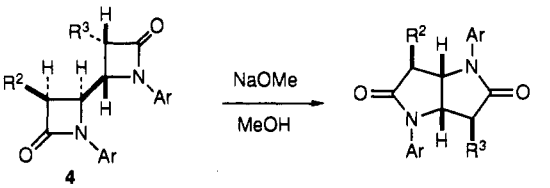
Synthesis of 4,4'-Bis(2-azetidinone)s 4. As stated above, either 1,4-diaza 1,3-dienes 1 or 4-imino-2-azetidinones 2 may be suitable substrates for the synthesis of C4,C4'-bis-β-lactams. Therefore, the reaction of some compounds 2 and phenoxyacetyl chloride in the presence of Et_3N was investigated. To our delight, a clean, almost quantitative, conversion of compounds 2 into the desired compounds 4 was achieved. Moreover, when diimine 1 was reacted with acid chlorides that are precursors of activated ketenes (ca., alkoxyacetyl, malimidyl, or phtalimidyl chlorides) in a 1:2 imine/acid chloride ratio, compounds 4 ($R^1 = R^2$) were the sole reaction products in almost quantitative yields (Scheme V, Table II). The two-step approach to compounds 4 allows for the introduction of different substituents in position 3 of the first β-lactam ring. However, acid chloride precursors of activated ketenes have to be used to build the second β-lactam ring. When imino β-lactams 2 were reacted with alkyl- or aryl-substituted acid chlorides at room temperature, unaltered starting compound 2 was recovered even after long reaction times. Extensive decomposition of the reagents to a myriad of unknown compounds was obtained by forcing the reaction conditions (boiling benzene or toluene). An analogous limitation was observed for the one-pot synthesis of compounds 4 starting from diimine 1. In this case, only acid chloride presursors of activated ketenes are useful for the building of the bis-β-lactam system.

Regarding the observed stereochemistry in building the bis-β-lactam system, compounds 4 were always obtained as single stereoisomers, configurations being identical independently of which route was used. The cis-stereochemistry of both rings was assigned by the coupling constant $J_{3,4}$ (4.8–5.4 Hz) and $J_{3',4'}$ (3.3–5.4 Hz) in their ^1H NMR spectra. However, the choice between the two possible cis–cis configurations (represented as **4A** and **4B** in Chart II) could not be resolved based only on spectroscopic data. Therefore, the structure and stereochemistry of compounds 4 was established by X-ray diffraction analysis carried out on compound **4e**, unequivocally confirming configuration **4B** (3*S**,4*R**,3'*R**,4'*S** for compounds **4d–o** and 3*S**,4*S**,3'*R**,4'*S** for compounds **4a–c**). While this work was in progress Bose reported[19] the synthesis of some bis-β-lactams 4, establishing the stereochemistry of compounds 4 by coincidence also by X-ray diffraction analysis of compound **4e**. Our results are in total agreement with those obtained by Bose.[19] It is noteworthy the total stereoselectivity observed in the synthesis of compounds 4. Related work by Ojima[31] accounts for the high stereoselectivity found in the [2 + 2] cycloaddition of azidoketenes and 3-imino β-lactams to yield C3,N'-bis-β-lactams on the base of lone pair–lone pair interaction of the β-lactam carbonyl oxygen and the betaine oxygen in the zwitterionic intermediate. These interactions favor one of the two possible intermediates, hence the observed high selectivity. However, in our case the reacting imino group should be placed away from the β-lactam oxygen not allowing for the interactions proposed by Ojima. Efforts to understand the origin of the observed selectivity are now in progress.

Scheme VI



Scheme VII



5a $R^2 = R^3$ = PhO (80 %)
5b $R^2 = R^3 = PhCH_2O$ (87 %)
5c R^2 = PhO, R^3 = Me (70 %)
5d R^2 = PhO, R^3 = Cl (77 %)

As previously stated, Bose has reported[19] the synthesis of compounds related to 4 by using 4-imino β-lactams as the key intermediates. However, while our approach requires only one or two steps from glyoxal diimine 1 giving usually good to excellent yields, Bose's approach makes use of cinnamaldehyde imines, which are converted stepwise into 4-formyl-2-azetidinones, 4-imino β-lactams, and finally bis-β-lactams, in low overall yields and limited to alkoxy or amino substituents in the three sole examples described. The method reported here is clearly more versatile, easy, and efficient in terms of overall yields. Compare, for example, the 4% yield (crude product) reported by Bose for compound **4e** with our own result (90% of pure compound obtained in one single step from aza diene **1a**).

Additionally, some aspects of the chemistry of compounds 4 were studied. Firstly, the possibility of manipulation of the groups attached both at C3 and N1 was addressed using compound **4j** as model (Scheme VI). Thus, selective deprotection of benzyloxy groups was achieved by hydrogenolysis (10% Pd on charcoal) leading to bis(hydroxy-β-lactam) **13** in almost quantitative yield. On the other hand, oxidative cleavage (CAN)[25] of the *p*-methoxyphenyl group attached to nitrogen was also effective giving N,N-unprotected-bis-β-lactams, **14**, in good yields. Those reactions showed that the bis-β-lactam system is as suitable for standard manipulations of protective groups as are monocyclic β-lactams, without any

(30) Deuteration experiments were performed by using KOD/CD_3OD, and reaction progress was monitored by ^1H NMR. However, only very complex reaction mixtures were observed. Therefore, epimerization by C4 deprotonation may be an alternate reaction pathway.

(31) (a) Ojima, I.; Nakahashi, K.; Brandstadter, S. M.; Hatanaka, N. *J. Am. Chem. Soc.* **1987**, *109*, 1798. (b) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K. *J. Org. Chem.* **1991**, *56*, 5263.

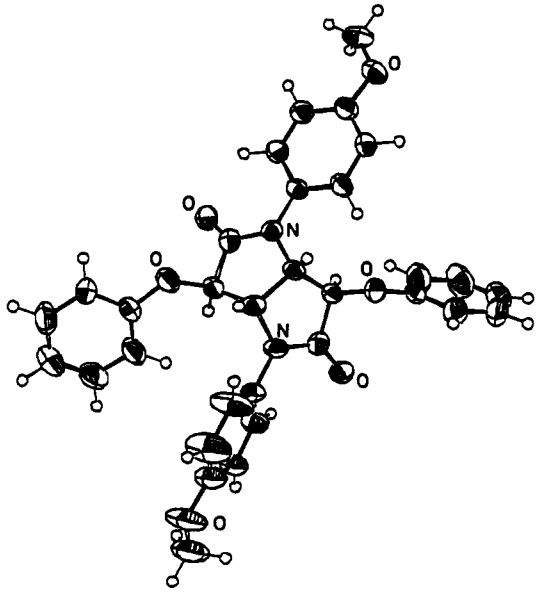


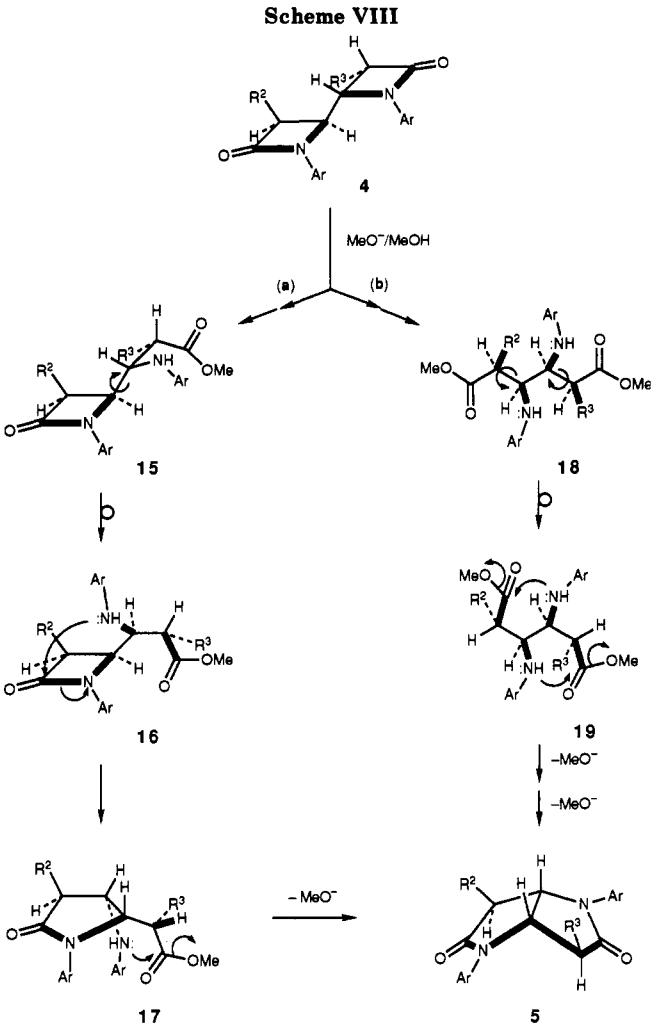
Figure 1. ORTEP drawing of the molecular structure of the fused bis-γ-lactam **5a**.

secondary reaction arising from its bicyclic nature.

