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Construction of Quaternary Stereogenic Centers via [2 + 2] Cycloaddition Reactions. Synthesis of Homochiral 4,4-Disubstituted 2-Azetidinones and Imine Substituent Effects on β-Lactam Formation

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A study on the asymmetric construction of quaternary stereogenic centers via [2 + 2] cycloaddition reaction of ketenes with ketimines is described. Reaction of achiral ketenes and chiral α-alkoxy ketone-derived imines resulted in formation of new β-lactams as single diastereomers. The cycloaddition was extended to pyruvate imines, aralkyl ketone-derived imines, and dialkyl ketimines. In these cases the asymmetric induction was satisfactorily achieved using β-silylalkanoyl ketenes and the Evans−Sjögren ketene. *C,C*-Bis (trimethylsilyl)methylamine ketimines derived from enolizable dialkyl ketones cleanly led to the corresponding C(4) disubstituted β-lactams without deprotonation. Therefore, a general methodology for a convergent asymmetric synthesis of β-lactams in which C(4) exists as a quaternary carbon is provided.

Introduction

Synthesis of molecules with a quaternary carbon center as building blocks for natural products and biologically active compounds is an active area of investigation and often presents a number of important synthetic challenges.[2] A variety of methods have been developed to satisfactorily accomplish this goal.[3] These methods can be categorized into two main groups: those involving enantioselective synthesis and those involving diastereoselective creation of quaternary centers. The latter include the usual carbon−carbon bond-forming processes such as the alkylation of chiral enamines and enolates, the aldol reaction, the asymmetric Michael addition, and the Diels−Alder cycloaddition.[4] Successful implementation of these procedures to heterocyclic synthesis has provided expedient approaches to five- and six-membered rings, often embodied in a wide variety of natural products. However, methodologies for construction of four-membered rings with quaternary stereogenic centers are still scarce. In this context, [2 + 2] cycloadditions which generate these small rings in a single step have been the subject of very few investigations.[5] Virtually all of these studies are based on photochemical reactions of alkenes, although the thermal cycloaddition of dichloroketene with chiral enol ethers has also been documented.[6]

Among the many targets that might be obtained by [2 + 2] cycloadditions, β-lactams with quaternary stereogenic centers at the C(4) position are of particular interest for several reasons. The β-lactam ring is the key structural element of the most widely employed class of antimicrobial agents, the β-lactam antibiotics.[7] Consequently, understanding the reactivity of 4,4-disubstituted β-lactams would provide new opportunities for the study of structure−activity relationships and further insight into the design of new antibiotics and/or enzyme inhibitors.[8] In fact, the discovery by the Squibb group[9] that tigemonam, Figure 1, possesses superior activity than other oral β-lactam antibiotics, specially when the pathogen was a β-lactamase producer, firmly establishes the necessity to address the problem of the stereocontrolled synthesis of 4,4-disubstituted β-lactams. In addition to

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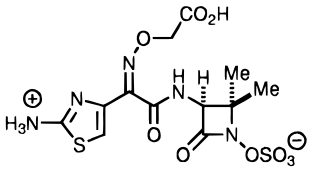

Figure 1.

these general aspects, work in this laboratory[10] and others[11] suggests that β-lactams with quaternary stereogenic centers at the C(4) position would be powerful, small building blocks for natural product synthesis, Figure 2, providing access to a wide variety of non-β-lactam products.

Thus, we have studied diastereoselective synthesis of β-lactams with quaternary stereogenic centers at C(4) using [2 + 2] cycloaddition reactions. Results of this study are presented below.

Results and Discussion

Prior to the present study, no efficient strategies either for the creation of quaternary centers at the C(4) position of the β-lactam ring or for controlling the stereochemistry at the newly created stereogenic centers have been described in the literature.[12] In a pioneering approach, Slusarchyk and Godfrey[13] applied the well established hydroxamate methodology[13c] to the formation of C(4) disubstituted β-lactams, but the method was overshadowed by rearrangement processes. Ternansky and Morin[14] reiterate the fact that, in general, most of the methods reported thus far for the synthesis of the β-lactam ring do not satisfactorily address this synthetic challenge. Consequently, we undertook a study on this subject and found that the cycloaddition of ketenes, generated from acid chlorides and triethylamine, with ketimines fulfills the above criteria and provides a general route to optically active β-lactams in which C(4) exists as a quaternary carbon.[15] Since this work represents the first systematic study on this topic, the scope and limitations of the cycloaddition reaction were explored by using a number of structurally different ketimines, i.e. α-alkoxy ketone-derived imines, pyruvate imines, aralkyl ketone-derived imines, and dialkyl ketimines. During the course of our investigations, we found that these ketimines showed different chemical and stereochemical behavior. Therefore, each class of substrate will be discussed separately.

