Contribution to the Development of New Substitution Patterns of Optically Active β-Lactams: Synthesis of Homochiral 4-(1-Aminoalkyl)azetidin-2-ones from *N*-(*tert*-Butyloxycarbonyl) α-Amino Aldehyde-Derived Imines via Asymmetric Staudinger Reaction

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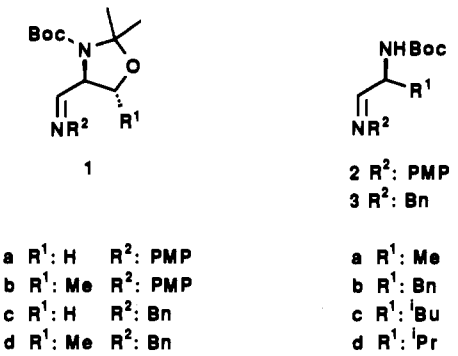
Abstract: Imines derived from *N*-(*tert*-butyloxycarbonyl) (*N*-Boc) α-amino aldehydes react with alkoxyketenes, generated from their corresponding acid chlorides and triethylamine, to produce homochiral *cis*-3-alkoxy-4-(1-aminoalkyl) β-lactams with virtually complete control of diastereoselectivity. In a similar manner, the reaction of phthalimidoacetyl chloride with these imines in the presence of triethylamine afforded the corresponding 3-phthalimido β-lactams as single diastereomers. The same reaction employing the Dane salt of glycine as the aminoketene synthon, activated with phenyl phosphorodichloridate, produced 3-amino β-lactams in better chemical yields. Some aspects related to the degree of asymmetric induction of the above imines with respect to the known Evans-Sjögren ketenes, as well as their mechanistic implications within the context of the general model proposed by Hegedus for the stereochemical outcome of the Staudinger reaction, are also discussed.

Introduction

The concept of structural modifications at the C_4 position of azetidin-2-ones is of current interest in the study of β-lactam antibiotics.[1] While abundant information on diverse substitution patterns of optically active β-lactams exists, the synthesis and applications of 4-(1-aminoalkyl) β-lactams have been the subject of very few investigations.[2] Recent research from this laboratory has addressed these issues, and complete control of the level of reaction diastereoselection has been observed in the cycloaddition of alkoxyketenes to imines derived from *N*-(*tert*-butyloxycarbonyl)-L-serinal acetonide.[3] In general, the [2 + 2] cycloaddition reaction of ketenes to imines, known as the Staudinger reaction, has acquired central importance in the asymmetric synthesis of β-lactams due to its versatility and stereochemical predictability.[4] This reaction, in contrast to the ester enolate–imine condensation,[5] generally affords *cis*-β-lactams in high yields and is widely employed in the synthesis of α-amino-β-lactams as intermediates of diverse monobactam antibiotics.[6] In view of this, we reasoned that this method, employing different *N*-(*tert*-butyloxycarbonyl) (*N*-Boc) α-amino imines, would be attractive for the synthesis of optically active β-lactams with new substitution patterns either as potential monobactam derivatives or as synthetic intermediates for the construction of other heterocycles of interest.

In our formulation, a range of ketenes could be employed to give a wide variety of homochiral cis-3-substituted 4-(1-aminoalkyl) β-lactams, whose conversion into 3-substituted 4-aminopyrrolidinones, carrying three contiguous chiral centers, can be easily envisaged. Our interest in these compounds was stimulated, initially, by the recently published investigations of β-amino-γ-lactam-bridged dipeptides[7] and, subsequently, by their potential utility in the synthesis of γ-lactam analogues of β-lactam antibiotics.[8] In particular, for reasons which will be outlined later, the cycloaddition reaction of alkoxyketenes to *N*-Boc α-amino imines was selected for development.[9] This reaction should possess a broader degree of generality than the ester enolate–imine condensation since the latter reaction is subject to the limitations of enolate basicity, which in certain situations, might cause a loss of optical purity or complete racemization.[10] This aspect becomes of crucial importance in our proposal because some N-protected

Chart I



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α-amino aldehydes, in particular *N*-Boc derivatives, are very sensitive toward partial racemization.[11]

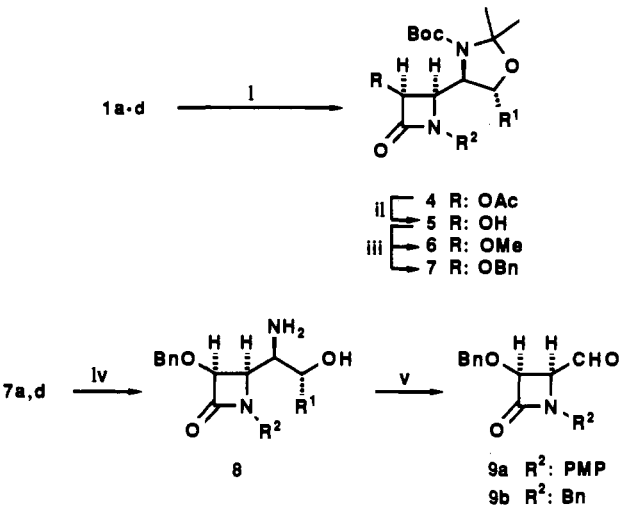
In this paper, we disclose our results concerning the successful application of *N*-Boc α-amino imines in the Staudinger reaction, leading to homochiral β-lactams with virtually complete control of the level of reaction diastereoselection. Another paper[12] will deal with the synthesis of 3,5-dialkylpyrrolidin-2-ones and 3-amino deoxyazasugars employing the above β-lactams as chiral templates.

Results and Discussion

Starting Materials. The imines used in our work (Chart I) were prepared in the usual way by treating the corresponding N-protected α-amino aldehydes[13] with *p*-anisidine in methylene chloride as solvent in the presence of $MgSO_4$. After 4 h at room temperature and subsequent filtration, the resulting imine solutions were used immediately in the cycloaddition reactions. None of the imines prepared showed loss of optical purity as judged by the cycloadducts formed (vide infra). The only case in which we found racemization was the imine derived from *N*-Boc-α-phenylglycinaldehyde. In all other cases the procedure for the preparation of these imines was judged as satisfactory for our synthetic purposes. Under the above conditions, formation of imines **1c** and **1d**, derived from either *N*-Boc-L-serinal acetonide or *N*-Boc-L-threoninal acetonide and benzylamine, proceeded cleanly without detectable loss of optical integrity. However, as a note of caution, formation of imines **3a–d** must be carried out at 0 °C to prevent the partial racemization which takes place if the reaction is performed at room temperature.

Synthesis of Homochiral 3-Alkoxy-4-(1-aminoalkyl) β-Lactams. The first outstanding contribution to the asymmetric synthesis of β-lactams via the Staudinger reaction was reported by Hubschwerlen and Schmid in which complete control of the diastereoselectivity could be achieved using imines derived from 1-(*S*)-glyceraldehyde acetonide.[14] Subsequent to this study, similar results were reported by Bose and co-workers starting from 1-(*R*)-glyceraldehyde acetonide as the source of chirality.[15] By analogy with these reactions, our investigation was initiated with the aim of establishing whether *N*-Boc α-amino imines are suitable chiral sources for the diastereoselective synthesis of homochiral *cis*-3-alkoxy-4-(1-aminoalkyl) β-lactams. We selected to study first the above reaction for several reasons. First, the alkoxy group in the azetidinones could be easily transformed into the amino function, present in some monobactam antibiotics, with complete inversion of configuration at the C_3 position of the β-lactam ring.[15] Second, these alkoxy β-lactams could also be transformed into *trans*-3-alkyl-4-(1-aminoalkyl) β-lactams, not directly accessible through the Staudinger reaction.[16] Third, all of these β-lactams, upon rearrangement, would render pyrrolidinones and hence pyrrolidines carrying three contiguous chiral centers.[12] Finally, precedent from this laboratory[17] would indicate that these 3-alkoxy β-lactams might be attractive precursors of α,β-diamino acids and related compounds.

Scheme I[a]



[a] Reagents and conditions: (i) RCH_2COCl, NEt_3, CH_2Cl_2, −78 °C → room temperature; (ii) NaOH, THF–MeOH, 0 °C; (iii) NaH, THF–HMPA then IMe or BrBN, 0 °C, 1.5 h; (iv) 3 N HCl, MeOH, reflux, 1–1.5 h; (v) $NaIO_4$, Me_2CO–H_2O, room temperature, 24 h.

A prior report from this laboratory has documented the utility of imine **1a**, derived from *N*-Boc-L-serinal acetonide, for the synthesis of homochiral β-lactams via the Staudinger reaction.[3] Treatment of imine **1a** with alkoxyacetyl chlorides or acetoxyacetyl chloride and triethylamine in methylene chloride as solvent at −78 °C to room temperature led to the corresponding β-lactams **4a**, **6a**, and **7a** as single diastereomers in yields of 70%, 74%, and 85%, respectively. In a similar manner, imine **1b** gave **4b** in 50% yield and **7b** in 86% yield when treated, in the presence of triethylamine, with acetoxyacetyl chloride and (benzyloxy)acetyl chloride, respectively, and imines **1c** and **1d**, upon treatment with acetoxyacetyl chloride, led to **4c** and **4d** under identical reaction conditions. In all cases, only one diastereomer was observed by both 300-MHz NMR and HPLC analysis of the crude reaction products. As expected,[18] the ^1H NMR spectra of these adducts showed two sets of signals in ca. 2:1 ratio when recorded at room temperature. When the solution was heated to 90 °C, they coalesced to a single set of resonances, whereas cooling the sample restored the spectrum to its original condition, thus suggesting the existence of a dynamic equilibrium related to conformational changes with a high interconversion barrier which were attributed to the two possible rotamers around the carbamate moiety (Scheme I).