More interesting is the reaction of these bis-β-lactams with NaOMe in anhydrous methanol. Under the above conditions a clean, almost quantitative conversion into the novel bis-γ-lactam system **5** (derived from 2,6-diazabicyclo[3.3.0]octane-3,7-dione or 2,5-dioxopyrrolo[3,2-*b*]pyrrole) was obtained (Scheme VII). The conversion of compounds **4** to compounds **5** occurs in a totally stereoselective fashion, one single isomer being isolated in all cases tested. The fused bis-γ-lactam nature of these compounds was established from their spectroscopic (^{1}H and ^{13}C NMR and IR) data. Thus, the amide absorption in their IR spectra appears between 1690 and 1710 cm^{-1}, clearly shifted to lower wavelength in comparison with the precursor β-lactam. On the other hand, ^{1}H NMR spectra for symmetrically substituted compounds **5** (**5a** and **5b**) were very simple, only two resonances for the aliphatic protons, corresponding to both protons attached at C4-C8, and the two at the bridge, respectively, were observed. This is in good agreement with the high degree of internal symmetry expected for compounds **5a** and **5b** if the transformation from bis-β-lactam to the bis-γ-lactam had occurred with formal total retention of configuration. Analogously, ^{13}C NMR spectra for compounds **5a** and **5b** showed resonances corresponding to half of the six carbons of the bicyclic ring. Therefore, it is reasonable to assume that the stereochemistry present in the bis-β-lactam ring is transferred unaltered to the fused bis-γ-lactam ring. This hypothesis was confirmed by an X-ray diffraction analysis carried out in a single crystal of compound **5a**, showing that stereochemistry is maintained through the base-induced opening of the bis-β-lactam system and the cyclization to the bis-γ-lactam. An ORTEP drawing of the structure of compound **5a** is shown in Figure 1.

Two possible alternate reaction pathways for the rearrangement of bis-β-lactams **4** to compounds **5** are shown in Scheme VIII. Firstly, monocyclic intermediate **15** (either in amino or amide form) arising from the methoxide ring opening of the bicyclic system of **4** may undergo ring expansion via intramolecular nucleophilic attack over the β-lactam carbonyl to give γ-lactam **17** (path a). This new intermediate would yield the final bis-γ-lactam **5** by intramolecular aminolysis. Alternately, double ring opening may occur to yield the acyclic diester **18** (path b). The double step-by-step intramolecular aminolysis on **18** would

Scheme VIII



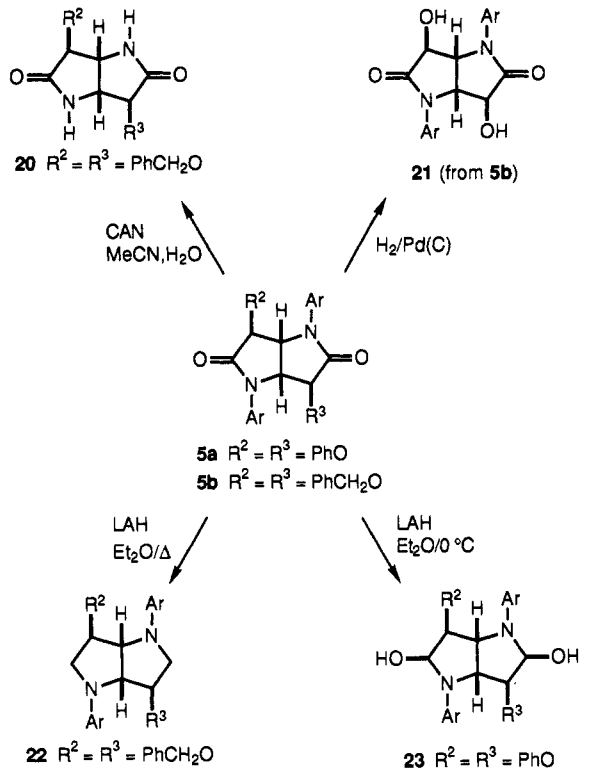
rend compound **5** through the reactive conformation **19**. In both cases the final stereochemistry is set by the chiral centers at C4 and C4′ in the starting bicyclic β-lactam **4**. Thus, the rearrangement of compounds **4** to **5** is a stereospecific process. Had any epimerization occurred the stereochemical outcome would be different from that obtained. Therefore, partial or total epimerization either in starting compounds **4** or final bicyclic γ-lactam **5** must be disregarded.[32]

The novel rearrangement described above formally is the elongation of glyoxal in four carbons bearing four contiguous stereocenters which in turn are formed in a totally stereoselective fashion. The overall yields in compounds **5** are good, and the synthetic methodology is easy allowing for different groups to be attached to the bicyclic ring. To the best of our knowledge the only related process dealing with the synthesis of a fused pyrrolo[3,2-*b*]pyrrole system starting from glyoxal diimines is by tom Dieck[33] who reported the isolation of the aromatic N-substituted parent system upon heating the cyclic silanized derivative of glyoxal diimine **1** (R = Bu^t). Compounds **5** may be regarded as analogs of aminosugars, namely aminoglycaric acids with a idaric acid structure. Naturally occurring and synthetic azasugars and their derivatives are useful inhibitors of enzymes associated with carbohydrate pro-

(32) Homochiral bis-β-lactams related to **4** remain unaltered upon NaOMe/MeOH treatment during longer reaction times than those required in the transformation of **4** to **5**. Alcaide, B.; Pérez-Castells, J.; Sierra, M. A., unpublished results.

(33) tom Dieck, H.; Verfürth, U.; Diblitz, K.; Ehlers, J.; Fendesak, G. *Chem. Ber.* **1989**, *122*, 129.

Scheme IX



cessing.[34] Moreover, 2-oxa-6-aza analogues[35] of compounds **5** have been successfully used in the synthesis of Geissman–Waiss' lactones, which play a key role in the synthesis of indolizine-derived alkaloids.[36]

Due to the fact that other products with structures related to **5** but lacking the amide functionality are also interesting synthetic intermediates or have other biological activities, we explored some reactions on the carbonyl carbon and the possibility of sequential deprotection of the groups attached to nitrogen and oxygen in the bicyclic system. Compound **5b** was chosen as model (Scheme IX). Again, CAN oxidation[25] gave cleanly the N-substituted fused bis-γ-lactam **20**,[37] while catalytic hydrogenolysis (Pd on charcoal) yielded the unprotected diol **21**. On the other hand, lithium aluminum hydride reduction (boiling diethyl ether) formed smoothly 4,8-bis(benzyloxy)-2,6-diazabicyclo[3.3.0]octane, **22**. In addition, when the biphenoxy derivative **5a** was reacted under the same conditions but at 0 °C diol **23** was obtained as a single epimer. The stereochemistry depicted for compound **23** may arise from the attack of the hydride to the less hindered face, anti to the phenoxy groups. Compounds **22** and **23** may be regarded as azaanalogs of isosorbide,[38] a powerful diuretic, and some furo[3,2-*b*]pyrrole derivatives which are active as bronchodilators.[39] The above transformations show the potential of compounds **5** as intermediates in the synthesis of potentially active compounds.

In conclusion, easily available glyoxal diimines are suitable and versatile substrates in the synthesis of β-lactam intermediates. Easy, efficient, and highly stereoselective routes to 4-imino, 4-formyl, and C4,C4′-bis-β-lactams have been developed. Transformation of the above compounds in other products both retaining the β-lactam structure (as shown for the preparation of intermediates in the synthesis of carbapenems) or not (fused bis-γ-lactams) has been achieved by using standard methodology, with good stereocontrol. Studies dealing with the chiral, nonracemic version of the above reaction are currently underway in our laboratories.