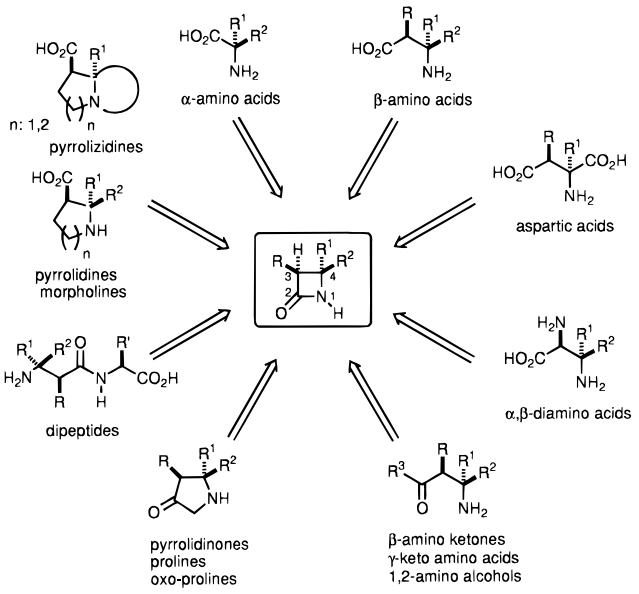

Figure 2. Potential uses of a β-lactam framework with a quaternary stereogenic center at the C(4) position.

Cycloadditions of α-Alkoxy Ketone-Derived Imines. Recent reports from this laboratory and others have

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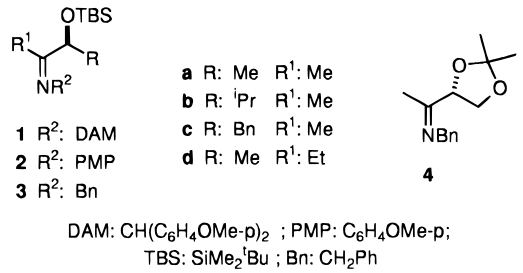
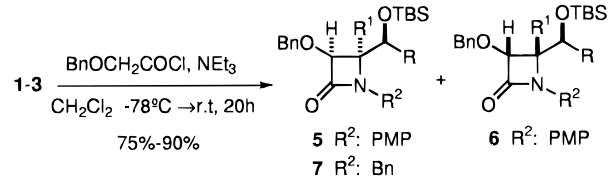


Figure 3.

Scheme 1

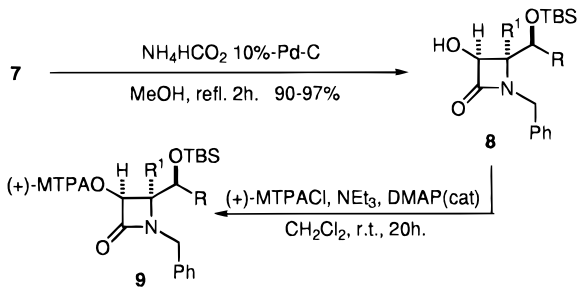


documented that cycloaddition reactions of ketenes with both α-alkoxy aldehyde-derived imines[16] and *N*-Boc α-amino aldehyde-derived imines[17] give complete induction of asymmetry from the starting imines to the newly created stereogenic centers. In contrast, the potential in asymmetric synthesis of the cycloaddition of ketenes with α-alkoxy ketone-derived imines has yet to be demonstrated. Therefore, we investigated this reaction through application of the recently advanced origins of the asymmetric induction.[17a,b]

The starting ketimines employed in this study (Figure 3) were prepared by condensation of the corresponding α-alkoxy ketones with the respective amines promoted by $TiCl_4$ following Weingarten's procedure.[18] Otherwise, a loss of optical purity was observed, *vide infra*, in the formation of the corresponding cycloadducts.

To assay the diastereoselection for this reaction, the ketimines **1a**, **1b**, **2a**, and **3a** were treated with (benzyloxy)ketene, generated from (benzyloxy)acetyl chloride and triethylamine at low temperature (Scheme 1). The experiments revealed that treatment of both **1a** and **1b** with (benzyloxy)ketene in methylene chloride at −78 °C to room temperature overnight resulted in the formation of a complex mixture in which we did not detect the expected β-lactam products. Under identical conditions ketimine **2a** led to β-lactam formation, although a mixture of diastereomeric β-lactams **5** and **6** was obtained in a ratio 70:30, respectively. Finally, we observed that **3a** efficiently produced **7a** in 85% yield and, most notably, with high diastereoselectivity. However, some limitations arose when the reaction was applied to different ketenes. For instance, haloketenes, (phenylthio)ketene,

Scheme 2



and monoalkylketenes failed to react with **3a**. In order to establish the scope of this alkoxyketene−ketimine cycloaddition, we subjected ketimines **3b**, **3c**, and **3d** to treatment with (benzyloxy)acetyl chloride and triethylamine under the above reaction conditions. In every case, a single β-lactam product was detected by ^{1}H-NMR analysis of the corresponding crude reaction mixture, and in each case a strong NOE (≈13%) was observed between the alkyl group protons at the C(4) position and the C(3)-hydrogen, indicating that these two units were in a *syn* relationship. This is particularly significant when a new β-lactam product of previously unassigned absolute stereochemistry is prepared.