Correlation of the absolute stereochemical course of the above reactions was established by chemical degradation of the C_4 substituents derived from each imine to a common derivative. Our plan was to take advantage of the facile oxidative cleavage of vicinal amino alcohols as the means by which the latent aldehyde

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functionality is unmasked.[19] Accordingly, simultaneous N,O-deprotection of the amino ketal and Boc groups in both β-lactams **7a** and **7b** by means of 3 N HCl in boiling methanol produced the corresponding amino alcohols **8a** and **8b** in 70% yield. These amino alcohols, upon oxidative cleavage with sodium periodate[20] in acetone–water at room temperature for 24 h, gave the same 4-formyl β-lactam **9** with nearly quantitative yields. On the other hand, the acetoxy derivative **4a** was transformed into compounds **6a** and **7a** by mild saponification of the acetoxy group and further treatment of the resulting hydroxy derivative **5a** with the corresponding alkyl halides, as previously described from this laboratory.[3] In both cases the resulting products showed the same physical and spectroscopic characteristics as those prepared by the cycloaddition reaction. The stereochemistry of the adducts **4c** and **4d** was established in the same manner as that above by conversion of both **4c** and **4d** into the corresponding hydroxy derivatives **5c** and **5d** followed by treatment with sodium hydride and benzyl bromide in THF–HMPA as solvent. The resulting 3-benzyloxy β-lactams thus formed were then converted into their corresponding amino alcohols **8c** and **8d**, which were identical to those derived from β-lactams **7c** and **7d** obtained by the cycloaddition approach. Finally, compound **6a** was submitted to a single-crystal X-ray analysis to prove its absolute configuration and therefore the configurations of those compounds formed from derivatization sequences.

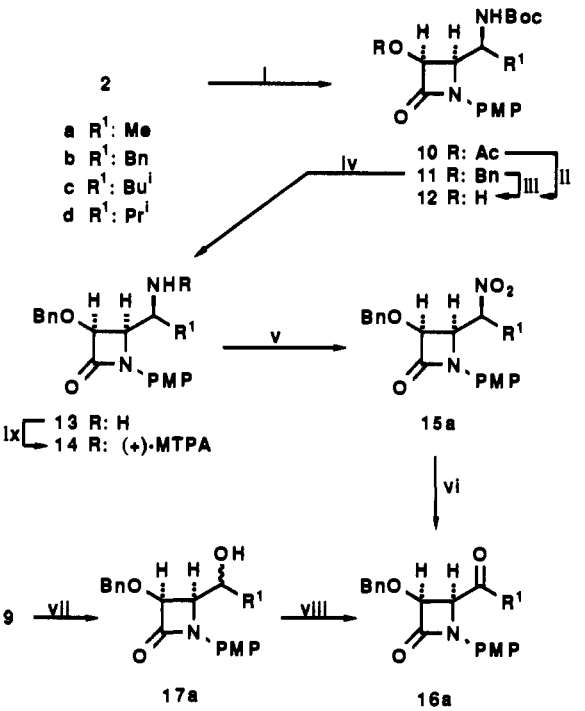
A view of the solid-state structure of **6a** is provided in the supplementary material. The most interesting structural features of this compound are the geometry of the carbamate moiety, which probably should be the predominant one in solution (vide supra), and the flat pyramidal disposition of the three valences of the nitrogen atom of the β-lactam ring.[21] This latter aspect adds interest to these unusual β-lactams, because it has been reported[22] that the relative pyramidalization of the nitrogen atom in both monocyclic and bicyclic β-lactam antibiotics is directly related with their biological activity.

Taking into account the ready availability of *N*-Boc α-amino imines **2**, the next question we examined was their behavior in such a cycloaddition reaction (Scheme II). By analogy with the results obtained employing homochiral lactaldehyde-derived imines in the Staudinger reaction,[16,23] we expected variable levels of reaction diastereoselection with *N*-Boc α-amino imines. Thus, treatment of imine **2c** with acetoxyacetyl chloride and triethylamine at −78 °C to room temperature overnight led to a mixture of the corresponding β-lactam **10c** and its cis diastereomer in a ratio of 3:1, respectively. The major isomer was separated by column chromatography and transformed into the 3-hydroxy derivative **12c** to assess the assigned stereochemistry. Similar results were obtained with imines **2a** and **2b**. However, when these imines were allowed to react with (benzyloxy)acetyl chloride, under the above reaction conditions, a single diastereomer was observed in every case by HPLC analysis of the crude reaction products. In order to confirm the assigned cis stereochemistry, compound **11c** was subjected to hydrogenolysis to produce the hydroxy derivative **12c** identical to that obtained from saponification of the acetoxy group in **10c**.

The optical purities of the resulting β-lactams **11** were determined as shown in Scheme II. After removal of the *N*-Boc group in each compound **11**, the resulting 4-(1-aminoalkyl) β-lactam **13** was acylated using (+)-MTPA acid chloride and triethylamine.[24] All of the resulting amide derivatives **14** showed a single set of signals in the ^1H and ^{19}F NMR spectra as well as in their capillary column GLC chromatograms, thus proving that there had been no loss of optical purity during *N*-Boc α-amino imine formation and the cycloaddition reactions. Although the configuration at the newly created stereocenters of the cycloaducts could be deduced by analogy with compounds **7**, further evidence was provided by formation of the 4-acetyl β-lactam **16a** starting from β-lactams **13a** and **9**. First, compound **13a** was transformed into the nitro derivative **15a** in 50% yield by means of an excess of *m*-CPBA in boiling 1,2-dichloroethane.[25] Since the exocyclic stereogenic center of this compound would be destroyed in the next step, its stereochemistry was not determined. However, inspection of its ^1H NMR spectral data indicated that only one stereoisomer had been formed. Conversion of the nitro derivative **15a** into the 4-acetyl β-lactam **16a** was accomplished by a Nef reaction developed in this laboratory.[26] On the other hand, the aldehyde **9**, whose absolute configuration had already been determined, was treated with methylmagnesium bromide in THF–diethyl ether to afford an epimeric mixture of carbinols **17a**. This mixture, when subjected to oxidation with triphosgene–DMSO and triethylamine,[27] gave the 4-acetyl β-lactam **16a** identical to that prepared above. The stereochemical assignments of the other adducts were established by analogy.

Some examples of this asymmetric Staudinger reaction are summarized in Table I. The resulting homochiral β-lactams were isolated in the indicated yields after chromatographic purification on silica gel. From the data in the table it is evident that this

Scheme II[a]



[a] Reagents and conditions: (i) $ROCH_2COCl$, NEt_3, −78 °C → room temperature; (ii) NaOH, THF–MeOH, 0 °C; (iii) HCO_2NH_4, Pd/C, MeOH, reflux; (iv) 3 N HCl, MeOH, reflux; (v) *m*-CPBA, $ClCH_2CH_2Cl$, reflux, 3 h; (vi) bis(trimethylsilyl)acetamide (BSA), DBU, CH_2Cl_2, 20 min, 0 °C then CrO_3–nicotinic acid (NDC) (4 equiv); (vii) MeMgBr, THF–Et_2O, −40 °C → room temperature, 3 h; (viii) $(Cl_3CO)_2CO$–DMSO, NEt_3, −78 °C → room temperature; (ix) (+)-MTPA-Cl, NEt_3, CH_2Cl_2, room temperature, 24 h.

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(21) The N–C_{aryl} bond forms an angle of 18.8° with respect to the plane determined by the azetidin-2-one ring, and the distance of the C_{21} atom from that plane is ca. 0.37 Å. This result differs to some extent from the usual values, (ca. 9.3° and 0.23 Å, respectively) since the three valences of nitrogen in monocyclic *N*-aryl β-lactams are reported to be almost coplanar; see: *Physical Methods in Heterocyclic Chemistry*; Gupta, P. R., Ed.; Wiley: New York, 1984; pp 340–354.

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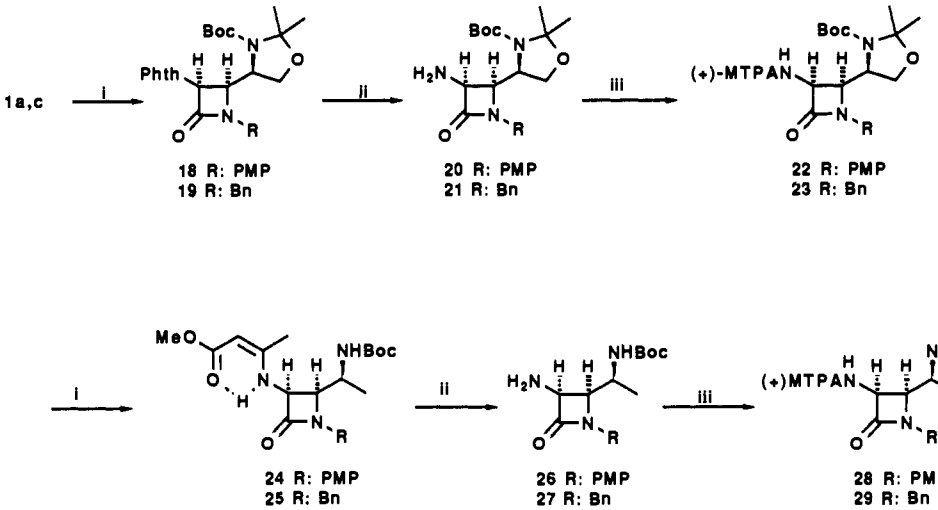
Table I. Asymmetric [2 + 2] Cycloaddition Reaction of Ketenes to Imines **1** and **2**

compd	R	R^1	R^2	yield (%)	mp (°C)	$[\alpha]^{25}_D$ (deg)
4a	OAc	H	PMP[a]	70	164–166 (AcOEt–hexane)	−90.2 (c = 1.0, CH_2Cl_2)
4b	OAc	Me	PMP	50	168–169 (Et_2O–hexane)	−112.0 (c = 1.0, CH_2Cl_2)
4c	OAc	H	Bn	55	oil	*b*
4d	OAc	Me	Bn	79	123–124 (hexane)	+0.3 (c = 1.0, CH_2Cl_2)
5a	OH	H	PMP	98	138–140 (Et_2O–hexane)	−96.1 (c = 1.0, CH_2Cl_2)
6a	OMe	H	PMP	74	119–121 (CH_2Cl_2–hexane)	−174.8 (c = 1.0, CH_2Cl_2)
7a	OBn	H	PMP	85	oil	*c*
7b	OBn	Me	PMP	86	oil	*d*
8a	OBn	H	PMP	70	128–130 (AcOEt)	−89.5 (c = 1.0, DMSO)
8b	OBn	Me	PMP	70	141–142 (MeOH)	−94.1 (c = 1.0, CH_2Cl_2)
8c	OBn	H	Bn	74	120–121 (Et_2O–hexane)	−36.5 (c = 1.0, CH_2Cl_2)
8d	OBn	Me	Bn	75	102–103 (toluene)	−31.0 (c = 1.0, CH_2Cl_2)
11a	OBn	Me		58	161–162 (Et_2O–hexane)	−107 (c = 1.0, CH_2Cl_2)
11b	OBn	Bn		55	224–225 (Et_2O–hexane)	−92.6 (c = 1.0, CH_2Cl_2)
11c	OBn	^{i}Bu		40	201–202 (MeOH)	−110.5 (c = 1.0, CH_2Cl_2)
11d	OBn	^{i}Pr		57	174–175 (Et_2O–hexane)	−100.1 (c = 1.0, CH_2Cl_2)

[a] PMP, *p*-methoxyphenyl group. [b] Purity determined by its conversion into **8c**; see text. [c] Purity determined by its conversion into **8a**. [d] Purity determined by its conversion into **8b**.