Experimental Section

General. Melting points were taken on a Büchi 512 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded, except when otherwise stated, in $CDCl_3$ on a Varian XL-300 instrument at 300 and 75.43 MHz, respectively. Chemical shifts are given in ppm relative to TMS (^{1}H, 0 ppm) or $CDCl_3$ (^{13}C, 76.9 ppm). IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. Mass spectra were recorded on a Varian MAT-711 spectrometer (electron impact). Elemental analyses were performed in the UCM Microanalysis Service (Facultad de Farmacia, UCM, Madrid).

For purification of crude reaction mixtures by flash chromatography, Merck silica gel (230–400 Mesh) was used as the stationary phase.

All commercially available compounds were used without further purification. The following chemicals were prepared according to literature procedures: *N,N′*-di-*p*-anisylethylenediimine,[40] phthalimidylacetyl chloride,[41] and malimidylacetyl chloride.[42] *N,N′*-Bis(4,4′-methoxybenzhydryl)ethylenediimine was prepared from 30% aqueous glyoxal, 4,4′-methoxybenzhydrylamine according to the literature,[43] and catalytic formic acid following the procedure reported by tom Dieck.[44] Thiophenoxyacetyl chloride was prepared from commercially available thiophenoxyacetic acid and $SOCl_2$ following the standard procedure. Toluene and triethylamine were dried over CaH_2 and freshly distilled before use.

General Procedure for the Synthesis of 4-Iminoazetidin-2-ones 2. A solution of acid chloride (2 mmol for **2a,b,e** or 1 mmol for **2c,d,f**) in anhydrous toluene (5 mL) was added dropwise via syringe to a suspension of diimine **1** (1 mmol) in toluene (10 mL) containing triethylamine (3 mmol for **2a,b,e** or 2 mmol for **2c,d,f**) at room temperature under argon. The mixture was stirred until complete disappearance of starting diimine (TLC). Then, the reaction mixture was diluted with $CHCl_3$ and successively washed with aqueous $NaHCO_3$ (saturated solution, 20 mL) and water (2 × 10 mL) and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, residues were purified by crystallization (EtOAc or mixtures of EtOAc/hexanes) or flash chromatography (silica gel, hexanes/EtOAc mixtures) to yield analytically pure compounds **2**. Spectroscopic and analytical data for some representative forms of **2** follow.[45]

***cis*-1-*p*-Anisyl-4-(*N*-*p*-anisylazomethinyl)-3-methylazetidin-2-one (2a).** Reaction time: 30 min. White crystalline solid. Yield: 51%. Mp: 131–133 °C (EtOAc). ^{1}H-NMR: δ 1.36 (d, 3 H, J = 7.8 Hz, CH_3), 3.71 (t, 1 H, J = 6.9 Hz, H3), 3.76 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.76 (t, 1 H, J = 6.3 Hz, H4), 6.84 (d, 2 H, J = 8.7 Hz, Ar), 6.88 (d, 2 H, J = 8.7 Hz, Ar), 7.11 (d, 2 H, J = 8.7 Hz, Ar), 7.36 (d, 2 H, J = 8.7 Hz, Ar), 7.95 (d, 1 H, J = 6.9 Hz, CH=N). ^{13}C-NMR: δ 167.1 (C=O), 159.7 (C=N), 143.3, 122.1, 117.8, 114.4, 57.8 (C4), 55.4 (OCH_3), 48.8 (C3), 10.0 (CH_3). IR (Cl_3CH): ν 1760 (C=O), 1660 (C=N). Anal. Calcd for $C_{19}H_{20}O_3N_2$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.51; H, 6.28; N, 8.71.

***cis*-1-Bis(*p*-anisylmethyl)-4-[*N*-(4,4′-methoxybenzhydryl)azomethinyl]-3-phenoxyazetidin-2-one (2c).** Reaction time: 1 h. Oil. Yield: 65%. ^{1}H-NMR: δ 3.68 (s, 3 H,

(34) Liu, K. K.-C.; Kajimoto, T.; Chen, L.; Zhong, Z.; Ichikawa, Y.; Wong, C.-H. *J. Org. Chem.* **1991**, *56*, 6280 and references cited therein.
(35) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Shiro, M. *J. Org. Chem.* **1989**, *54*, 5211.
(36) For recent reviews see: Robins, D. J. *Nat. Prod. Rep.* **1984**, *1*, 235; **1985**, *2*, 213, 391; **1986**, *3*, 297.
(37) Compound **20** was also obtained from **14b** by reaction with methanolic TMSCl in almost quantitative yield.
(38) *The Merck Index*, 9th ed.; Windholz, M., Ed.; Merck: Rahway, NJ, 1976.
(39) Beecham Group Ltd., Jpn. Kokai Tokkyo Koho 80 55,190; *Chem. Abstr.* **1980**, *93*, 853 (Abstr. 239387p).
(40) (a) Kliegman, J. M.; Barnes, R. K. *J. Org. Chem.* **1970**, *35*, 3140. (b) Kliegman, J. M.; Barnes, R. K. *Tetrahedron* **1970**, *26*, 2555.
(41) Balenovic, K. *J. Org. Chem.* **1951**, *16*, 1308.
(42) Paul, R.; Dittwar, A.; Rusch, Ch. *Ber.* **1967**, *100*, 2757.
(43) Dugat, D.; Just, G.; Sahoo, S. *Can. J. Chem.* **1987**, *65*, 88.
(44) tom Dieck, H.; Dietrich, J. *Chem. Ber.* **1984**, *117*, 694.
(45) Full spectroscopic and analytical data of compounds not included in this Experimental Section are described in the supplementary material.

CH_3O), 3.71 (s, 3 H, CH_3O), 3.77 (s, 3 H, CH_3O), 3.78 (s, 3 H, CH_3O), 4.64 (dd, 1 H, J_1 = 4.8 Hz, J_2 = 7.2 Hz, H4), 5.02 (s, 1 H, CH), 5.38 (d, 1 H, J = 4.8 Hz, H3), 6.07 (s, 1 H, CH), 6.63 (m, 4 H, Ar), 6.74–6.87 (m, 8 H, Ar), 7.08 (m, 6 H, Ar), 7.18 (m, 3 H, Ar), 7.38 (d, 1 H, J = 7.2 Hz, CH=N). ^{13}C-NMR: δ 164.8 (C=O), 160.3 (C=N), 159.1, 159.0, 158.5, 156.8, 134.3, 129.6, 128.6, 122.3, 115.3, 114.1, 113.9, 113.6, 113.5, 80.9 (C3), 75.8 (CH), 61.5 (CH), 59.0 (C4), 55.2 (OCH_3), 55.1 (OCH_3). IR (Cl_3CH): ν 1760 (C=O), 1610 (C=N). Anal. Calcd for $C_{40}H_{38}N_2O_6$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.62; H, 5.84; N, 4.28.

General Procedures for the Synthesis of 4-Formyl-2-azetidinones 3.

One-Pot Procedure. To a vigorously stirred suspension of diimine **1** (1 mmol) and triethylamine (2.2 mmol for **3a–d,i,j,o** or 1.2 mmol for **3e–h,k–n,p–s**) in toluene as solvent (10 mL) was added a solution of the corresponding acid chloride (2 mmol for **3a–d,i,j,o** or 1.1 mmol of **3e–h,k–n,p–s**) in the same solvent (5 mL) dropwise at room temperature under argon. The resulting mixture was stirred until complete reaction (TLC). Then, 5% aqueous HCl (10 mL) was added and the heterogeneous mixture was vigorously stirred for 1.5 h. The organic layer was diluted with toluene (25 mL), successively washed with 5% aqueous HCl (2 × 10 mL), water (10 mL), and brine (10 mL), and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the residues were purified by column chromatography (silica gel, hexanes/EtOAc mixtures) or crystallization to yield pure compounds **3**.

From 4-Imino β-Lactams 2 (Compounds 3h,k,l). A solution of the corresponding 4-imino β-lactam (1 mmol) in chloroform (20 mL) was vigorously stirred with 5% aqueous HCl (10 mL) for 2 h. Pure compounds **3** were obtained as above.