To establish whether racemization occurred during the process of β-lactam formation, each compound **7** was subjected to hydrogenolysis, and the resulting 3-hydroxy β-lactams **8a**−**d** were acylated with (+)-MTPA acid chloride[19] and triethylamine in the presence of DMAP as catalyst (Scheme 2). HPLC analysis of the resulting Mosher esters **9** showed homogeneous material under conditions that cleanly resolved the corresponding esters derived from racemic material. In addition, all of these derivatives showed a single set of signals in the ^{1}H, ^{13}C, and ^{19}F NMR spectra, thus confirming the absence of racemization during ketimine formation and cycloaddition reaction. The temperature effect on the enantiomeric purity of benzyl ketimines **3** and, hence, β-lactams **7** was evidenced preparing the *N*-benzyl imine **3a** from benzylamine and the corresponding ketone at room temperature without $TiCl_4$. (Benzyloxy)ketene cycloaddition under the above conditions afforded a 70:30 mixture of **7a** and its enantiomer, respectively, as determined by the Mosher test. Finally, to assess the stereochemical assignment, compound **8b** was submitted to a single-crystal X-ray analysis.[20] Results of the cycloaddition reaction with different *N*-benzyl imines are listed in Table 1 (compounds **7a**−**d**) and show the effectiveness of this reaction to create quaternary centers, with predictable stereochemistry.

On the basis of results presented in Table 1, the imine **4**, upon treatment with (benzyloxy)ketene should generate the β-lactam **10** with absolute C(4) stereochemistry opposite to that observed for cycloadducts **7**. Indeed, as shown in Scheme 3, this was the case, and the absolute configuration of **10** was established by chemical correlation with **7a**. This correlation was carried out by conversion of **10** into the 4-carboxy β-lactam **12** by simple removal of the acetonide group in **10** followed by oxidative cleavage of the resulting glycol **11**. On the other hand,

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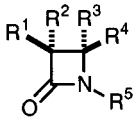
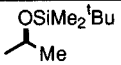
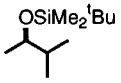
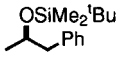
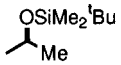
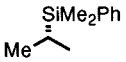
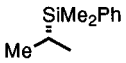
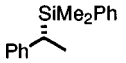
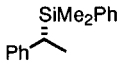
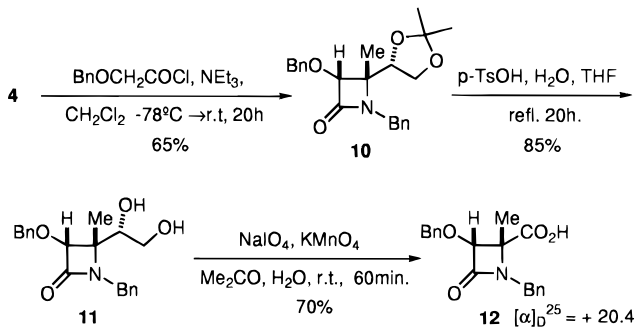
Table 1. C_3-Alkoxy- and C_3-alkyl- C_4-disubstituted β-lactams Prepared by Asymmetric Ketene-imine [2 + 2] Cycloaddition



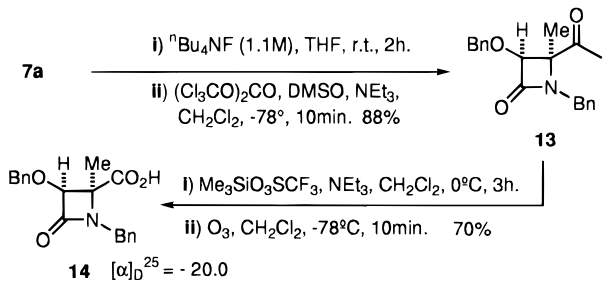
Compound	R^1	R^2	R^3	R^4	R^5	Yield[a] (%)	*d.e.* [b] (%)	m.p.[c] (°C)
7a [d]	BnO	H	Me		Bn	70	>98	Oil
7b [d]	BnO	H	Me		Bn	55	>98	Oil
7c [d]	BnO	H	Me		Bn	70	>98	Oil
7d [d]	BnO	H	Et		Bn	50	>98	Oil
10 [d]	H	BnO		Me	Bn	65	>98	Oil
21a [e]	H		CO_2Me	Me	PMP	72 (53)	44	80-81
21b [e]	H		CO_2Me	Me	$CH(SiMe_3)_2$	73 (50)	54	78-80
22a [e]	H		CO_2Me	Me	PMP	87 (69)	60	121-122
22b [e]	H		CO_2Me	Me	$CH(SiMe_3)_2$	77 (68)	91	109-112

[a] Yield of isolated reaction mixture. Isolated major product yield in parenthesis. [b] Determined by 300 MHz ^{1}H-NMR spectroscopy. d.e. values referred to both *cis* diastereomers. [c] Physical data referred to the major diastereomer. Solid compounds were crystallized from hexane and oily products were purified by preparative HPLC. [d] For reaction conditions, see Scheme 1. [e] For reaction conditions, see Scheme 6.