Scheme III[a]



[a] Reagents and conditions: (i) $MeO_2CHC{=}CH(Me)NHCH_2CO_2K$, $PhOPOCl_2$, NEt_3, CH_2Cl_2, −40 °C → room temperature; (ii) *p*-TosOH, Me_2CO, room temperature; (iii) (+)-MTPA-Cl, NEt_3 CH_2Cl_2, room temperature, 24 h.

ketene–imine cycloaddition reaction enjoys wide scope while displaying virtually complete control of the level of diastereoselectivity.

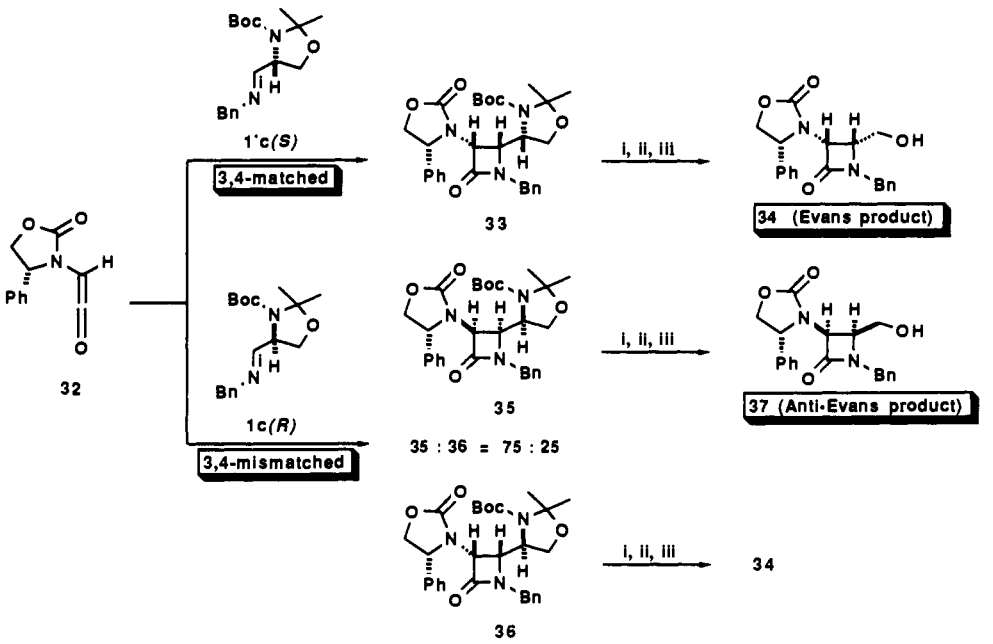
Synthesis of 3-Amino-4-(1-aminoalkyl) β-Lactams. Because of the importance of *cis*-3-aminoazetidin-2-ones in the synthesis of β-lactam antibiotics, we next explored the reaction of aminoketene synthons with *N*-Boc α-amino imines (Scheme III). Phthalimidoacetyl chloride and the Dane salt of glycine were chosen as ketene precursors, the latter being activated with phenyl phosphorodichloridate as previously described from this laboratory.[28] Treatment of imines **1a** and **1c** with phthalimidoacetyl chloride and triethylamine under the same reaction conditions as those used for the synthesis of 3-alkoxy β-lactams (vide supra) gave the expected β-lactams **18** and **19** in yields of 41% and 85%, respectively. After removal of the phthalimido group in each β-lactam by means of hydrazine hydrate,[29] the resulting 3-amino β-lactams **20** and **21** were then acylated with (+)-MTPA acid chloride. Subsequent gas chromatographic and NMR analysis of the resulting amide derivatives **22** and **23** provided the overall diastereomeric purity for the deprotection and cycloaddition steps. In a similar manner, the reaction of the Dane salt of glycine with imines **2a** and **3a** in the presence of phenyl phosphorodichloridate and triethylamine gave the vinylamino β-lactams **24** and **25** in yields of 48% and 64%, respectively.

As shown in Scheme III, the depicted stereochemistry is based, first, on the assumption that the absolute configuration of all stereogenic centers corresponds to that observed for the other

(28) (a) Arrieta, A.; Cossío, F. P.; Palomo, C. *Tetrahedron* **1985**, *41*, 1703. (b) Arrieta, A.; Lecea, B.; Cossío, F. P.; Palomo, C. *J. Org. Chem.* **1988**, *53*, 3784.

(29) Sheehan, J. C.; Ryan, J. J. *J. Am. Chem. Soc.* **1951**, *73*, 1204.

Scheme IV[a]



[a] Reagents and conditions: (i) 3 N HCl, MeOH, reflux; (ii) Me_2CO, H_2O, $NaIO_4$, room temperature; (iii) $NaBH_4$, MeOH, 0 °C → room temperature.

cycloadducts (vide supra) and, second, on analysis of the ^1H NMR coupling constants for the C_3 and C_4 protons (J = 5 Hz). Further, the homochirality of each cycloadduct was evidenced by their conversion into the corresponding 3-aminoazetidin-2-ones **26** and **27** followed by acylation with Mosher acid chloride and triethylamine. First, β-lactams **24** and **25** were treated with 2 equiv of *p*-toluenesulfonic acid[30] at room temperature during 5 min in CH_2Cl_2 as solvent to give the 3-aminoazetidin-2-ones **26** and **27** in yields of 85% and 98%, respectively. Prolonged exposure to the product to the reaction conditions caused partial deprotection of the *N*-Boc group. The free amino β-lactams **26** and **27** were then acylated using (+)-MTPA acid chloride in the presence of triethylamine to give **28** and **29**, respectively. Subsequent gas chromatographic and NMR analysis of the resulting (+)-MTPA amide derivatives provided the overall diastereomeric purity for the hydrolysis and derivatization sequences.[31] It should be noted that the dynamic equilibria observed in compounds **4–7** and **10–12** were detected again in β-lactams **18–19** and **24–25**, although in the latter case the rotational barriers were found to be higher, and therefore the two sets of signals observed in their ^1H NMR spectra could not be unified at 90 °C. However, conversion of compounds **18–19** and **24–25** into their 3-amino derivatives **20–21** and **26–27** resulted in the observation of a single set of signals for these compounds when the ^1H NMR spectra were recorded at 90 °C.

Mechanistic Considerations. The high degree of asymmetric induction observed for these reactions correlates with the analogous reactions of imines derived from (*S*)-glyceraldehyde acetonide.[14,15] However, on the basis of the proposed mechanism for this type of reaction the question of what the steeochemical outcome is when a homochiral ketene reacts with homochiral imines still remains unclear. Ojima in his seminal study on the "β-lactam synthon method" reported that the cycloaddition reaction of (4(*S*)-phenyloxazolidinyl)ketene with imines derived from either (*R*)- or (*S*)-α-amino esters afforded β-lactams with the same (3*R*,4*S*)-cis stereochemistry at the newly created stereogenic centers.[32] This implies that the diastereoselectivity of these reactions is completely governed by the configuration of the starting ketene. This fact, although remarkable, is not surprising since studies employing amino acid derivatives or in general chiral amines demonstrate that the level of asymmetric induction achieved from this position is lower than that derived from the ketene or aldehyde components.[4b,6] Within this context, we were particularly intrigued by the reaction of (*R*)-(4-phenyloxazolidinyl)ketene **32** with *N*-Boc α-amino aldehyde-derived imines for two reasons. First, it should be possible to invert the stereochemistry at the C_3 and C_4 positions of the β-lactam ring if the ketene partner effected the stereochemical control in the step of carbon–carbon bond formation, and second, the contraposition between the sense of induction of both chiral sources could add significant new information on the main factors governing the stereochemical outcome of this type of reactions.[33]

The experiments designed by us in order to find some answers for the above questions are depicted in Scheme IV. Since the stereochemical outcome of the Staudinger reaction of the Evans–Sjögren ketenes with achiral imines is known,[34] we first examined the reaction of the ketene **32** with the imine **1'c**(*S*). Thus, in this experiment the sense of induction of both chiral templates was matched, and therefore only one β-lactam adduct should be expected. In effect, this was the case, and the absolute configuration at the C_3 and C_4 positions of compound **33** was univocally established by acid hydrolysis of both the ketal and Boc protective groups of **33**, followed by oxidative cleavage of the resulting amino alcohol and subsequent reduction to give the "Evans product" **34**, whose absolute configuration (3*R*,4*R*) has been previously established.[35] With this result in hand, the next step was to confront the sense of induction of the Evans–Sjögren ketene **32** with the

(30) Bose, A. K.; Manhas, M. S.; Van der Veen, J. M.; Amin, S. G.; Fernandez, I. F.; Gala, K.; Gruska, R.; Kapur, J. C.; Khajavi, M. S.; Kreder, J.; Mukkavilli, L.; Ram, B.; Sugiura, M.; Vincent, J. E. *Tetrahedron* **1981**, *37*, 2321.

(31) We have found partial racemization in compound **25** when the imine **3a** was prepared at room temperatue. The corresponding racemic mixture of compound **25** was also prepared and subsequently transformed into its Mosher amide to confirm the above result. This observation is general for imines derived from *N*-Boc α-amino aldehydes and aliphatic amines.

(32) (a) Ojima, I.; Chen, H.-J. C. *J. Chem. Soc., Chem. Commun.* **1987**, 625. (b) Ojima, I.; Chen, H.-J. C.; Qui, X. *Tetrahedron* **1988**, *44*, 5307. (c) Ojima, I.; Komata, T.; Qui, X. *J. Am. Chem. Soc.* **1990**, *112*, 770.