Spectroscopic and analytical data for some representative forms of **3** follow.[45]

***cis*-1-*p*-Anisyl-4-formyl-3-isopropylazetidin-2-one (3d).** Reaction time: 6 h. White crystalline solid. Yield: 80%. Mp: 91–93 °C (EtOAc/hexanes). ^{1}H-NMR: δ 0.94 (d, 3 H, J = 6.6 Hz, CH_3), 1.19 (d, 3 H, J = 6.6 Hz, CH_3), 2.0–2.2 (m, 1 H, CH), 3.34 (dd, 1 H, J_1 = 6.0 Hz, J_2 = 10.3 Hz, H3), 3.76 (s, 3 H, OCH_3), 4.43 (dd, 1 H, J_1 = 4.2 Hz, J_2 = 6.0 Hz, H4), 6.84 (d, 2 H, J = 9.3 Hz, Ar), 7.21 (d, 2 H, J = 9.3 Hz, Ar), 9.88 (d, 1 H, J = 4.2 Hz, CH=O). ^{13}C-NMR: δ 199.9 (CH=O), 165.1 (NC=O), 156.3, 131.0, 117.4, 114.4, 61.5, 60.3 (C3 and C4), 55.3 (OCH_3), 25.7 (CH), 21.4 (CH_3), 20.5 (CH_3). IR (KBr): ν 1755 (NC=O), 1735 (CH=O). MS: m/e 247 (M^+), 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.

***cis*-1-*p*-Anisyl-4-formyl-3-thiophenoxyazetidin-2-one (3i).** Reaction time: 35 min. White powdered solid. Yield: 80%. Mp: 153–154 °C (EtOAc/hexanes). ^{1}H-NMR: δ 3.78 (s, 3 H, OCH_3), 4.62 (t, 1 H, J = 5 Hz, H4), 4.90 (d, 1 H, J = 5.4 Hz, H3), 6.85–7.47 (m, 9 H, Ar), 9.73 (d, 1 H, J = 3.9 Hz, CH=O). ^{13}-NMR: δ 199.6 (CH=O), 161.0 (NC=O), 156.8, 132.5, 131.3, 130.5, 129.4, 128.1, 117.9, 114.5, 61.7, 56.6 (C3 and C4), 55.4 (OCH_3). IR (KBr): ν 1750 (NC=O), 1710 (CH=O). MS: m/e 313 (M^+), 242, 164, 149 (parent), 134, 121, 110, 91, 86, 77. Anal. Calcd for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.82; N, 4.47. Found: C, 65.10; H, 4.88; N, 4.59.

General Procedure for the Synthesis of 4-Carboxy β-Lactams 9. To a stirred solution of the corresponding 4-formyl β-lactam **3** (1 mmol) in acetone (30 mL) cooled to 0 °C was added dropwise chromic acid solution (Jones' reagent). The mixture was stirred until disappearance of starting material (TLC). Then, methanol was added (1 mL), the reaction crude filtered through Celite, and the solvent evaporated under reduced pressure. The residue was then diluted with chloroform, washed successively with water and brine, and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, pure compounds **9** were obtained upon crystallization from EtOAc/hexanes mixtures.

***cis*-1-*p*-Anisyl-4-carboxy-3-ethylazetidin-2-one (9a).** Reaction time: 30 min. White powdered solid. Yield: 95%. Mp: 162–164 °C (EtOAc/hexanes) (lit.[20d] mp 166 °C). ^{1}H-NMR: δ 1.12 (t, 3 H, J = 7.5 Hz, CH_3), 1.62–1.98 (m, 2 H, CH_2), 3.54 (dd, 1 H, J_1 = 6.0 Hz, J_2 = 10.0 Hz, H3), 3.78 (s, 3 H, OCH_3), 4.63 (d, 1 H, J = 6.0 Hz, H4), 6.86 (d, 2 H, J = 9.0 Hz, Ar), 7.25 (d, 2 H, J = 9.0 Hz, Ar). ^{13}C-NMR: δ 170.6 (CO_2H), 165.9 (NC=O), 155.6, 131.2, 117.7, 114.4, 55.3, 54.9, 53.2, 18.7 (CH_2), 11.8 (CH_3). IR (KBr): ν 1740 (NC=O), 1710 (CO_2H). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.06; N, 5.62. Found: C, 62.71; H, 6.24; N, 5.77.

***cis*-1-*p*-Anisyl-4-carboxy-3-isopropylazetidin-2-one (9b).** Reaction time: 4 h. White powdered solid. Yield: 90%. Mp: 190–192 °C (EtOAc/hexanes) (lit.[20d] mp 186 °C). ^{1}H-NMR: δ 1.15 (d, 3 H, J = 6.7 Hz, CH_3), 1.25 (d, 3 H, J = 6.7 Hz, CH_3), 2.17 (m, 1 H, CH), 3.33 (dd, 1 H, J_1 = 6.0 Hz, J_2 = 10.6 Hz, H3), 3.77 (s, 3 H, OCH_3), 4.57 (d, 1 H, J = 6.0 Hz, H4), 5.64 (s, 1 H, OH), 7.24 (d, 2 H, J = 9.0 Hz, Ar), 7.26 (d, 2 H, J = 9.0 Hz, Ar). ^{13}C-NMR: δ 171.4 (CO_2H), 165.7 (NC=O), 156.3, 130.9, 117.9, 114.4, 55.5, 55.1, 54.5, 30.9 (CH), 19.0 (CH_3), 11.8 (CH_3). IR (KBr): ν 1740 (NC=O), 1710 (CO_2H). MS: m/e 263 (M^+), 221, 195, 191, 190, 179, 176, 149, 134 (parent), 123, 109, 77. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.77; H, 6.55; N, 5.27.

General Procedure for the Synthesis of 1-*p*-Anisyl-4-acetoxyazetidin-2-ones 10a,b. To a stirred suspension of the corresponding acid (1 mmol) in acetonitrile (25 mL) was added $Pb(OAc)_4$ (2.2 mmol) and a small amount of $Cu(OAc)_2$. The resulting suspension was heated at 80 °C under argon for 1.5 h. Then, the mixture was filtered through Celite, which was washed with EtOAc. After the evaporation of the solvent under reduced pressure, the crude product was purified by chromatography (silica gel, hexanes/EtOAc (1:1)).

4-Acetoxy-1-*p*-anisyl-3-ethylazetidin-2-one (10a). Obtained as a trans–cis (90:10) mixture of isomers. Pure trans isomer was obtained after purification. White powdered solid. Yield: 73%. Mp: 71–72 °C (EtOAc/hexanes). ^{1}H-NMR: δ 1.09 (t, 3 H, J = 7.5 Hz, CH_3), 1.83–1.93 (m, 2 H, CH_2), 2.13 (s, 3 H, CH_3), 3.17 (t, 1 H, J = 7.2 Hz, H3), 3.78 (s, 3 H, OCH_3), 6.19 (s, 1 H, H4), 6.87 (d, 2 H, J = 9.0 Hz, Ar), 7.34 (d, 2 H, J = 9.0 Hz, Ar). ^{13}C-NMR: δ 170.2 (OC=O), 165.3 (NC=O), 156.6, 129.7, 118.5, 114.4, 79.8 (C4), 59.8 (C3), 55.4 (OCH_3), 20.9, 20.1, 11.0 (CH_3). IR (KBr): ν 1755 (NC=O), 1730 (OC=O). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.91; H, 6.61; N, 5.24.

^{1}H-NMR cis isomer (from spectrum mixture trans and cis): δ 3.37–3.45 (m, 1 H, H3), 6.59 (d, 1 H, J = 4.5 Hz, H4).

4-Acetoxy-1-*p*-anisyl-3-isopropylazetidin-2-one (10b). Obtained as a trans–cis (90:10) mixture of isomers. Pure trans isomer was obtained after purification. White powdered solid. Yield: 78%. Mp: 81–82 °C (EtOAc/hexanes). ^{1}H-NMR: δ 1.08 (d, 3 H, J = 6.6 Hz, CH_3), 1.12 (d, 3 H, J = 6.6 Hz, CH_3), 2.02–2.22 (m, 4 H, CH and CH_3CO), 3.07 (d, 1 H, J = 7.4 Hz, H3), 3.79 (s, 3 H, OCH_3), 6.36 (s, 1 H, H4), 6.88 (d, 2 H, J = 9.0 Hz, Ar), 7.34 (d, 2 H, J = 9.0 Hz, Ar). ^{13}C-NMR: δ 170.1 (OC=O), 164.7 (NC=O), 156.5, 129.5, 118.4, 114.3, 77.9 (C3), 64.7 (C4), 55.3 (OCH_3), 26.7 (CH), 20.9 (CH_3), 20.1 (CH_3), 19.5 (CH_3). IR (KBr): ν 1765, 1750. MS: m/e 277 (M^+), 235, 217, 193, 190, 175, 149 (parent), 134, 123, 108. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.45. Found: C, 64.89; H, 6.95; N, 5.09.

^{1}H-NMR cis isomer (from spectrum mixture trans and cis): δ 3.18 (dd, 1 H, J = 4.5, 10.1 Hz, H3), 6.72 (d, 1 H, J = 4.5 Hz, H4).