Scheme 3



Scheme 4



as shown in Scheme 4, **7a** was desilylated and the resulting hydroxy compound oxidized to the 4-acetyl β-lactam **13** in 88% overall yield. Subsequent ozonolysis of the corresponding trimethylsilyl enol ether led to the β-lactam **14** which was found to be the enantiomer of **12**. Enantiomerically pure 4-carboxy β-lactams are of diverse interest. For instance, ring opening is expected to give α-branched β-alkoxy aspartic acid derivatives which would be valuable elements for the design of conformationally restricted peptides.[21]

Another very useful reaction for β-lactam ring construction is the addition of metallo ester enolates to imines, a reaction that has been widely documented in the literature.[22] However, the lower reactivity of ketimines, when compared with that of aldimines, and their competitive α-deprotonation, makes the ester enolate–imine condensation impracticable for the synthesis of β-lactams disubstituted at the C(4) position. Indeed, the significance of the cycloaddition as the key reaction for diastereoselective construction of quaternary centers was

(21) For example, β-alkoxy aspartic acids, occurring in macrocyclic antibiotics, have been incorporated into peptides by the sodium azide-promoted reaction of *N*-Boc-3-alkoxy-4-alkoxycarbonyl β-lactams with α-amino acid esters. More detailed information is provided in refs 10e and 10h.

(22) Reviews: (a) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447. (b) Brown, M. J. *Heterocycles* **1989**, *29*, 2225. (c) Georg, G. I. In *Studies in Natural Product Chemistry*; Rahman, A.-ur, Ed.; Elsevier: Amsterdam, 1989; Vol. 4, p 431. (d) Fujisawa, T.; Shimizu, M. *Rev. Heteroatom Chem.* **1996**, *15*, 203. (e) Cainelli, G.; Panuncio, M.; Andreoli, P.; Martelli, G.; Spunta, G.; Giacomini, D.; Bandini, E. *Pure Appl. Chem.* **1990**, *62*, 605.

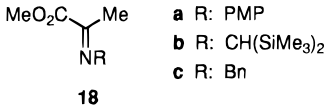
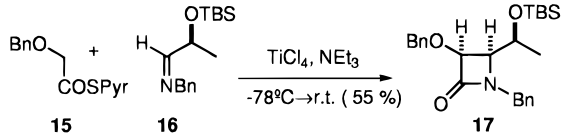
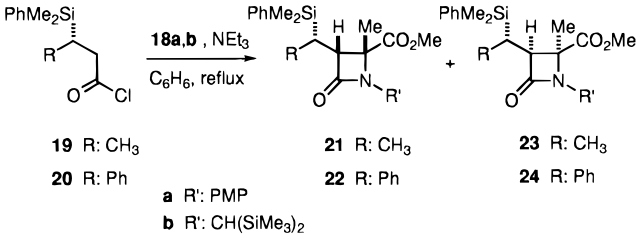


Figure 4.

Scheme 5



Scheme 6



emphasized by the failure of the titanium or lithium enolates derived from 2-pyridyl thioester **15**[23] to give the expected cycloadducts with the ketimine **3a** using the same conditions to transform the parent aldehyde-derived imine **16** into **17** (Scheme 5).

Cycloadditions of Pyruvate Imines. Interest in 4-alkoxycarbonyl β-lactams as antibiotics and as masked forms of aspartic acid derivatives led our exploration to pyruvate imines **18** (Figure 4). Since these starting materials were achiral, asymmetric induction required the use of chiral ketenes. The first system examined was based on previous studies using unactivated ketenes and glyoxylate imines for the production of 3-alkyl β-lactams.[24] We elected to use β-silylalkylketenes (Scheme 6), generated from optically active β-silylalkanoyl chlorides and triethylamine, for two reasons. First, the silyl group can be removed from the reaction product after the stereochemical control has been effected; second, it can be converted into a hydroxyl group with retention of configuration.[25] As a consequence, the resulting cycloadducts could be transformed into either β-alkyl α,α-disubstituted aspartates[10k] or branched aminosugars[11m,n] and also might be employed as precursors of structurally modified new carbapenems.[26] As shown in Scheme 6, reaction of the β-(dimethylphenylsilyl)butanoyl chloride (**19**)[27] with the pyruvate imine **18a** in the presence of triethylamine led to the formation of the β-lactam product

Scheme 7

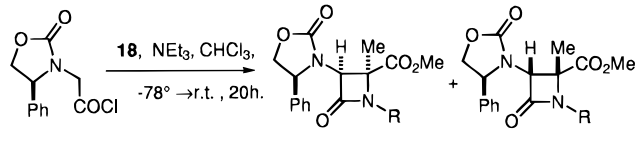
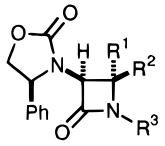


Table 2. C_3-Amido- C_4-disubstituted β-lactams Prepared by Asymmetric Ketene-imine [2 + 2] Cycloaddition



compound	R^1	R^2	R^3	yield[a] (%)	de[b] (%)	mp[c] (°C)
26a	Me	CO_2Me	C_6H_4OMe-*p*	60 (36)	20[d]	165−166
26b	Me	CO_2Me	$CH(SiMe_3)_2$	39 (33)	10[d]	136−138
26c	Me	CO_2Me	Bn	68 (41)	20[d]	oil
32a	Me	Ph	Bn	65 (65)	>98	145−146
32b	Me	C_6H_4OMe-p	Bn	65 (65)	>98	143−144
32c	Me	*(E)*-CH=CHPh	Bn	77 (67)	80	168−170
35a[e]	Me	Me	$CH(SiMe_3)_2$	70	>98	101−103
35b[e]	Et	Et	$CH(SiMe_3)_2$	69	>98	101−102
35c[e]	nPr	nPr	$CH(SiMe_3)_2$	70	>98	195−197
35d[e]	Me	Et	$CH(SiMe_3)_2$	80[f]	70	124−126
35e[e]	Me	CH_2CH_2Ph	$CH(SiMe_3)_2$	60[f]	44	120−122
35f	H	Me	$CH(SiMe_3)_2$	75 (49)	40	142−144
35g	H	CH_2CH_2Ph	$CH(SiMe_3)_2$	78 (60)	66	oil