(33) For a detailed discussion of the Staudinger reaction mechanism, see: Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784. For a pioneering investigation on the mechanism of the Staudinger reaction including MNDO calculations, see ref 4a and Boyd, D. B. Computer-Assisted Molecular Design Studies of β-Lactam Antibiotics. In *Frontiers on Antibiotic Research*, Umezawa, H., Ed.; Academic Press: Tokyo, 1987; pp 339–356.

(34) (a) Evans, D. A.; Sjögren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783. (b) Evans, D. A.; Sjögren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3788.

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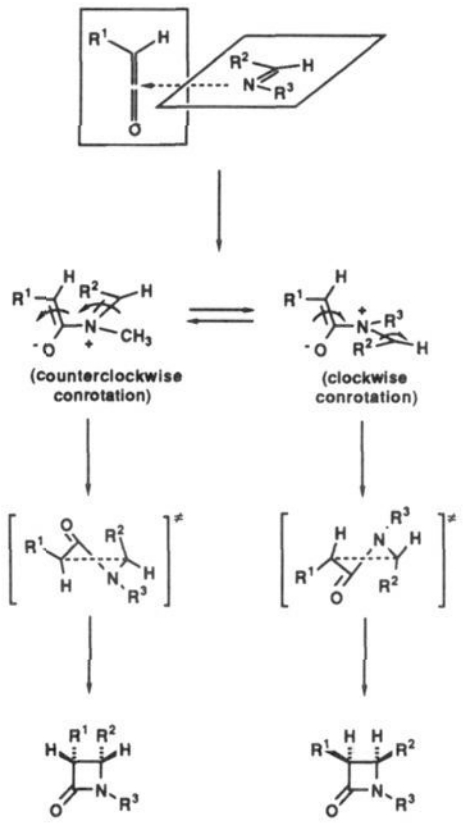
Scheme V



chiral α-amino imine **1c(*R*)**. In this second experiment, both chiral templates were mismatched and the result was the obtention of a mixture of compounds **35** and **36** in a 3:1 ratio, as it was determined by ^{1}H NMR and HPLC. The absolute configuration of these adducts was established again by their conversion into the corresponding 4-(hydroxymethyl) derivatives **34** and **37**. Thus, whereas the compound **36** was transformed into **34**, its diastereomer **35** yielded the "anti-Evans product" **37**. This second result proves that, first, it is possible to synthesize 1,2,3-triamino compounds[36] in both "Evans" and "anti-Evans" configurations, depending upon the matching between both chirality sources, and second, the degree of asymmetric induction exerted by the chiral N-protected α-amino imines **1** is higher than that exerted by the chiral ketene **32**. This later result constitutes an experimental support to the mechanistic rationalization of the stereochemistry of the Staudinger reaction recently proposed by Hegedus et al.[33] Thus, if we assume that the nucleophilic attack of the imine nitrogen takes place through the exo region of the ketene (see Scheme V), it is reasonable to expect that the R^2 chiral template is a closer neighbor to the two prochiral carbons than is the R^1 chiral auxiliary, resulting in the predominance of the corresponding "anti-Evans" adduct.

The final objective of our research has been to elucidate the origin of the extremely high asymmetric induction exerted by the chiral substituents at C_4. We have depicted in Scheme V the reaction mechanism usually proposed[33] for the Staudinger reaction between ketenes and imines. Thus, the first step leads to the formation of two zwitterionic intermediates, whose conrotatory electrocyclic reaction leads to the two possible *cis*-β-lactams. According to this mechanism, the origin of the diastereoselection between these β-lactams must lie in the different energies of the transition states (TS's) corresponding to the two possible conrotatory ring closures. In order to investigate the structures and the energies of these stationary points, we calculated the geometries and the principal thermodynamic magnitudes of the TS's **38** and **39**, corresponding to the formation of *cis*-(3*R*,4*S*)-4-[(*S*)-1-aminoethyl-3-methoxyazetidin-2-one and *cis*-(3*S*,4*R*)-4-[(*S*)-1-aminoethyl]-3-methoxyazetidin-2-one, respectively. For these calculations we used the AM1 methodology,[37] which has proved to be adequate for this type of compounds.[38] The geometries and the enthalpies of formation of these TS's are depicted in Figure 1. According to our results, the $\Delta\Delta H_f = \Delta H_f(\mathbf{38}) - \Delta H_f(\mathbf{39})$ and $-T\Delta S° = -T[S°(\mathbf{38}) - S°(\mathbf{39})]$ values for these stationary points calculated at 298 K are 1.4 and 0.5 kcal/mol, respectively. This corresponds to a calculated diastereomeric excess of 92% (the abundance of the (3*S*,4*R*) isomer is 96%), in qualitative agreement with the complete level of reaction diastereoselection observed. The explanation of this high asymmetric induction can be readily deduced by inspection of Figure 1. In effect, we can observe that TS **38** leading to the minor product (the adduct having the (3*R*,4*S*) configuration) exhibits an *angular* arrangement between C_3 and the exocyclic C–N bond, whereas TS **39** corresponding to the major product (the β-lactam with the (3*S*,4*R*) configuration) has a *linear* disposition for the same atoms. The reason for the angular arrangement in **38** is the steric interaction between the methyl group and the forming β-lactam ring. Thus, as is depicted in Scheme VI, the angular disposition between C_3 and the C–N (or in general C–X) bond minimizes this steric repulsion, but at the cost of a loss of efficiency of the stabilizing two-electron interaction between the HOMO and the σ*(C–X) orbital. Accordingly, a higher energy is obtained for TS **38** leading to the (3*R*,4*S*) product. By contrast, in the case of TS **39** leading to the major

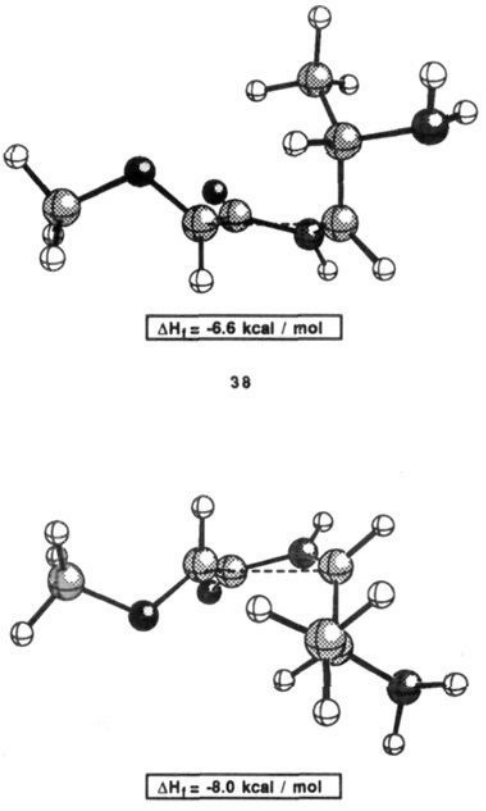


Figure 1. Computer plot of the AM1 calculated transition states **38** and **39**, corresponding to the conrotatory ring closure leading to the formation of *cis*-(3*R*,4*S*)-4-[(*S*)-1-aminoethyl]-3-methoxyazetidin-2-one and *cis*-(3*S*,4*R*)-4-[(*S*)-1-aminoethyl]-3-methoxyazetidin-2-one, respectively.

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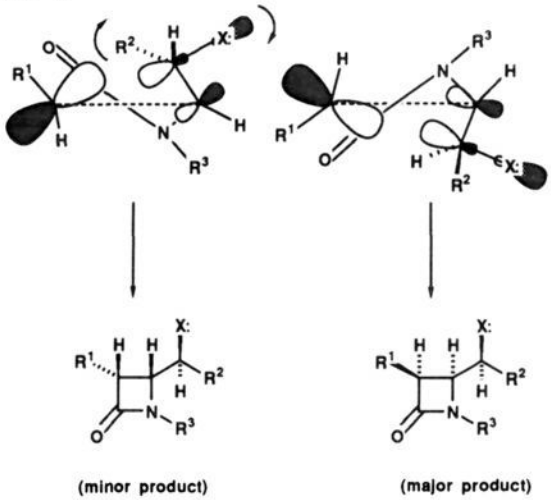
(38) (a) Wirth, D. D.; Deeter, J. B. *J. Org. Chem.* **1991**, *56*, 447. (b) Frau, J.; Coll, M.; Donoso, J.; Muñoz, F.; García-Blanco, F. *J. Mol. Struct. (Theochem)* **1991**, *231*, 109. (c) Frau, J.; Donoso, J.; Muñoz, F.; García-Blanco, F. *J. Mol. Struct. (Theochem)* **1991**, *251*, 205. (d) Nangia, A. *J. Mol. Struct. (Theochem)* **1991**, *251*, 237.

Scheme VI



(3*S*,4*R*)-β-lactam, the aforementioned steric interaction does not occur, and therefore the HOMO–σ* stabilization takes place more efficiently, favored by the linear arrangement between C_3 and the exocyclic C–N (or in general C–X) bond. Therefore, this latter TS has lower energy. This result agrees with the qualitative arguments exposed by Evans[39] in order to rationalize the high asymmetric induction observed in the Staudinger reaction between achiral ketenes and chiral α,β-epoxy imines. Consequently, the above exposed rationalization can be extended to any Staudinger reaction between ketenes and chiral imines derived from aldehydes having a C*–X moiety at the α position. This subject is currently underway in our laboratory, and the results will be published elsewhere.

Concluding Remarks

From the results in the present study, three key points deserve to be mentioned: (1) Although *N*-Boc α-amino aldehydes are prone to undergo racemization, the corresponding imines are suitable chiral sources for the development of new substitution patterns of optically active β-lactams via the Staudinger reaction. (2) Since methods for the synthesis of α-amino acids in their (*R*) or (*S*) forms are now abundant,[40] the present procedure opens up new perspectives not only in the field of β-lactam antibiotics, but also in the chemistry that employs β-lactams as chiral starting materials.[41] (3) The stereochemical outcome of the Staudinger reaction between ketenes and imines derived from homochiral aldehydes having C*–X bonds (X being an electronegative atom and C* a chiral carbon) can be rationalized on the basis of the stereoelectronic effect exerted by the $\sigma^*_{(C-X)}$ orbital over the HOMO of the transition states leading to the formation of the C_3–C_4 bond.