General Procedure for the Isomerization of β-Lactams 3r and 3s. To a solution of the corresponding β-lactam (1 mmol) in benzene (30 mL) was added DBU (2 drops), and the reaction mixture was refluxed under argon for 6 h. Then, it was successively washed with 5% aqueous HCl, 10% aqueous $NaHCO_3$, water, and brine and dried ($MgSO_4$). Removal of benzene under reduced pressure afforded compounds **11a,b** which were purified by chromatography (silica gel, hexanes/EtOAc (1:1)).

***cis*-1-*p*-Anisyl-4-formyl-3-isopropylideneazetidin-2-one (11a).** White crystalline solid. Yield: 90%. Mp: 121–123 °C (EtOAc/hexanes). ^{1}H-NMR: δ 1.78 (s, 3 H, CH_3), 2.18 (s, 3 H, CH_3), 3.78 (s, 3 H, OCH_3), 4.70 (d, 1 H, J = 5.4 Hz, H4), 6.86 (d, 2 H, J = 9.0 Hz, Ar), 7.27 (d, 2 H, J = 9.0 Hz, Ar), 9.48 (d, 1 H, J = 5.4 Hz, CH=O). ^{13}C-NMR: δ 199.6 (CH=O), 156.3 (NC=O), 142.9, 131.8, 127.0, 116.9, 114.6, 65.2 (C4), 55.4 (OCH_3), 20.8 (CH_3), 20.4 (CH_3). IR (KBr): ν 1750 (NC=O), 1730 (CH=O). MS: m/e 245 (M^+), 216 (parent), 188, 173, 149, 134, 107, 92, 83, 77. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.50; H, 6.25; N, 5.59.

1-*p*-Anisyl-3-ethylidene-4-formylazetidin-2-one (11b). Pale yellow oil. Yield: 96% as a mixture of *Z*:*E* isomers (40:60). Crystallization from EtOAc/hexanes gave pure *E* isomer. Yield: 45%. Mp: 121–123 °C. ^{1}H-NMR: δ 1.82 (d, 3 H, J = 7.0 Hz,

CH_3), 3.78 (s, 3 H, OCH_3), 4.81 (d, 1 H, J = 5.0 Hz, H4), 6.53 (q, 1 H, J = 7.0 Hz, =CH), 6.88 (d, 2 H, J = 9.0 Hz, Ar), 7.28 (d, 2 H, J = 9.0 Hz, Ar), 9.56 (d, 1 H, J = 5.0 Hz, CH=O). ^{13}C-NMR: δ 198.1 (CH=O), 159.5 (NC=O), 156.6, 133.9, 131.5, 127.9 (CH=), 117.3, 114.7, 65.3 (C4), 55.5 (OCH_3), 13.9 (CH_3). IR (KBr): ν 1755 (NC=O), 1730 (CH=O). MS: m/e 231 (M^+), 202 (parent). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N. 6.06. Found: C, 67.33; H, 5.69; N, 6.25.

^{1}H-NMR Z isomer (from spectrum mixture Z and E): δ 2.13 (d, 3 H, J = 7.0 Hz, CH_3), 3.78 (s, 3 H, OCH_3), 4.65 (d, 1 H, J = 5.0 Hz, H4), 5.89 (q, 1 H, J = 7.0 Hz, =CH), 6.88 (d, 2 H, J = 9.0 Hz, Ar), 7.28 (d, 2 H, J = 9.0 Hz, Ar), 9.51 (d, 1 H, J = 5.0 Hz, CH=O).

General Procedure for the Synthesis of 4-(Hydroxymethyl)azetidin-2-ones 12. To a stirred solution of 4-formyl β-lactam (1 mmol) in methanol (10 mL) was added $NaBH_4$ (2 mmol) in small portions. The resulting mixture was stirred until complete reaction (TLC). After evaporation of the solvent under reduced pressure, the residue was washed with water and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and evaporated yielding the corresponding compound 12 which was recrystallized from the EtOAc/hexanes mixture.

***cis*-1-*p*-Anisyl-3-ethyl-4-(hydroxymethyl)azetidin-2-one (12a).** Reaction time: 10 min. White powdered solid. Yield: 95%. Mp: 102–104 °C (EtOAc/hexanes). ^{1}H-NMR: δ 1.14 (t, 3 H, J = 7.5 Hz, CH_3), 1.77 (m, 3 H, CH_2 and OH), 3.75 (ddd, 1 H, J = 7.5, 7.2, 5.7 Hz, H3), 3.78 (s, 3 H, OCH_3), 3.81 (dd, 1 H, J = 12.0, 5.4 Hz, CH_2OH), 4.21 (q, 1 H, J = 5.4 Hz, H4), 4.55 (dd, 1 H, J = 12.0, 5.4 Hz, CH_2OH), 6.85 (d, 2 H, J = 9.0 Hz, Ar), 7.43 (d, 2 H, J = 9.0 Hz, Ar). ^{13}C-NMR: δ 168.2 (NC=O), 155.8, 131.0, 118.6, 114.1, 60.2, 55.9, 55.3, 18.0, 12.7. IR (KBr): ν 3400 (OH), 1700 (NC=O). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.50; H, 7.11; N, 5.89.

***cis*-1-*p*-Anisyl-4-(hydroxymethyl)-3-isopropylazetidin-2-one (12b).** Reaction time: 10 min. White crystalline solid. Yield: 95%. Mp: 117–119 °C (EtOAc/hexanes). ^{1}H-NMR: δ 0.98 (d, 3 H, J = 6.6 Hz, CH_3), 1.21 (d, 3 H, J = 6.6 Hz, CH_3), 2.26 (m, 1 H, CH), 3.04 (dd, 1 H, J = 10.8, 5.7 Hz, H3), 3.77 (s, 3 H, OCH_3), 3.94 (dd, 1 H, J = 12.0, 4.2 Hz, CH_2OH), 4.18 (m, 2 H, CH_2OH and H4), 6.83 (d, 2 H, J = 9.0 Hz, Ar), 7.40 (d, 2 H, J = 9.0 Hz, Ar). ^{13}C-NMR: δ 167.4 (NC=O), 155.9, 130.9, 118.7, 114.2, 60.0, 58.5, 56.4, 55.3, 25.3, 22.5, 20.9. IR (KBr): ν 3410 (OH), 1720 (NC=O). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.58; H, 7.63; N, 5.71.

1-*p*-Anisyl-4-(hydroxymethyl)-3-thiophenoxyazetidin-2-one (12c). Reaction time: 30 min. Obtained as a cis–trans (10:90) mixture of isomers. Crystallization from EtOAc/hexanes gave pure trans isomer. White solid. Yield: 82%. Mp: 79–80 °C (EtOAc/hexanes). ^{1}H-NMR: δ 3.69 (s, 3 H, OCH_3), 3.84 (dd, 1 H, J = 12.3, 9.0 Hz, CH_2OH), 3.90 (m, 1 H, H4), 4.03 (dd, 1 H, J = 12.3, 2.7 Hz, CH_2OH), 4.35 (d, 1 H, J = 2.4 Hz, H3), 6.77 (d, 2 H, J = 9.0 Hz, Ar), 7.30 (m, 7 H, Ar). ^{13}C-NMR: δ 163.4 (NC=O), 156.4, 132.3, 131.9, 130.0, 129.0, 127.9, 119.0, 114.3, 60.8, 59.3, 55.3, 52.7. IR (KBr): ν 3400 (OH), 1715 (NC=O). Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44. Found: C, 64.85; H, 5.38; N, 4.65.

^{1}H-NMR cis isomer (from spectrum mixture cis and trans): δ 4.66 (d, 1 H, J = 5.4 Hz, H3).

General Procedures for the Synthesis of Bis-2-azetidinones.

From Diimine 1 (Compounds 4d–f,j,k,m–o). The method was identical to that used for the preparation of 4-imino-2-azetidinones 2 (1 mmol of diimine, 2 mmol of acid chloride, and 3 mmol of Et_3N). Compounds 4, which precipitate from the crude reaction mixture, were purified by crystallization (EtOAc/hexanes mixtures) to yield pure compounds 4.