[a] Yield of isolated reaction mixture. Isolated major product yield in parentheses. [b] Determined by 300 MHz ^{1}H-NMR spectroscopy. de values refer to both *cis* diastereomers. [c] Solid compounds were crystallized from hexane, and oily products were purified by preparative HPLC. [d] de value referred to C_3 *(R)* and *(S) cis* stereoisomers. [e] For reaction conditions, see Scheme 10. [f] Reaction carried out using a two-fold excess of acid chloride.

21 together with its diastereomer **23** in a ratio of 75:25. A somewhat better result was obtained when the reaction was performed with the acid chloride **20** to give β-lactams **22**/**24** in a ratio of 90:10, respectively. Next, for reasons that will be outlined later, we investigated the pyruvate imine **18b** for such a cycloaddition. Although chemical yields and stereoselectivities were analogous to that from **18a** (see Table 1), the *N*-bis(trimethylsilyl)methyl moiety could be removed cleanly by the action of cerium(IV) ammonium nitrate to give the corresponding *N*-H-azetidin-2-ones in theoretical yields and without the necessity of further purifications, *vide infra*. The sense of asymmetric induction for these reactions was established on the basis of a single crystal X-ray analysis of the cycloadduct **22b** (see Experimental Section) and by the assumption of a uniform reaction mechanism.

At this stage, we sought out alternative ketenes with the aim to improve the stereochemical outcome of the above cycloadditions. Literature precedent covering this topic suggested that the Evans−Sjögren ketene,[28] derived from **25**, Scheme 7, should be the most suitable candidate to achieve high levels of reaction diastereoselection. However, as shown in Table 2, while the above chiral alkylketenes gave reasonably good stereochemical outcome for cycloadditions, the pyruvate imines **18** on treatment with **25** and triethylamine failed to produce

(23) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Ponzini, F. *J. Org. Chem.* **1993**, *58*, 4746.

(24) Palomo, C.; Aizpurua, J. M.; Urchegui, R.; Iturburu, M. *J. Org. Chem.* **1992**, *57*, 1571.

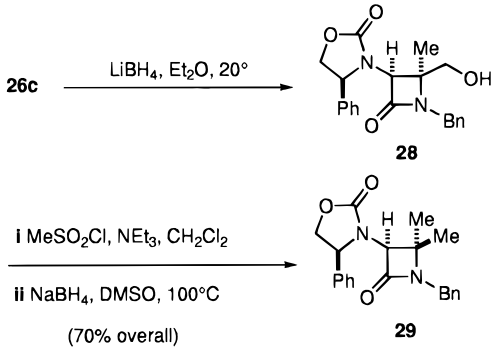
(25) (a) Fleming, I. *Pure Appl. Chem.* **1988**, *60*, 71. (b) Hwu, J. R.; Wang, N. *Chem. Rev.* **1989**, *89*, 1599. (c) Ager, D. J.; East, M. B. *Tetrahedron* **1992**, *48*, 2803.

(26) Owing to the easy conversion of the 4-alkoxycarbonyl group into different functional groups and/or the possibility to replace it directly by alkyl chains via decarboxylative radical conjugate addition to Michael acceptors, renders these azetidinones attractive potential building-blocks in β-lactam chemistry. See for example ref. 22 and (a) Sumi, K.; DiFabio, R.; Hanessian, S. *Tetrahedron Lett.* **1992**, *33*, 749. (b) Veiberg, G. A.; Lukevics, E. *Heterocycles* **1994**, *38*, 2309. (c) Kant, J.; Walker, D. G. In "The Organic Chemistry of β-Lactams", Georg, G. I. Ed. VCH: New York, **1992**, p 121. (d) Kametani, T. *Heterocycles* **1982**, *17*, 463.

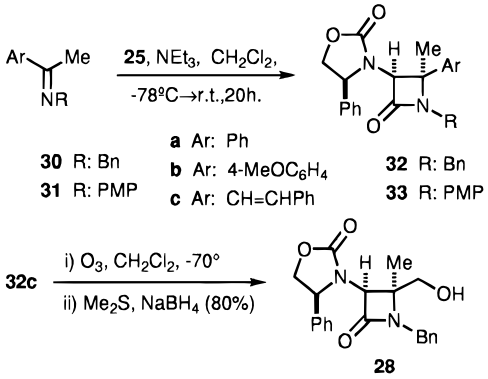
(27) For the preparation of homochiral β-silylalkanoyl chlorides, see: Palomo, C.; Aizpurua, J. M.; Iturburu, M.; Urchegui, R. *J. Org. Chem.* **1994**, *59*, 240, and references therein.