Further studies of applications of the above exposed methodology to the chemical synthesis of natural products are underway in our laboratory.

Experimental Section

General Experimental. Commercially available compounds were used without further purification unless otherwise noted. Hexane was purified by distillation. Tetrahydrofuran and diethyl ether were distilled over sodium with benzophenone as indicator. Methylene chloride was shaken with concentrated H_2SO_4, dried over K_2CO_3, and distilled. Chiral α-amino aldehydes and the acyl chloride **32** were prepared as previously described.[16,33] Melting points were determined on either Büchi SMP-20 or Mettler FP61 instruments and are uncorrected. Infrared spectra were obtained on a Shimadzu IR-435 spectrometer. Mass spectra were obtained on a Shimadzu GCMS-QP2000 spectrometer operated at 70 eV. Capillary GLC analyses were performed on a Shimadzu GC-14A gas chromatograph equipped with a 15 m × 0.25 mm fused-silica Supelco SPB-5 column. HPLC analyses and purifications were performed on a Shimadzu LC-8A system equipped with Merck Lichosorb Si 60 (7 μm) columns. Specific rotations were determined on a Perkin-Elmer 243B polarimeter, thermostated at 25 °C by means of a Selecta-Frigiterm 6000382 apparatus. NMR spectra were recorded on a Varian VXR300 spectrometer at either 90 °C or ambient temperature. ^1H and ^{19}F nuclei were observed at 300 and 282.2 MHz, respectively. ^1H NMR chemical shifts are reported in δ vs Me_4Si. ^{19}F chemical shifts are reported in δ vs $CFCl_3$ at 0.00 ppm.

MO-SCF Calculations. The semiempirical AM1[37] calculations were carried out with the standard parameters[37] using a locally modified version[42] of the MOPAC package.[43] The structures of the stationary points **38** and **39** were optimized with respect to all of their internal coordinates using the NLLSQ algorithm[44] and increasing 100 times the convergence criteria (NLLSQ and PRECISE keywords). The transition states were conveniently characterized by performing a frequency calculation and a subsequent inspection of the number of negative eigenvalues occuring in their corresponding force constant matrices.[45] Both structures showed only one imaginary frequency, thus proving to be true transition states. All of the calculations were performed on a MicroVAXII computer.

General Procedure for the Preparation of Imines 1–3. To a stirred solution of the chiral aldehyde (11 mmol) in methylene chloride (15 mL) at 0 °C were added the corresponding amine (10 mmol) and a large excess of $MgSO_4$, successively. The resulting mixture was stirred for 4 h at room temperature (imines derived from *p*-anisidine) or at 0 °C (imines derived from benzylamine) and then filtered and washed with cold 0.1 N HCl (3 × 10 mL) and a saturated solution of $NaHCO_3$ (10 mL), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give the corresponding crude imine, which showed a correct ^1H NMR spectrum and was used as such in the next step.

General Procedure for the Synthesis of β-Lactams 4–7, 10, 11, 18, and 19. A solution of the corresponding substituted acetyl chloride (11.5 mmol) in dry methylene chloride (7.5 mL) was added dropwise to a stirred solution containing the Schiff base (10 mmol) and triethylamine (3.2 mL, 32 mmol) in dry methylene chloride (20 mL) under nitrogen atmosphere at −78 °C. The resulting mixture was stirred overnight under nitrogen, and the temperature of the bath was allowed to rise from −78 °C to room temperature. The mixture was washed with water (10 mL), 0.1 N HCl (10 mL), and a saturated solution of $NaHCO_3$ (10 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure to give the crude β-lactam, which was further purified by column chromatography (silica gel 70–230 mesh, CH_2Cl_2–hexane (1:4) as eluent) or by trituration in Et_2O–hexane. The pure product was conveniently characterized after recrystallization.

(3*S*,4*R*)-4-[(*R*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl]-3-hydroxy-1-(4-methoxyphenyl)azetidin-2-one (5a).[14] A solution of NaOH (0.43 g, 10 mmol) in methanol (22 mL) was added dropwise to a solution of (3*S*,4*R*)-3-acetoxy-4-[(*R*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl]-1-(4-methoxyphenyl)azetidin-2-one (**4a**) (4.06 g, 10 mmol) in tetrahydrofuran (22 mL) and methanol (15 mL) at 0 °C, and the resulting mixture was stirred at the same temperature for 1 h. Then, the solvents were evaporated under reduced pressure and methylene chloride (50 mL) was added. The resulting mixture was washed with water (3 × 20 mL) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the crude title product, which was purified by crystallization from diethyl ether–hexane: yield, 3.84 g (98%); IR (KBr) ν 3328 (OH), 1740 (C=O, β-lactam), 1700 (C=O) cm^{-1}; ^1H NMR (DMSO, 90 °C) δ 7.35 (d, 2 H, *J* = 9.0 Hz, arom), 6.86 (d, 2 H, *J* = 9.0 Hz, arom), 6.16 (d, 1 H, *J* = 4.9 Hz, C_3H), 4.93 (dd, 1 H, *J* = 4.9 Hz, *J* = 7.4 Hz, C_4H), 4.30–4.28 (m, 1 H, CH), 4.01 (dd, *J* = 5.5 Hz, *J'* = 9.6 Hz, CH), 3.84 (dd, *J* = 0.9 Hz, *J'* = 9.6 Hz, CH), 3.71 (s, 3 H, OCH_3), 2.98 (s_b, 1 H, OH), 1.66 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 1.07 (s, 9 H, Boc). Anal. Calcd for $C_{20}H_{28}N_2O_6$: C, 61.22; H, 7.14; N, 7.14. Found: C, 61.25; H, 7.27; N, 7.38.

(3*S*,4*R*)-4-[(*R*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl]-3-methoxy-1-(4-methoxyphenyl)azetidin-2-one (6a). The title compound was prepared from (*S*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-formyloxazolidine (2.51 g, 11 mmol), *p*-anisidine (1.23 g, 10 mmol), and methoxyacetyl chloride (1.05 mL, 11.5 mmol): yield, 3.0 g (74%); IR

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(45) McIver, J. W.; Komornicki, A. *J. Am. Chem. Soc.* **1972**, *94*, 2625.

(CH_2Cl_2) ν 1745 (C=O, β-lactam), 1694 (C=O) cm^{-1}; ^1H NMR (DMSO, 90 °C) δ 7.35 (d, 2 H, J = 8.5 Hz, arom), 6.88 (d, 2 H, J = 8.5 Hz, arom), 4.74 (d, 1 H, J = 5.4 Hz, C_3H), 4.40 (dd, 1 H, J = 5.4 Hz, J' = 9.6 Hz, C_4H), 4.37–4.25 (m, 1 H, CH), 4.02 (dd, 1 H, J = 9.6 Hz, J' = 6.15 Hz, *H*CH), 3.78 (d, 1 H, J = 9.6 Hz, HC*H*), 3.71 (s, 3 H, OCH_3), 3.53 (s, 3 H, $OCOCH_3$), 1.67 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 1.06 (s, 9 H, Boc). Anal. Calcd for $C_{21}H_{30}N_2O_6$: C, 62.06; H, 7.38; N, 6.89. Found: C, 62.38; H, 7.39; N, 6.67.

(3*S*,4*R*)-4-[(*R*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl]-1-(4-methoxyphenyl)-3-phthalimidoazetidin-2-one (18). The title compound was prepared from (*S*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-formyloxazolidine (2.51 g, 11 mmol), *p*-anisidine (1.23 g, 10 mmol), and phthalimidoacetyl chloride (2.46 g, 11.5 mmol): yield, 2.14 g (41%); mp 215–216 °C (MeOH); $[\alpha]^{25}_D$ = +88.1° (c = 1.02, CH_2Cl_2); IR (KBr) ν 1760, 1723, 1694 (C=O) cm^{-1}; ^1H NMR (DMSO, 90 °C) δ 7.94–7.90 (m, 4 H, arom), 7.43 (d, 2 H, J = 8.2 Hz, arom), 6.94 (d, 2 H, J = 8.2 Hz, arom), 5.60 (d, 1 H, J = 5.1 Hz, C_3H), 4.68–4.65 (m, 1 H, C_4H), 4.40–4.38 (m, 1 H, CH), 3.89–3.84 (m, 1 H, *H*CH), 3.74 (s, 3 H, OCH_3), 3.44–3.41 (m, 1 H, HC*H*), 1.63 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 1.12 (s, 9 H, Boc). Anal. Calcd for $C_{28}H_{31}O_7N_3$: C, 64.49; H, 5.95; N, 8.06. Found: C, 64.75; H, 6.17; N, 8.11.

(3*S*,4*R*)-1-Benzyl-4-[(*R*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl]-3-phthalimidoazetidin-2-one (19). The title compound was prepared from (*S*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-formyloxazolidine (2.51 g, 11 mmol), benzylamine (1.09 mL, 10 mmol), and phthalimidoacetyl chloride (2.46 g, 11.5 mmol) and then purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2–hexane 1:2 as eluent) followed by preparative HPLC (AcOEt as eluant, 10 mL/min, retention time 16.3 min): yield, 4.29 g (85%), syrup; $[\alpha]^{25}_D$ = +59.6° (c = 1.00, CH_2Cl_2); IR (KBr) ν 1766, 1722, 1694 (C=O) cm^{-1}; ^1H NMR (DMSO, 90 °C) δ 7.94–7.87 (m, 4 H, arom), 7.40–7.24 (m, 5 H, arom), 5.48 (d, 1 H, J = 5.3 Hz, C_3H), 4.87 (d, 1 H, J = 15.4 Hz, *H*CH), 4.27 (dd, 1 H, J = 5.3 Hz, J' = 9.8 Hz, C_4H), 4.04 (d, 1 H, J = 15.4 Hz, HC*H*), 3.84 (dd, 1 H, J = 5.5 Hz, J' = 9.8 Hz, CH), 3.71 (dd, 1 H, J = 5.5 Hz, J' = 9.5 Hz, CH), 3.30 (d, 1 H, J = 9.5 Hz, CH), 1.52 (s, 9 H, Boc), 1.34 (s, 3 H, CH_3), 1.12 (s, 3 H, CH_3).