From 4-Imino-2-azetidinones 2 (Compounds 4a–c,g–i,l). Acid chloride (2 mmol) in anhydrous toluene (5 mL) was added dropwise via syringe to a solution of compound 2 (1 mmol) in toluene (10 mL) containing Et_3N (3 mmol) at room temperature under argon. The resulting mixture was stirred until complete desaparition of starting material 2 (TLC). Then the crude reaction mixture was diluted with Cl_3CH, washed with aqueous $NaHCO_3$ (saturated solution, 20 mL) and water (3 × 10 mL), and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the residues were purified by crystallization (EtOAc/hexanes mixtures) to yield analytically pure compounds 4.

Spectroscopic and analytical data for some representative compounds 4 follow.[45]

(3*S,4*S**,3′*R**,4′*S**)-1-*p*-Anisyl-4-(1′-*p*-anisyl-2′-oxo-3′-phenoxyazetidin-4′-yl)-3-methylazetidin-2-one (4a).** Reaction time: 30 min. White powdered solid. Yield: 90%. Mp: 239–241 °C. ^{1}H-NMR: δ 1.43 (d, 3 H, J = 7.8 Hz, CH_3), 3.65 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3), 3.72–3.82 (m, 1 H, H3′), 4.64–4.75 (m, 2 H, H4 and H4′), 5.50 (d, 1 H, J = 4.8 Hz, H3), 6.45 (d, 2 H, J = 9.0 Hz, Ar), 6.46 (d, 2 H, J = 9.0 Hz, Ar), 6.92–7.43 (m, 9 H, Ar). ^{13}C-NMR: δ 168.2 (NC=O), 163.4 (NC=O), 157.3, 156.7, 156.3, 130.3, 129.7, 123.0, 119.8, 119.5, 116.2, 113.7, 80.3 (C3), 58.1 (C4), 55.8 (C4′), 55.3 (2×OCH_3), 47.3 (C3′), 9.7 (CH_3). IR (Cl_3CH): ν 1760 (NC=O). Mass spectrum: m/z 458 ($M^{+\bullet}$, parent), 362, 157, 131. Anal. Calcd for $C_{27}H_{26}N_2O_5$: C, 70.73; H, 5.71; N, 6.11. Found: C, 70.49; H, 5.81; N. 6.09.

(3*S,4*R**,3′*R**,4′*S**)-4,4′-Bis[1-(*p*,*p*′-dimethoxybenzhydryl)-3-phenoxyazetidin-2-one] (4f).** Reaction time: 2 h. White powdered solid. Yield: 64%. Mp: 159–161 °C. ^{1}H-NMR: δ 3.76 (s, 6 H, CH_3O), 3.77 (s, 6 H, CH_3O), 4.46 (m, 2 H, H4H4′), 5.29 (m, 4 H, H3H3′, CH), 6.79 (m, 8 H), 6.94 (m, 4 H), 7.01 (m, 6 H), 7.14 (m, 8 H). ^{13}C-NMR: δ 166.6 (NC=O), 159.1, 159.0, 157.4, 132.0, 130.3, 129.6, 129.5, 129.1, 122.6, 116.4, 114.0, 113.8, 80.7 (C3), 63.8 (CH), 58.9 (C4), 55.2 (CH_3O). IR (Cl_3CH): ν 1755 (NC=O). Anal. Calcd for $C_{48}H_{44}N_2O_8$: C, 74.21; H, 5.71; N, 3.61. Found: C, 73.99; H, 5.74; N, 3.53.

(3*S,4*R**,3′*R**,4′*S**)-4,4′-Bis[1-*p*-Anisyl-3-(benzyloxy)azetidin-2-one] (4j).** Reaction time: 2 h. White powdered solid. Yield: 80%. Mp: 166–168 °C. ^{1}H-NMR: δ 3.64 (s, 6 H, 2 × OCH_3), 4.69 (dd, 2 H, J_1 = 1.2 Hz, J_2 = 3.3 Hz, H4H4′), 4.87 (dd, 2 H, J_1 = 1.8 Hz, J_2 = 3.3 Hz, H3H3′), 4.86 (dd AB, 4 H, J_{AB} = 11.4 Hz, 2 × CH_2), 6.49 (d, 4 H, J = 9.0 Hz, Ar), 6.99 (d, 4 H, J = 9.0 Hz, Ar), 7.30–7.40 (m, 10 H, Ar). ^{13}C-NMR: δ 164.5 (NC=O), 156.3, 136.7, 130.2, 128.5, 128.1, 127.9, 119.1, 113.6, 81.2 (C3), 73.4 (CH_2), 56.6 (C4), 55.2 (CH_3O). IR (Cl_3CH): ν 1740 (NC=O). Anal. Calcd for $C_{34}H_{32}N_2O_6$: C, 72.32; H, 5.71; N, 4.96. Found: C, 72.38; H, 5.79; N, 4.87.

(3*S,4*R**,3′*R**,4′*S**)-1-*p*-Anisyl-4-(1′-*p*-anisyl-2′-oxo-3′-phthalimidylazetidin-4′-yl)-3-thiophenoxyazetidin-2-one (4l).** Reaction time: 1 h. White powdered solid. Yield: 62%. Mp: 229–231 °C. ^{1}H-NMR: δ 3.85 (s, 6 H, 2 × CH_3O), 4.47 (d, 1 H, J = 6.0 Hz, H3′), 4.75 (dd, 1 H, J_1 = 6.0 Hz, J_2 = 9.6 Hz, H4′), 5.14 (dd, 1 H, J_1 = 5.7 Hz, J_2 = 9.6 Hz, H4), 5.90 (d, 1 H, J = 5.7 Hz, H3), 6.44–7.90 (m, 17 H, Ar). ^{13}C-NMR: δ 163.9 (NC=O), 161.4 (CONCO), 156.4, 134.7, 133.1, 131.3, 130.7, 129.7, 129.1, 123.8, 119.7, 119.4, 113.7, 113.5, 60.4 (C3), 56.2 (C3′), 55.6 (C4′), 55.2 (CH_3O), 54.4 (C4). IR (Cl_3CH): ν 1750 (NC=O), 1715 (CONCO). Anal. Calcd for $C_{34}H_{27}N_3O_6S$: C, 67.43; H, 4.49; N, 6.94; S, 5.29. Found: C, 67.14; H, 4.50; N, 6.76; S, 5.40.

General Procedure for the Synthesis of 2,6-Di-*p*-anisyl-2,6-diazabicyclo[3.3.0]octane-3,7-diones 5. A solution of sodium methoxide (4 mmol) in absolute methanol (10 mL) was added dropwise via syringe to a solution of bis(azetidinone) 4 (1 mmol) in the same solvent (10 mL). The mixture was stirred under argon until complete disappearance of starting bis(azetidinone) (TLC). Then, the excess sodium methoxide 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 ethyl acetate and dried ($MgSO_4$). After filtration and evaporation of the solvent, residues were purified by flash chromatography (silica gel, hexanes/EtOAc mixtures) to yield pure compounds 5.

(1*R,4*S**,5*R**,8*S**)-2,6-Di-*p*-anisyl-4,8-diphenoxy-2,6-diazabicyclo[3.3.0]octane-3,7-dione (5a).** Reaction time: 5 h. White solid. Yield: 80%. Mp: 212–214 °C. ^{1}H-NMR: δ 3.80 (s, 6 H, CH_3O), 4.87 (s, 2 H, H4H8), 5.03 (s, 2 H, H1H5), 6.88–7.46 (m, 18 H, Ar). ^{13}C-NMR: δ 168.0 (NC=O), 158.4, 157.2, 129.5, 128.7, 124.7, 122.8, 116.6, 114.7, 78.4 (C4C8), 60.7 (C1C5), 55.5 (CH_3O). IR (Cl_3CH): ν 1690 (NC=O). Anal. Calcd for $C_{32}H_{28}N_2O_4$: C, 76.17; H, 5.59; N, 5.55. Found: C, 76.19; H, 5.39; N, 5.65.

(1*R,4*S**,5*R**,8*S**)-2,6-Di-*p*-anisyl-4,8-bis(benzyloxy)-2,6-diazabicyclo[3.3.0]octane-3,7-dione (5b).** Reaction time: 10 h. White solid. Yield: 87%. Mp: 194–196 °C. ^{1}H-NMR: δ 3.84 (s, 6 H, 2 × OCH_3), 4.04 (t, 2 H, J = 1.2 Hz, H4H8), 4.80

(t, 2 H, J = 1.2 Hz, H1H5), 4.80 (AB, 4 H, J_{AB} = 11.4 Hz, CH_2), 6.91 (d, 4 H, J = 9.0 Hz, Ar), 7.29 (m, 10 H, Ar), 7.46 (d, 4 H, J = 9.0 Hz, Ar). ^{13}C-NMR: δ 169.3 (NC=O), 157.8, 136.6, 129.2, 128.5, 128.1, 123.8, 114.8, 78.0 (C4C8), 72.8 (CH_2), 60.9 (C1C5), 55.5 (CH_3O). IR (Cl_3CH): ν 1710, 1690 (C=O). Anal. Calcd for $C_{34}H_{32}N_2O_6$: C, 72.32; H, 5.71; N. 4.96. Found: C, 72.31; H, 5.60; N, 4.89.