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

Scheme 8



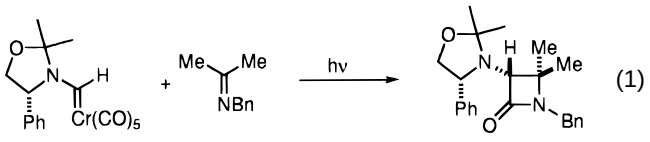
Scheme 9



good diastereoselectivity. For example, reaction of the ketene derived from **25** and the pyruvate imine **18a** furnished a mixture of **26a** and **27a** in a diastereomeric ratio of 60:40, respectively. In a similar way, the pyruvate imines **18b** and **18c** led to the corresponding β-lactams **26b,c** and **27b,c** without diastereoselection. In each β-lactam product, the NOE observed ≈10% between the methyl group at the C(4) position and the C(3)-hydrogen suggested a relative *cis*-stereochemistry for the adducts.

To confirm the proposed stereochemistry, the major isomer **26c** was transformed, Scheme 8, into the hydroxymethyl derivative **28**, and this into the 4,4-dimethylazetidinone **29**, which was also obtained by another independent route, *vide infra*.

Cycloadditions of Aralkyl Ketone-Derived Imines. Next, we evaluated the behavior of other achiral ketimines in such a cycloaddition process from both chemical and stereochemical standpoints. Prior to the present study, Hegedus and co-workers[29] reported the cycloaddition reaction of asymmetric ketenes, generated by photolysis of chromium aminocarbene complexes, with acetone benzyl imine (eq 1). In this process, however, a modest level of asymmetric induction, 70% de, which contrasts with that obtained using aldehyde-derived imines, was attained. Therefore, we were intrigued by the question of whether asymmetric induction could be effected employing the chiral ketene derived from **25**.



(1)

The reaction of oxazolidinylacetic acid chloride **25** and triethylamine, Scheme 9, with ketimines **30a**−**c** and **31a**−**c** was examined. In each case the reaction was conducted at low temperature by adding **25** to a solution of the corresponding ketimine and triethylamine. Under these conditions the corresponding β-lactam products **32a**−**c**, and **33a**−**c** were obtained in yields ranging from 60% to 70%, and in each case as single diastereomers. This result implies that, in principle, the stereochemical course of the reaction corresponds to that observed for aldimines, and, therefore, the general pattern seems to be unaffected by the presence of alkyl substituents on the ketimine component. The absolute stereochemistry at the C(3) position of the resulting cycloadducts is completely governed by the configuration of the stereogenic center of the oxazolidinone moiety, while the absolute configuration of the C(4) position is dictated by the *cis*/*trans* specificity of the β-lactam-forming process.[30] To test this hypothesis, the β-lactam product **32c** was transformed into the hydroxymethyl derivative **28** which was identical to that obtained by reduction of the methoxycarbonyl group in **26c**, *vide supra*.

With these results in hand, a direct comparison between the chemistry in eq 1 and reactions in Scheme 9 can be made. In particular, the high level of diastereoselectivity seems to be the most significant feature of these reactions although chemical yields were also good. However, attempts to extend this approach to ketimines derived from more easily enolizable ketones, i.e. dialkyl ketone-derived imines, resulted in the formation of enamides, along with substantial amounts of hydrolysis product. Consequently, at this stage we focused on this problem which also appears to be general for cycloadditions involving enolizable aldehyde-derived imines.[31]

Cycloadditions of Dialkyl Ketone-Derived Imines. Stimulated by the clinical development of the monocyclic β-lactam tigemonam,[9b] we investigated the problem of preparing 4,4-dialkyl β-lactams via this ketene−ketimine cycloaddition reaction. We reasoned that this convergent approach would be complementary to the hydroxamate methodology, overcoming drawbacks like dehydration, rearrangement processes,[13] or the need for a highly diastereoselective access to the starting chiral β-hydroxy acids with quaternary centers at the β-position which are not readily available or not easy to prepare.[32]

Recent semiempirical studies indicate that the cycloaddition of ketenes with imines to form β-lactams occurs through a zwitterionic intermediate.[30] It follows that any structural change that would serve to stabilize this intermediate and/or to circumvent competitive deprotonations should assist the β-lactam-forming process. A potential solution to the aforementioned problem may be inferred from the known ability of silicon to influence the reactivity at electron-deficient β- and γ-centers.[33] In the course of our studies on carbon−carbon bond-forming reactions, we have developed the *C*,*C*-bis(trimethylsilyl)-

(29) Hegedus, L. S.; Imiwinkelried, R.; Alarid-Sargent, M.; Dvorak, D.; Satoh, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1109.

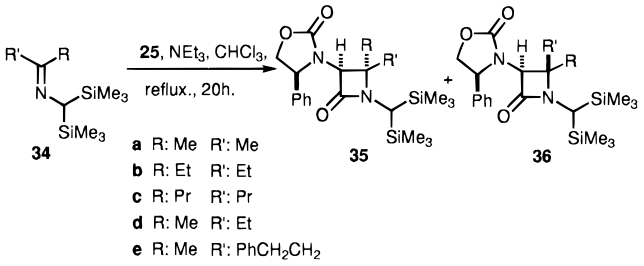
(30) (a) Cossio, F. P.; Ugalde, J. M.; Lopez, X.; Lecea, B.; Palomo, C. *J. Am. Chem. Soc.* **1993**, *115*, 995. (b) Sordo, J. A.; Gonzalez, J.; Sordo, T. L. *J. Am. Chem. Soc.* **1992**, *114*, 6249. (c) Arrieta, A.; Lecea, B.; Ugalde, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 2085.