General Procedure for the Synthesis of α-Vinylamino β-Lactams. A solution of phenyl phosphorodichloridate (2.25 mL, 15 mmol) in dry methylene chloride (10 mL) was added dropwise to a stirred solution containing the corresponding imine (10 mmol), potassium Dane's salt of glycine (3.18 g, 15 mmol), and triethylamine (4.2 mL, 30 mmol) in dry methylene chloride (20 mL) under nitrogen atmosphere at −20 °C. The resulting mixture was stirred overnight under nitrogen, whereas the temperature of the bath was allowed to rise from −20 °C to room temperature. After the usual workup, the resulting crude α-vinylamino β-lactam was purified by trituration with diethyl ether. The corresponding pure products were conveniently characterized after recrystallization in ethyl acetate.

(3*S*,4*R*)-4-[(*S*)-1-[(*tert*-Butoxycarbonyl)amino]ethyl]-1-(4-methoxyphenyl)-3-[[1-methyl-2-(methoxycarbonyl)vinyl]amino]azetidin-2-one (24). The title compound was prepared from the imine derived from 2-[(*S*)-(*tert*-butoxycarbonyl)amino]propionaldehyde (1.90 g, 11 mmol) and *p*-anisidine (1.23 g, 10 mmol): yield, 2.07 g (48%); mp 215–217 °C (AcOEt); $[\alpha]^{25}_D$ = −123.6° (c = 1.00, CH_2Cl_2); IR (KBr) ν 3360 (NH), 1740 (C=O, β-lactam), 1680, 1651 (C=O) cm^{-1}; ^1H NMR (DMSO, 90 °C) δ 8.98 (d, 1 H, J = 10.3 Hz, NH, both rotamers), 7.39 (d, 2 H, J = 9.1 Hz, arom), 6.88 (d, 2 H, J = 9.1 Hz, arom), 6.40 6.27 (d, 1 H, J = 9.0 Hz, NH, both rotamers), 5.24, 4.98 (dd, 1 H, J = 5.3 Hz, J' = 10.2 Hz, C_3H, both rotamers), 4.72, 4.62 (s, 1 H, =CH, both rotamers), 4.34, 4.32 (dd, 1 H, J = 5.3 Hz, J' = 9.1 Hz, C_4H, both rotamers), 3.98–3.80 (m, 1 H, CH, both rotamers), 3.74 (s, 3 H, $PhOCH_3$, both rotamers), 3.57, 3.50 (s, 3 H, OCH_3, both rotamers), 2.26, 1.99 (s, 3 H, $=CCH_3$, both rotamers), 1.15 (s, 9 H, Boc, both rotamers), 1.05, 0.98 (d, J = 6.8 Hz, CH_3, both rotamers). Anal. Calcd for $C_{22}H_{31}O_6N_3$: C, 60.96; H, 7.15; N, 9.69. Found: C, 60.79; H, 6.83; N, 9.77.

(3*S*,4*R*)-1-Benzyl-4-[(*S*)-1-[(*tert*-butoxycarbonyl)amino]ethyl]-3-[[1-methyl-2-(methoxycarbonyl)vinyl]amino]azetidin-2-one (25). The title compound was prepared from 2-[(*S*)-(*tert*-butoxycarbonyl)amino]-propionaldehyde (1.90 g, 11 mmol) and benzylamine (1.09 mL, 10 mmol): yield, 2.67 g (64%); mp 190–191 °C (AcOEt); $[\alpha]^{25}_D$ = −88.6° (c = 1.00, CH_2Cl_2); IR (KBr) ν 3347 (NH), 1746 (C=O, β-lactam), 1680, 1658 (C=O) cm^{-1}; ^1H NMR (DMSO, 90 °C) δ 8.87 (d, 1 H, J = 10.0 Hz, NH, both rotamers), 7.37–7.18 (m, 5 H, arom, both rotamers), 6.54, 6.45 (d, J = 7.9 Hz, NH, both rotamers), 5.14–5.07, 4.90–4.83 (m, 1 H, C_3H, both rotamers), 4.68, 4.56 (s, 1 H, =CH, both rotamers), 4.62, 4.58 (d, 1 H, J = 15.5 Hz, *H*CH, both rotamers), 4.18, 4.14 (d, 1 H, J = 15.5 Hz, HC*H*, both rotamers), 3.84–3.59 (m, 2 H, C_4H, CH, both rotamers), 3.55, 3.48 (s, 3 H, OCH_3, both rotamers), 2.22, 1.93 (s, 3 H, $=CCH_3$, both rotamers), 1.40, 1.38 (s, 9 H, Boc, both rotamers), 0.95, 0.89 (d, 3 H, J = 6.2 Hz, CH_3, both rotamers). Anal. Calcd for $C_{22}H_{31}O_5N_3$: C, 63.30; H, 7.43; N, 10.07. Found: C, 62.97; H, 7.45; N, 9.95.

General Procedure for the Synthesis of Amino Alcohols 8 from β-Lactams 7. A solution of the β-lactam **7** (10 mmol) in methanol (20 mL) and 3 N HCl (20 mL) was refluxed for 2–2.5 h, and then the solvent was evaporated under reduced pressure. Ethyl acetate (20 mL) and water (20 mL) were added to the resulting residue. The aqueous layer was separated and basified with 40% NaOH to pH 9. The mixture was extracted with ethyl acetate (3 × 20 mL), and the organic extracts were combined and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the crude amino alcohol **8** as a solid which was recrystallized in ethyl acetate.

General Procedure for the Synthesis of 4-Formyl β-Lactams 9. To an stirred solution of the corresponding β-lactam **8** (10 mmol) in acetone (100 mL) and water (10 mL) was added sodium metaperiodate (8.55 g, 40 mmol) in one portion at room temperature, and the resulting mixture was stirred at the same temperature for 24 h. Then, the precipitated salts were separated by filtration, and the solvent of the filtrate was evaporated under reduced pressure. The resulting residue was dissolved in methylene chloride (20 mL) and washed with water (10 mL) and 3 N HCl (10 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the corresponding crude 4-formyl β-lactam **9**, which was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2–hexane 4:1 as eluent) and recrystallization in ethyl acetate–hexane.

(3*S*,4*S*)-3-(Benzyloxy)-4-formyl-1-(4-methoxyphenyl)azetidin-2-one (9a). The title compound was prepared from (3*S*,4*R*)-4-[(*R*)-1-amino-2-hydroxyethyl]-3-(benzyloxy)-1-(*p*-methoxyphenyl)azetidin-2-one (**8a**) (3.42 g, 10 mmol): yield, 2.95 g (95%); mp 152–153 °C (AcOEt); $[\alpha]^{25}_D$ = 178.4° (c = 1.0, CH_2Cl_2); IR (KBr) ν 1749 (C=O, β-lactam), 1730 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.71 (d, 1 H, J = 3.8 Hz, CHO), 7.38–7.24 (m, 7 H, arom), 6.87 (d, 2 H, J = 9.0 Hz, arom), 5.04 (d, 1 H, J = 5.3 Hz, C_3H), 4.82 (d, 1 H, J = 11.6 Hz, *H*CH), 4.71 (d, 1 H, J = 11.6 Hz, HC*H*), 4.48 (dd, J = 3.8 Hz, J' = 5.3 Hz, C_4). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.45; H, 5.46; N, 4.50. Found: C, 69.40; H, 5.51; N, 4.48.

(3*S*,4*S*)-1-Benzyl-3-(benzyloxy)-4-formylazetidin-2-one (9b). The title compound was prepared from (3*S*,4*R*)-4-[(*R*)-1-amino-2-hydroxypropyl]-1-benzyl-3-(benzyloxy)azetidin-2-one (**8c**) (3.26 g, 10 mmol): yield, 2.83 g (96%); mp 112–113 °C (AcOEt); $[\alpha]^{25}_D$ = 85.9° (c = 1.0, CH_2Cl_2); IR (KBr) ν 1741 (C=O, β-lactam), 1713 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.32 (d, 1 H, J = 2.9 Hz, CHO), 7.36–7.19 (m, 10 H, arom), 4.90 (d, 1 H, J = 5.0 Hz, C_3H), 4.76 (d, 1 H, J = 11.7 Hz, *H*CHO), 4.61 (d, 1 H, J = 11.7 Hz, HC*H*O), 4.61 (d, 1 H, J = 14.8 Hz, *H*CH), 4.41 (d, 1 H, J = 14.8 Hz, HC*H*), 3.97 (dd, 1 H, J = 2.9 Hz, J' = 5.0 Hz, C_4H). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.22: H, 5.76; N, 4.79. Found: C, 73.20; H, 5.73; N, 4.82.

General Procedures for the Synthesis of α-Amino β-Lactams. Method A. To a stirred solution of the corresponding α-vinylamino β-lactam (5 mmol) in acetone (5 mL) was added *p*-toluenesulfonic acid monohydrate (1.78 g, 10 mmol) in one portion at room temperature, and the resulting mixture was stirred for 5 min. Then, water (20 mL) was added and the resulting solution was basified with 40% NaOH (5 mL). The reaction mixture was extracted with methylene chloride (2 × 20 mL). The organic extracts were combined and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give the corresponding α-amino β-lactam, which was crystallized from AcOEt and conveniently characterized.

Method B. To a solution of the corresponding α-phthalimido β-lactam (5 mmol) in ethanol (20 mL) was added hydrazine monohydrate (0.51 mL, 10 mmol), and the resulting mixture was stirred under reflux for 2–2.5 h. Then the solvent was evaporated under reduced pressure, and ethyl acetate (20 mL) was added in one portion. The precipitated solid was filtered off, and the organic layer was washed with 3 N HCl (2 × 20 mL). The aqueous extracts were combined and basified with 40% NaOH to pH 9–10. The resulting mixture was extracted with methylene chloride (4 × 20 mL). The organic extracts were combined and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the crude α-amino β-lactam, which was purified by crystallization.