(1*S,4*S**,5*R**,8*S**)-2,6-Di-*p*-anisyl-8-methyl-4-phenoxy-2,6-diazabicyclo[3.3.0]octane-2,7-dione (5c).** Reaction time: 3 h. White solid. Yield: 70%. Mp: 169–171 °C. ^{1}H-NMR: δ 1.32 (d, 3 H, CH_3, J = 6.8 Hz), 2.71 (dq, 1 H, J_1 = 6.8 Hz, J_2 = 1.5 Hz, H8), 3.80 (s, 3 H, CH_3O), 3.82 (s, 3 H, CH_3O), 4.70 (dd, 1 H, J_1 = 1.5 Hz, J_2 = 6.6 Hz, H1), 4.81 (s, 1 H, H4), 4.83 (d, 1 H, J = 6.6 Hz, H5), 6.87–6.98 (m, 6 H), 7.16–7.24 (m, 3 H), 7.36 (t, 4 H). ^{13}C-NMR: δ 174.2 (NC=O), 167.7 (NC=O), 158.2, 157.2, 129.5, 125.1, 124.7, 122.5, 116.5, 114.6, 78.1 (C4), 61.7 (C5), 60.5 (C1), 55.5 (CH_3O), 42.0 (C8), 15.8 (CH_3). IR (Cl_3CH): ν 1700 (NC=O). Anal. Calcd for $C_{27}H_{26}N_2O_5$: C, 70.73; H, 5.71; N, 6.11. Found: C, 70.74; H, 5.76; N, 5.98.

(1*R,4*S**,5*R**,8*S**)-2,6-Di-*p*-anisyl-8-chloro-4-phenoxy-2,6-diazabicyclo[3.3.0]octane-3,7-dione (5d).** Reaction time: 3 h. White solid. Yield: 77%. Mp: 148–150 °C. ^{1}H-NMR: δ 3.83 (s, 3 H, CH_3O), 3.84 (s, 3 H, CH_3O), 4.36 (s, 1 H, H8), 4.80 (s, 1 H, H4), 4.98 (dd, 1 H, J_1 = 0.6 Hz, J_2 = 6.3 Hz, H5), 5.10 (dd, 1 H, J_1 = 0.9 Hz, J_2 = 6.3 Hz, H1), 6.87–7.50 (m, 13 H, Ar). ^{13}C-NMR: δ 167.4 (NC=O), 167.1 (NC=O), 158.8, 158.4, 156.8, 129.6, 128.0, 125.4, 124.3, 122.9, 116.4, 115.1, 114.8, 77.3 (C4), 63.0 (C5), 60.4 (C1), 55.5 (CH_3O), 54.5 (C8). IR (Cl_3CH): ν 1710 (NC=O). Anal. Calcd for $C_{26}H_{23}N_2O_5Cl$: C, 65.20; H, 4.84; N, 5.85; Cl, 7.40. Found: C, 65.00; H, 4.81; N, 5.78; Cl, 7.20.

General Procedure for the Dearylation with Ceric(IV) Ammonium Nitrate (CAN). A solution of CAN (6 mmol) in water (10 mL) was added dropwise to a solution of the corresponding starting compound (1 mmol) in acetonitrile (30 mL) at 0 °C. The reaction was stirred for 1–3 h. Then, the mixture was diluted with 50 mL of water and extracted with EtOAc (3 × 30 mL). The organic layers were washed with aqueous $NaHCO_3$ (5%, 30 mL) and with 30-mL portions of $NaHSO_3$ (10%) until total decoloration of the aqueous layer. Then, it was washed once again with aqueous $NaHCO_3$ (5%, 30 mL) and brine (30 mL) and dried ($MgSO_4$). After filtration and evaporation of the solvent, the product was purified by chromatography (silica gel, hexanes/EtOAc mixtures) (**10c**, **10d**) or washed with ether to obtain after filtration pure compounds (**14a**, **14b**, **15**).

***trans*-4-Acetoxy-3-ethylazetidin-2-one (10c).** From **10a**. Reaction time: 4 h. Pale yellow oil. Yield: 87%. ^{1}H-NMR: δ 1.05 (t, 3 H, J = 7.5 Hz, CH_3), 1.65–1.90 (m, 2 H, CH_2), 2.11 (s, 3 H, CH_3CO), 3.14 (t, 1 H, J = 7.5 Hz, H3), 5.55 (s, 1 H, H4), 7.15 (s, 1 H, NH).

***trans*-4-Acetoxy-3-isopropylazetidin-2-one (10d).** From **10b**. Reaction time: 30 min. Pale yellow oil. Yield: 80%. ^{1}H-NMR: δ 1.03 (d, 3 H, J = 6.6 Hz, CH_3), 1.08 (d, 3 H, J = 6.6 Hz, CH_3), 2.04 (m, 1 H, CH), 2.11 (s, 3 H, CH_3CO), 3.00 (d, 1 H, J = 7.5 Hz, H3), 5.60 (s, 1 H, H4), 6.88 (s, 1 H, NH).

(3*S,4*R**,3′*R**,4′*S**)-4,4′-Bis(3-phenoxyazetidin-2-one) (14a).** From **4e**. Reaction time: 3 h. White powdered solid. Yield: 56%. Mp: 240 °C dec. ^{1}H-NMR (DMSO-d_6): δ 3.99 (d, 2 H, J = 4.2 Hz, H3H3′), 5.48 (t, 2 H, J = 2.4 Hz, H4H4′), 6.94–7.31 (m, 10 H, Ar), 8.27 (s, 2 H, 2 × NH). ^{13}C-NMR (DMSO-d_6): δ 163.5 (NC=O), 154.6, 127.0, 119.4, 112.8, 78.2 (C3), 49.7 (C4). IR (Cl_3CH): ν 3300 (NH), 1765, 1735 (C=O). Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.40; H, 4.88; N, 8.41.

(3*S*′,4*R,3′*R**,4′*S**)-4,4′-Bis[3-(benzyloxy)azetidin-2-one] (14b).** From **4j**. Reaction time: 1 h. White powdered solid. Yield: 70%. Mp: >250 °C. ^{1}H-NMR: δ 3.82 (d, 2 H, J = 4.5 Hz, H3H3′), 4.76 (AB, 2 H, J_{AB} = 11.4 Hz, CH_2), 4.77 (dd, 2 H, J_1 = 2.1 Hz, J_2 = 4.5 Hz, H4H4′), 6.29 (s, 2 H, 2 × NH), 7.30–7.40 (m, 10 H, Ar). ^{13}C-NMR (DMSO-d_6): δ 167.5 (NC=O), 137.4, 128.3, 82.4 (C3), 72.1 (CH_2), 52.9 (C4). IR (Cl_3CH): ν 3300 (NH), 1750 (C=O). Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.00; H, 5.58; N, 7.90.

(1*R,4*S**,5*R**,8*S**)-4,8-Bis(benzyloxy)-2,6-diazabicyclo-[3.3.0]octane-3,7-dione (20).** From **5b**. Reaction time: 1 h. White solid. Yield: 89%. Mp: 231 °C dec. ^{1}H-NMR: δ 3.84 (t, 2 H, J = 1.5 Hz, H4H8), 4.16 (s, 2 H, H1H5), 4.82, (AB, 4 H, J_{AB} = 11.7 Hz, 2 × CH_2), 6.61 (s, 2 H, 2 × NH), 7.30–7.40 (m, 10 H, Ar). ^{13}C-NMR: δ 173.2 (NC=O), 136.8, 128.6, 128.1, 128.0, 79.3 (C4C8), 73.0 (CH_2), 57.9 (C1C5). IR (Cl_3CH): ν 3210 (NH), 1765 (C=O). Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 67.94; H, 5.59; N, 7.91.