(31) Palomo, C.; Aizpurua, J. M.; Legido, M.; Galarza, R.; Deya, P. M.; Dunogues, J.; Picard, J. P.; Ricci, A.; Seconi, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *11*, 1239.

(32) After completion of this work, a paper dealing with the synthesis of 4,4-disubstituted β-lactams via hydroxamate methodology has been appeared. See: Ageno, G.; Banfi, L.; Cascio, G.; Guanti, G.; Manghisi, E.; Riva, R.; Rocca, V. *Tetrahedron* **1995**, *51*, 8121.

(33) Review: Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677.

Scheme 10

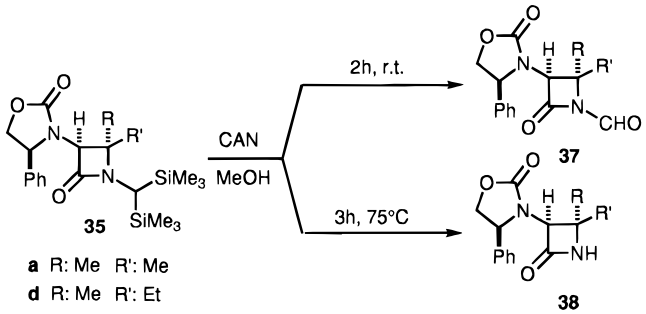


methylamine[34] as an α-aminomethyl carbanion equivalent and applied it to the synthesis of azadienes,[35] enamides and 1,2-dihydroisoquinolines,[36] pyrrolidines,[37] and bicyclic β-lactam compounds.[38] Therefore, to test the above hypothesis, the behavior of representative ketimines derived from this silyl-based methylamine reagent was examined.[39]

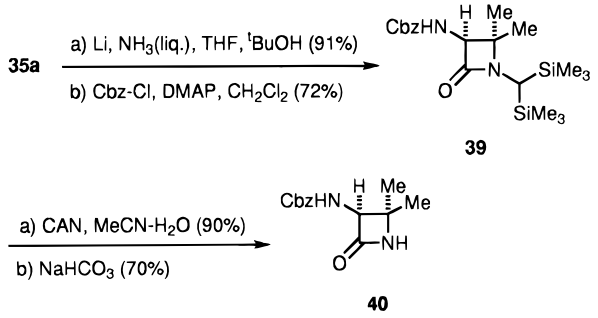
The reaction of imine **34a**, Scheme 10, with the ketene derived from **25** was first carried out at low temperature as in the previous cases. The expected β-lactam **35a** was formed, albeit in very poor yield. In contrast, heating a mixture of **34a**, **25**, and triethylamine in chloroform, free of ethanol, at reflux, produced exclusively **35a** in 70% yield. In a similar way, ketimines **34b** and **34c** produced the desired cycloadducts **35b** and **35c** in yields of 69% and 70%, respectively. When the reaction was examined from the unsymmetrical ketimines **34d** and **34e**, two diastereomeric pairs of β-lactams **35d**/**36d** (65% yield) and **35e**/**36e** (60% yield) were formed in 70:30 and 62:38 ratios, respectively. In an effort to improve this chemical yield, we repeated the cycloaddition of ketimine **34d** using a two-fold excess of acid chloride **25**. Remarkably, not only the yield was increased to 80%, but also the reaction diastereoselectivity improved to a 85:15 ratio. Under these conditions, the major isomers **35d** and **35e** were separated in 45% and 62% yield by silica gel column chromatography.

Since removal of the *N*-[bis(trimethylsilyl)methyl] moiety is an indispensable condition for these β-lactams to find application in β-lactam chemistry, at this stage, we addressed this issue and, after screening our previously reported method,[40] we found that cerium ammonium nitrate (CAN) was very effective in promoting the C−Si bond cleavage.[41] Thus, when both **35a** and **35d** were

Scheme 11



Scheme 12



subjected to treatment with CAN in methanol as solvent within about 2 h at room temperature, the *N*-formyl derivatives **37a** and **37d** were produced in >95% yields. In addition, a single crystal X-ray analysis of **37d** (see Experimental Section) confirmed the initially assigned relative stereochemistry for **35d**. Interestingly, the same reaction carried out under reflux conditions led to the *N*-unsubstituted β-lactams **38a** and **38d** in a single step, and in yields of 92% and 90%, respectively.

Alternatively, removal of the oxazolidinone moiety in **35a**, Scheme 12, followed by treatment of the resulting intermediate 3-amino β-lactam with benzyl chloroformate and DMAP, gave **39** in 65% over the two steps.[42] Subsequent exposure of **39** to CAN in acetonitrile−water and further *N*-deformylation[43] in a slightly basic medium afforded **40** in 41% overall yield (not improved). Finally, it should be mentioned that besides the utility of these β-lactams for the development of β-lactam antibiotics, they have also found application in the β-amino acid chemistry.[44]

(34) The *C,C*-bis(trimethylsilyl)methylamine can be prepared in gram quantities by reductive silylation (Li, $ClSiMe_3$, HMPA−THF) of either cyanotrimethylsilane or *N,N*-dimethylcyanamide. For details, see: (a) Picard, J. P.; Grelier, S.; Constantieux, T.; Dunogues, J.; Aizpurua, J. M.; Palomo, C.; Pétraud, M.; Barbe, B.; Lunazzi, L.; Leger, J. M. *Organometallics* **1993**, *12*, 1378. (b) Grelier, S.; Constantieux, T.; Deffieux, D.; Bordeau, M.; Dunogues, J.; Picard, J. P.; Palomo, C.; Aizpurua, J. M. *Organometallics* **1994**, *13*, 3711.