(3*S*,4*R*)-3-Amino-4-[(*R*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl]-1-(4-methoxyphenyl)azetidin-2-one (20). The title compound was prepared from (3*S*,4*R*)-4-[(*R*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl]-1-(4-methoxyphenyl)-3-phthalimidoazetidin-2-one (**18**) (2.60 g, 5 mmol) following method B. The described treatment gave the crude title compound as a syrup, which was purified by column chromatography (silica gel 70–230 mesh, CH_2Cl_2–hexane 1:2 as eluent) and then by preparative HPLC (AcOEt as eluent, 10 mL/min, retention time 13.7 min): yield, 1.1 g (56%); $[\alpha]^{25}_D$ = −89.5° (c = 1.14, CH_2Cl_2); IR (film) ν 3383, 3328 (NH_2), 1739 (C=O, β-lactam), 1694 (C=O) cm^{-1}; ^1H NMR (DMSO, 90 °C) δ 7.34 (d, 2 H, J = 9.0 Hz, arom), 6.85

(d, 2 H, J = 9.0 Hz, arom), 4.37 (d, 1 H, J = 5.6 Hz, C_3H), 4.37–4.31 (m, 1 H, CH), 4.19 (dd, J = 5.6 Hz, J' = 9.6 Hz, C_4H), 4.10–3.93 (m, 3 H, CH_2), 3.70 (s, 3 H, OCH_3), 2.99 (s_b, 2 H, NH_2), 1.64 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 1.08 (s, 9 H, Boc).

(3*S*,4*R*)-3-Amino-1-benzyl-4-[(*R*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl]azetidin-2-one (21). The title compound was prepared from (3*S*,4*R*)-1-benzyl-4-[(*R*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl]-3-phthalimidoazetidin-2-one (**19**) (2.52 g, 5 mmol) following method B. The described treatment gave the crude title compound as a syrup, which was purified by column chromatography (silica gel 70–230 mesh, CH_2Cl_2–hexane 1:2 as eluent) and then by preparative HPLC (AcOEt as eluent, 10 mL/min, retention time 31.7 min): yield, 0.98 g (52%), syrup; $[\alpha]^{25}_D$ = −27.3° (c = 1.55, CH_2Cl_2); IR (film) ν 3379, 3323 (NH_2), 1745 (C=O, β-lactam), 1691 (C=O) cm^{-1}; ^1H NMR (DMSO, 90 °C) δ 7.37–7.12 (m, 5 H, arom), 4.74 (d, 1 H, J = 15.1 Hz, *H*CHPh), 4.30 (d, 1 H, J = 5.3 Hz, J' = 9.9 Hz, C_4H), 4.23 (d, 1 H, J = 5.3 Hz, C_3H), 3.92–3.77 (m, 3 H, *H*CH, CH, HC*H*Ph), 3.41 (dd, 1 H, J = 5.2 Hz, J' = 10.0 Hz, HC*H*), 2.00 (s_b, 2 H, NH_2), 1.52 (s, 9 H, Boc), 1.46 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3).

(3*S*,4*R*)-3-Amino-4-[(*S*)-1-[(*tert*-butoxycarbonyl)amino]ethyl]-1-(4-methoxyphenyl)azetidin-2-one (26). The title compound was prepared from (3*S*,4*R*)-4-[(*S*)-1-[(*tert*-butoxycarbonyl)amino]ethyl]-1-(4-methoxyphenyl)-3-[[1-methyl-2-(methoxycarbonyl)vinyl]amino]azetidin-2-one (**24**) (2.17 g, 5 mmol) following method A: yield, 1.42 g (85%); mp 195–196 °C (Et_2O); $[\alpha]^{25}_D$ = −70.7° (c = 1.0, CH_2Cl_2); IR (KBr) ν 3340 (NH), 1723 (C=O, β-lactam), 1680 (C=O) cm^{-1}; ^1H NMR (DMSO, 90 °C) δ 7.35 (d, 2 H, J = 9.0 Hz, arom), 6.86 (d, 2 H, J = 9.0 Hz, arom), 6.35 (d, 1 H, J = 6.6 Hz, NH), 4.32 (d, 1 H, J = 5.1 Hz, C_3H), 4.08–3.96 (m, 2 H, C_4H, CH), 3.73 (s, 3 H, OCH_3), 2.98 (s_b, 2 H, NH_2), 1.19 (s, 9 H, Boc), 1.15 (d, 3 H, J = 6.4 Hz, CH_3). Anal. Calcd for $C_{17}H_{25}O_4N_4$: C, 60.85; H, 7.46; N, 12.53. Found: C, 60.90: H, 7.50; N, 12.61.

(3*S*,4*R*)-3-Amino-1-benzyl-4-[(*S*)-1-[(*tert*-butoxycarbonyl)amino]ethyl]azetidin-2-one (27). The title compound was prepared from (3*S*,4*R*)-1-benzyl-4-[(*S*)-1-[(*tert*-butoxycarbonyl)amino]ethyl]-3-[[1-methyl-2-(methoxycarbonyl)vinyl]amino]azetidin-2-one (**25**) (2.08 g, 5 mmol) following method A: yield, 1.56 g (98%); mp 163–164 °C (AcOEt); $[\alpha]^{25}_D$ = −21.1° (c = 1.0, CH_2Cl_2); IR (KBr) ν 3386, 3338 (NH), 1738 (C=O, β-lactam), 1678 (C=O) cm^{-1}; ^1H NMR (DMSO, 90 °C) δ 7.35–7.20 (m, 5 H, arom), 6.37 (d, 1 H, J = 8.7 Hz, NH), 4.53 (d, 1 H, J = 15.6 Hz, *H*CH), 4.13 (d, 1 H, J = 5.1 Hz, C_3H), 4.10 (d, 1 H, J = 15.6 Hz, HC*H*), 3.82–3.74 (m, 1 H, CH), 3.4 (dd, 1 H, J = 5.1 Hz, J' = 8.7 Hz, C_4H), 1.98 (s_b, 2 H, NH_2), 1.38 (s, 9 H, Boc), 1.06 (d, 3 H, J = 6.7 Hz, CH_3). Anal. Calcd for $C_{17}H_{25}N_3O_3$: C, 63.94; H, 7.83; N, 13.16. Found: C, 64.02; H, 8.09; N, 12.78.

General Procedure for the Determination of Enantiomeric Purity of Amino Compounds. A mixture of (+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (100 mg, 0.42 mmol) in thionyl chloride (2 mL) was refluxed under nitrogen for 5 h. The resulting solution was then cooled and evaporated under reduced pressure to dryness. The (+)-MTPA-Cl thus prepared was dissolved in methylene chloride (1 mL) and added dropwise via syringe to a solution of the corresponding amino compound (0.21 mmol) and triethylamine (0.12 mL, 0.84 mmol) in methylene chloride (5 mL) at 0 °C. The resulting mixture was stirred under nitrogen at room temperature for 24 h. Then, water (2 mL) was added and stirring was resumed for an additional 1 h. The organic layer was separated and washed with 1 N HCl (2 × 5 mL) and a saturated solution of $NaHCO_3$ (5 mL). The organic extract was dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a residue which was analyzed by capillary GLC–EIMS and NMR (vide supra). In order to test the viability of the method, two blank assays were performed by using previously prepared racemic compounds **13a** and **27**. In those cases the capillary GLC analysis showed two peaks, and two sets of signals were obtained from ^1H and ^{19}F NMR spectra. In all subsequent assays, a single peak was observed in the GL chromatogram for each compound, and a single set of signals corresponding to the ^1H and ^{19}F NMR spectra was detected (see the supplementary material).

General Procedure for the Synthesis of *cis*-3-[4(*R*)-Phenyloxazolidin-3-yl]azetidin-2-ones 33, 35, and 36. Triethylamine (2.12 mL, 15 mmol) was added at −78 °C to a solution of the acyl chloride **32** (2.31 g, 10 mmol) in dichloromethane (30 mL). After 15 min, a solution of the imine **1c** (3.5 g, 11 mmol) in toluene (15 mL) was added dropwise at the same temperature, and the resulting mixture was stirred under nitrogen at 0 °C for 2 h and at room temperature overnight. Then, the usual workup gave a crude oily residue which was purified by flash chromatography (silica gel, dichloromethane as eluent) and then by preparative HPLC (AcOEt as eluent).

***cis*-(3*R*,4*S*)-1-Benzyl-3-[(*R*)-2-oxo-4-phenyloxazolidin-3-yl]-4-[(*S*)-3-[(*tert*-butoxycarbonyl)amino]-2,2-dimethyloxazolidin-4-yl]azetidin-2-one (33).** The title compound was prepared from the imine **1'c**(*S*) (3.18 g, 10 mmol) and purified by crystallization in methanol: yield, 2.56 g (54%); mp 180–182 °C (MeOH); $[\alpha]^{25}_D$ = −107.0° (c = 1.00, CH_2Cl_2); IR (KBr) ν 1757, 1754, 1690 (C=O) cm^{-1}; ^1H NMR (DMSO, 90 °C) δ 7.47–7.08 (m, 10 H, arom), 5.01 (dd, 1 H, J = 3.6 Hz, J' = 8.7 Hz, HCPh), 4.77 (d, 1 H, J = 15.1 Hz, *H*CHPh), 4.68 (t, 1 H, J = 8.7 Hz, *H*CHOCO), 4.43 (d, 1 H, J = 5.3 Hz, C_3H), 4.34 (dd, 1 H, J = 5.3 Hz, J' = 10.0 Hz, C_4H), 4.11 (dd, 1 H, J = 3.6 Hz, J' = 8.7 Hz, HC*H*OCO), 3.96 (dd, 1 H, J = 5.4 Hz, J' = 9.3 Hz, *H*CH), 3.87 (d, 1 H, J = 15.1 Hz, HC*H*Ph), 3.72 (d, 1 H, J = 9.3 Hz, HC*H*), 3.57 (dd, 1 H, J = 5.4 Hz, J' = 10.0 Hz, CH), 1.51 (s, 9 H, Boc), 1.44 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3). Anal. Calcd for $C_{29}H_{35}N_3O_6$: C, 66.78; H, 6.76; N, 8.06. Found: C, 66.51; H, 6.66; N, 8.10.

***cis*-1-Benzyl-3-[(*R*)-2-oxo-4-phenyloxazolidin-3-yl]-4-[(*R*)-3-[(*tert*-butoxycarbonyl)amino]-2,2-dimethyloxazolidin-4-yl]azetidin-2-ones 35 and 36.** The title compounds were prepared from the imine **1c**(*R*) (3.5 g, 11 mmol). The procedure described above gave compounds **35** and **36** as a 60:40 mixture, which was separated by preparative HPLC.