Table III. Crystal and Refinement Data for Compound 5a

formula	$C_{32}N_2O_6H_{28}$
M_r	536.6
crystal system	monoclinic
space group	$P2_1/n$
a, Å	11.662 (5)
b, Å	8.421 (4)
c, Å	27.475 (9)
β, (°)	102.00 (4)
V, Å^3	2639 (2)
Z	4
F(000)	1128
ρ (calcd), g cm^{-3}	1.35
temp, °C	22
μ, cm^{-1}	0.88
cryst. dimens., mm	0.08 × 0.12 × 0.03
diffractometer	Enraf-Nonius CAD4
radiation	graphite-monochromated Mo Kα (λ = 0.71069 Å)
scan technique	Ω/2θ
data collected	(−13,0,0) to (13,10,32)
rflns collected	5199
unique data	4691
unique data (I) ≥ 2σ(I)	2163
RF, %	6.5
R_wF, %	7.5
avg shift/error	0.09

General Procedure for the Hydrogenation of Compounds 4j and 5b. To a solution of starting compound (1 mmol) in methanol (10 mL) was added 10% Pd (C) and the mixture hydrogenated in a Parr apparatus at 40 psi until complete disappearance of starting material (TLC). The mixture was filtered through Celite, and the evaporation of the solvent gave the corresponding pure product.

(3*S,4*R**,3′*R**,4′*S**)-4,4′-Bis(1-*p*-anisyl-3-hydroxyazetidin-2-one) (13).** Reaction time: 3 h. White powdered solid. Yield: 92%. Mp: 252 °C dec (EtOH). ^{1}H-NMR (DMSO-d_6): δ 3.59 (s, 6 H, CH_3O), 4.61 (s, 2 H, H3H3′), 5.08 (s, 2 H, H4H4′), 6.57 (m, 6 H), 7.07 (d, 4 H). ^{13}C-NMR (DMSO-d_6: δ 164.7 (C=O), 153.4, 128.9, 116.6, 111.5, 73.2 (C3C3′), 55.0, 53.1 (C4C4′ and CH_3O). IR (KBr): ν 3500, 3400, 3300, 1720 (C=O). Anal. Calcd for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29. Found: C, 62.40; H, 5.21; N, 7.11.

(1*R,4*S**,5*R*,8*S*)-2,6-Di-*p*-anisyl-4,8-dihydroxy-2,6-diazabicyclo[3.3.0]octane-3,7-dione (21).** Reaction time: 3 h. Oil. Yield: 88%. ^{1}H-NMR (DMSO-d_6): δ 3.79 (s, 6 H, 2 × CH_3O), 4.36 (s, 2 H, H4H8), 4.64 (s, 2 H, H1H5), 6.35 (br s, 2 H, OH), 6.97 (d, 4 H), 7.75 (d, 4 H). ^{13}C-NMR: δ 169.5 (C=O), 154.7, 128.9, 121.4, 111.9, 72.0 (C4C8), 59.9 (C1C5), 53.5 (CH_3O). IR (KBr): ν 3460, 3360, 1700 (C=O). Anal. Calcd for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29. Found: C, 62.30; H, 5.12; N, 7.09.

(1*R,4*R**,5*R**,8*R**)-2,6-Di-*p*-anisyl-4,8-bis(benzyloxy)-2,6-diazabicyclo[3.3.0]octane (22).** To a suspension of $LiAlH_4$ (4 mmol) in diethyl ether (3 mL) at 0 °C under argon was added a solution of product **5b** (1 mmol) in the same solvent (3 mL). After 1 h the reaction was heated at reflux until the first reduction product disappeared (2 h). Then, it was hydrolyzed with 2–3 drops of water and dried ($MgSO_4$) and the solvent evaporated to give pure compound **22** (460 mg, 90%) as a white powdered solid. Mp: 176 °C dec. ^{1}H-NMR: δ 3.32 (B dd, 2 H, J_1 = 3.9 Hz, J_{AB} = 10.8 Hz), 3.39 (A, 2 H, J_{AB} = 10.8 Hz), 3.75 (s, 6 H, CH_3O), 4.11 (d, 2 H, J = 3.9 Hz, H4H8), 4.52 (s, 2 H, H1H5), 4.58 (AB, 4 H, J_{AB} = 12.0 Hz), 6.49 (d, 4 H), 6.76 (d, 4 H), 7.35 (m, 10 H). ^{13}C-NMR: δ 151.2, 140.7, 137.9, 128.4, 127.9, 114.9, 113.3, 78.1 (C4C8), 71.2 (CH_2), 67.0 (C1C5), 55.8 (CH_3O), 53.1 (C3C7). IR (KBr): ν 1510, 1240. Anal. Calcd for $C_{34}H_{36}N_2O_4$: C, 76.09; H, 6.76; N, 5.22. Found: C, 76.30; H, 6.88; N, 5.32.

(1*R,3*S**,4*S**,5*R**,7*S**,8*S**)-2,6-Di-*p*-anisyl-3,7-dihydroxy-4,8-diphenoxy-2,6-diazobicyclo[3.3.0]octane (23).** To a suspension of $LiAlH_4$ (4 mmol) in diethyl ether (3 mL) at 0 °C under argon was added a solution of **5a** (1 mmol) in the same

solvent (3 mL). The reaction was completed after 1 h (TLC). Then, it was hydrolyzed with 2-3 drops of water and dried ($MgSO_4$) and the solvent evaporated to give pure compound **23** (520 mg, 97%) as a colorless oil. ^{1}H-NMR: δ 3.73 (s, 6 H, CH_3O), 3.76 (d, 2 H, J = 4.5 Hz, H4H8), 4.85 (s, 2 H, H1H5), 4.92 (s, 2 H, OH), 5.41 (d, 2 H, J = 4.5 Hz, H3H7), 6.82 (m, 8 H), 6.96-7.02 (m, 6 H), 7.28 (t, 4 H). ^{13}C-NMR: δ 156.7, 153.0, 137.5, 129.6, 121.8, 115.6, 114.9, 114.2, 87.9 (C3C7), 82.9 (C4C8), 66.3 (C1C5), 55.7 (CH_3O). IR (KBr): ν 3450 (OH). Anal. Calcd for $C_{32}H_{32}N_2O_6$: C, 71.10; H, 5.97; N, 5.18. Found: C, 71.17; H, 6.08; N, 5.15.

Crystal Structure Determination. A summary of the fundamental crystal data is given in Table III. A crystal of prismatic shape was resin epoxy coated and mounted in a Kappa diffractometer. The cell dimensions were refined by least-squares fitting the values of 25 reflections. The intensities were corrected for Lorentz and polarization effects. Scattering factors for neutral atoms were taken from the *International Tables for X-Ray Crystallography*.[46] The structure was solved by Multan and Fourier methods. An empirical absorption correction[47] was applied at the end of the isotropic refinement. Final refinement with fixed isotropic factors and coordinates for H atoms, except for H4 and H8 whose coordinates were located in a ΔF and refined. Most of the calculations were carried out with the X-ray 80 system.[48]

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Supplementary Material Available: Full spectral data for compounds **2**, **3**, and **4** and tables of X-ray data for **5a** (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Asymmetric Syntheses of All Four Stereoisomers of 2,3-Methanomethionine

Kevin Burgess* and Kwok-Kan Ho

Chemistry Department, Texas A & M University, College Station, Texas 77843

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Asymmetric syntheses of all four stereoisomers of 2,3-methanomethionine ((**Z**)- and (**E**)-**cyclo-Met**) are described. The source of chirality in these reactions is the trifluoromethylsulfonate ester **1b** which reacts with di-*tert*-butyl malonate via direct displacement of trifluoromethylsulfonate followed by lactonization to give 1-(*tert*-butoxycarbonyl)-2-oxo-3-oxabicyclo[3.1.0]hexane (**2**). Conversion of compound **2** into (**Z**)-**cyclo-Met** can be achieved via ring opening of the lactone, Hoffmann rearrangement, mesylation, and displacement with thiomethoxide. A route to (**E**)-**cyclo-Met** was developed using a lipase to effect a critical ester hydrolysis.

Introduction

Substitution of protein amino acids with 2,3-methano analogs ("methanologs")[1] produces peptidomimetics with interesting and potentially valuable properties. First, this modification imposes severe conformational restraints which, in turn, influence the biological properties of these molecules. For instance, substitution of phenylalanine by **cyclo-Phe** gave *tasteless* analogs of aspartame (Asp-PheOMe)[2-4] and peptidomimetics of Leu^5-enkephalin which are opiate *antagonists*.[5-17] Second, proteolytic cleavage is more difficult at sites linking 1-aminocyclopropanecarboxyl fragments than cleavage of normal peptide bonds,[5,18-20] and this enhances the bioavailability of

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