(3*S*,4*R*) Isomer 35: yield, 2.00 g (38%); white, low-melting solid; purified by preparative HPLC (AcOEt as eluant, 10 mL/min, retention time 15.23 min); $[\alpha]^{25}_D$ = −26.2° (c = 1.00, CH_2Cl_2); IR (KBr) ν 1757, 1550 (C=O) cm^{-1}; ^1H NMR (DMSO, 90 °C) δ 7.46–7.10 (m, 10 H, arom), 4.95 (dd, 1 H, J = 6.2 Hz, J' = 8.7 Hz, HCPh), 4.81 (d, 1 H, J = 5.4 Hz, C_3H), 4.75 (d, 1 H, J = 15.4 Hz, *H*CHPh), 4.74 (t, 1 H, J = 8.7 Hz, *H*CHOCO), 4.54 (dd, 1 H, J = 5.4 Hz, J' = 9.9 Hz, C_4H), 4.31 (dd, 1 H, J = 6.2 Hz, J' = 8.7 Hz, HC*H*OCO), 3.83 (d, 1 H, J = 15.4 Hz, HC*H*Ph), 3.71 (dd, 1 H, J = 5.3 Hz, J' = 9.4 Hz, *H*CH), 3.40 (dd, 1 H, J = 5.3 Hz, J' = 9.9 Hz, CH), 2.83–2.81 (m, 1 H, HC*H*), 1.51 ()s, 9 H, Boc), 1.38 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3). Anal. Calcd for $C_{29}H_{35}N_3O_6$: C, 66.78; H, 6.76; N, 8.06. Found: C, 66.75; H, 6.54; N, 8.00.

(3*R*,4*S*) Isomer 36: yield, 0.57 g (11%); white low-melting solid; purified by preparative HPLC (AcOEt as eluant, 10 mL/min, retention time 10.23 min); $[\alpha]^{25}_D$ = −31.90° (c = 1.00, CH_2Cl_2); IR (KBr) ν 1758, 1658 (C=O) cm^{-1}; ^1H NMR (DMSO, 90 °C) δ 7.46–7.17 (m, 10 H, arom), 4.99 (dd, 1 H, J = 5.7 Hz, J' = 8.8 Hz, HCPh), 4.78 (t, 1 H, J = 8.8 Hz, *H*CHOCO), 4.70 (d, 1 H, J = 15.5 Hz, *H*CHPh), 4.37 (d, 1 H, J = 5.5 Hz, C_3H), 4.21–4.08 (m, 4 H, *H*CH, HC*H*Ph, HC*H*OCO, C_4H), 3.92–3.90 (m, 1 H, HC*H*), 3.86–3.81 (m, 1 H, CH), 1.44 (s, 3 H, CH_3), 1.42 (s, 9 H, Boc), 1.41 (s, 3 H, CH_3). Anal. Calcd for $C_{29}H_{35}N_3O_6$: C, 66.78; H, 6.76; N, 8.06. Found: C, 66.62; H, 6.54; N, 8.01.

General Procedure for the Synthesis of 4-(Hydroxymethyl)azetidin-2-ones 34 and 37. A solution of the β-lactam **33**, **35**, or **36** (5.24 g, 10 mmol) in methanol (20 mL) and 3 N HCl (20 mL) was refluxed for 2 h. Then, the resulting mixture was concentrated under reduced pressure and the residue was diluted with ethyl acetate (25 mL) and water (25 mL). The biphasic mixture was vigorously stirred and basified at 0 °C with 40% NaOH. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (2 × 25 mL). The organic layers were combined and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave an oily residue which was dissolved in acetone (90 mL) and water (10 mL). $NaIO_4$ (7.6 g, 35.22 mmol) was added in one portion, and the resulting suspension was stirred at room temperature for 24 h. Then the precipitated salts were filtered off, and the filtrate was concentrated in vacuo. The residue was diluted with dichloromethane and washed with water (20 mL). The aqueous phase was extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, washed with 3 N HCl (20 mL), and dried (Na_2SO_4). Evaporation of the solvents gave a residue which was dissolved in methanol (30 mL). The solution was cooled at 0 °C, and sodium borohydride (0.29 g, 7.95 mmol) was added. The resulting mixture was stirred at room temperature for 45 min. Then, the reaction mixture was poured into water (40 mL). The mixture was acidified with concentrated HCl and extracted with dichloromethane (3 × 20 mL). Evaporation of the solvent under reduced pressure gave the corresponding 4-(hydroxymethyl)azetidin-2-one in 71% overall yield after purification.

***cis*-(3*R*,4*S*)-1-Benzyl-4-(hydroxymethyl)-3-[(*R*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (34).** The title compound was prepared as above starting from the β-lactams **33** or **36**: yield, 2.42 g (71%). The physical and spectroscopic properties of this compound were coincident with those previously reported.[35]

***cis*-(3*S*,4*S*)-1-Benzyl-4-(hydroxymethyl)-3-[(*R*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (37).** The title compound was prepared as above starting from the β-lactam **35** and purified by column chromatography (silica gel 70–230 mesh, CH_2Cl_2 as eluent) and preparative HPLC (AcOEt as eluent, 10 mL/min, retention time 16.55 min): yield, 2.06 g (61%); white, low-melting solid; $[\alpha]^{25}_D$ = −33.0° (c = 1.00, CH_2Cl_2); IR (KBr) ν 3584 (OH), 1761, 1760 (C=O) cm^{-1}, ^1H NMR ($CDCl_3$) δ 7.44–7.25 (m, 10 H, arom), 4.99 (dd, 1 H, J = 7.2 Hz, J' = 8.6 Hz, HCPh), 4.72 (t, 1 H, J = 8.6 Hz, *H*CHOCO), 4.65 (d, 1 H, J

= 15.0 Hz, HCHPh), 4.39 (d, 1 H, J = 5.1 Hz, C_3H), 4.30 (d, 1 H, J = 15.0 Hz, HCHPh), 4.26 (dd, 1 H, J = 7.2 Hz, J' = 8.6 Hz, HCHO-CO), 3.86 (dd, 1 H, J = 5.0 Hz, J' = 12.3 Hz, HCHOH), 3.68 (dd, 1 H, J = 5.0 Hz, J' = 12.3 Hz, HCHOH), 3.56–3.51 (m, 1 H, C_4H), 3.17 (s_b, 1 H, OH). Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.00; H, 5.88; N, 8.12.

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Supplementary Material Available: Listings of experimental details and spectral data for **4a–d**, **7a,b**, **8a–d**, **11a–d**, **14a–d**, **15a**, **16a**, **22**, **23**, **28**, and **29**, tables of X-ray data and structures for **6a**, **38**, and **39**, and ^{1}H NMR spectra for **4c**, **7a,b**, and **19–21** (18 pages); table of observed and calculated structure factors (19 pages). Ordering information is given on any current masthead page.

Studies on the Thermal Generation and Reactivity of a Class of (σ,π)-1,4-Biradicals

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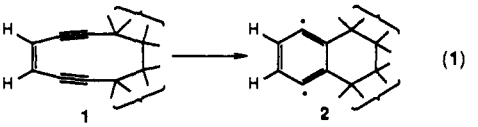
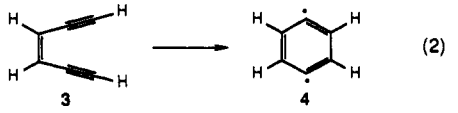
Abstract: (Z)-1,2,4-Heptatrien-6-yne and compounds that contain the (Z)-allene–ene–yne functional group or that form it in a serial reaction sequence were prepared and shown to undergo a mild thermal reaction to form aromatic products. All observations suggest that the initial step in the formation of these products is an electrocyclization reaction that forms α,3-dehydrotoluene in the parent case or the corresponding α,3-dehydroalkylbenzene in other examples. These dehydroaromatic intermediates are not observed directly but react to form products conventionally ascribed to both free radical and polar species. For example, (Z)-1,2,4-heptatrien-6-yne forms both 2-phenylethanol and phenyl methyl ether when heated in methanol. Mechanistic studies suggest that both products arise from a common intermediate, the so-called α,3-dehydrotoluene, that is best described as a singlet σ,π-biradical with substantial polar character. The partitioning between polar and free radical reaction pathways is influenced by biradical substitution and by the reaction medium in which the intermediate is generated. These results are discussed with reference to electrocyclization reactions occurring within the enediyne family of natural antitumor agents. The possibility that an α,3-dehydrotoluene intermediate might function as a DNA damaging agent and criteria for the design of molecules to implement such a strategy are discussed.

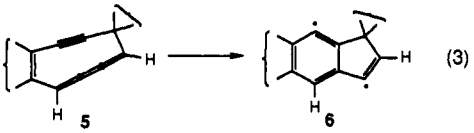
Introduction

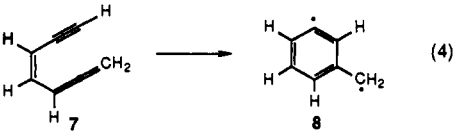
Several lines of evidence now support the intermediacy of 1,4-biradicals as a common feature in the mechanism of action of the class of natural antitumor antibiotics comprising neocarzinostatin, calichemicin, esperamicin, and, most recently, dynemicin (the enediyne antibiotics).[1] These biradical intermediates are proposed to arise by electrocyclization of highly unsaturated precursors, formed from the native antibiotic as the result of a prior chemical "activation" step.[1] In the case of the natural products calichemicin, esperamicin, and dynemicin, cyclization may be generally represented by the transformation of the (Z)-enediyne **1** to the dehydrobenzene derivative **2** (eq 1) and is recognized to be a cyclic version of a hydrocarbon thermal rearrangement studied extensively by Bergman and co-workers (**3** → **4**, eq 2), now known as the Bergman reaction.[2]





Cyclization of the (Z)-cumulene–ene–yne **5** to form the biradical **6** (eq 3) is proposed as the key step in the mechanism of action of the antitumor agent neocarzinostatin.[1a–c] This reaction





shares many features of reactions 1 and 2 but lacks precedent in known hydrocarbon thermal rearrangements. These factors led us to consider the feasibility of the related rearrangement of the acyclic hydrocarbon **7** to the biradical **8** (eq 4).[3,4] Though inspired

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