(35) Lasarte, J.; Palomo, C.; Picard, J. P.; Dunogues, J.; Aizpurua, J. M. *J. Chem. Soc., Chem. Commun.* **1989**, 72.

(36) Palomo, C.; Aizpurua, J. M.; Legido, M.; Picard, J. P.; Dunogues, J.; Constantieux, T. *Tetrahedron Lett.* **1992**, *33*, 3903.

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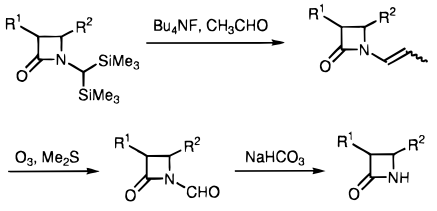
(39) These ketimines were prepared by mixing an excess of the corresponding ketone (20 mL) and *C,C*-bis(trimethylsilyl)methylamine (10 mmol) and stirring overnight either at room temperature (for **34a**, **34b**, and **34d**) or at reflux temperature for (**34c**). On completion, the excess of ketone was evaporated, and the imines were purified by reduced pressure distillation.

(40) The bis(trimethylsilyl)methyl moiety was first removed using the following three-step sequence according to the procedure given in ref 35.



(41) This method was inspired in the work by Mariano: Zhang, X. M.; Jung, Y. S.; Mariano, P. S.; Fox, M. A.; Martin, P. S.; Merkert, J. *Tetrahedron Lett.* **1993**, *34*, 5239.

(42) The acylation of the intermediate 3-amino β-lactam with Cbz-Cl produced a side product which was not identified. On the other hand, removal of the oxazolidinone ring after deprotection of the *N*-substituent caused complete destruction of the corresponding β-lactam.

(43) For *N*-deformylation methods, see: Georg, G. I.; He, P.; Kant, J.; Wu, Z. J. *J. Org. Chem.* **1993**, *58*, 5771.

Conclusion

Studies herein demonstrate the chemical and stereochemical efficiency of the Staudinger reaction, relative to the alternative ester-enolate imine approach, for the construction of homochiral β-lactams with quaternary stereogenic centers at the C(4) position. Consequently, this work helps to close a gap in the field of β-lactam synthesis by providing for the first time a wide variety of structurally different C(4)-disubstituted β-lactams in a single synthetic step. Most of these compounds can be further transformed into other targets of biological interest including amino acids, peptides, sugars, and heterocycles involving a quaternary carbon and, thereby, an open access to classes of compounds beyond those shown here. We believe that this method can lead to strategies for library generation that combine the case of solution synthesis with the solid-supported synthetic methodology recently highlighted by Gallop.[45] Further studies will address these possibilities.

Experimental Section

General Experimental.[46] Melting points were determined with capillary apparatus and are uncorrected. Proton nuclear magnetic resonance (300 MHz) spectra and ^{13}C spectra (75 MHz) were recorded at room temperature for $CDCl_3$ solutions, unless otherwise stated. All chemical shifts are reported as δ values (ppm) relative to residual $CDCl_3$ δ_H (7.26 ppm) and $CDCl_3$ δ_C (77.0 ppm) as internal standards, respectively. Mass spectra were obtained on a mass spectrometer (70 eV) using GC-MS coupling (column: fused silica gel, 15 m, 0.25 mm, 0.25 μm phase SPB-5). Optical rotations were measured at 25 $\pm$ 0.2 °C in methylene chloride unless otherwise stated. HPLC analyses were performed on a preparative column (25 cm, 3.0 cm 7 μm phase Lichrosorb-Si60) with flow rates of 10 mL/min and using a UV detector (254 nm). Flash chromatography was executed with Merck Kiesegel 60 (230−400 mesh) using mixtures of ethyl acetate or methylene chloride and hexane as eluants. Hexane was dried and purified by distillation. Tetrahydrofuran was distilled over sodium and benzophenone (indicator). Methylene chloride and chloroform were shaken with concentrated sulfuric acid, dried over potassium carbonate, and distilled. Commercially available compounds were used without further purification unless otherwise noted. [(4*S*)-2-oxo-4-phenylxazolidin-3-yl]acetyl chloride was prepared according to literature procedures.[28a]

General Procedure for the Preparation of Imines 1−4. The corresponding amine (15 mmol) and triethylamine (2.77 mL, 20 mmol) were successively added dropwise to a cooled solution (−78 °C) of the corresponding ketone (10 mmol) in dry CH_2Cl_2 (50 mL). $TiCl_4$ (1 M solution in CH_2Cl_2, 5.0 mL) was carefully added dropwise to the above mixture, maintaining the temperature below −70 °C. The resulting suspension was stirred at −78 °C for 90 min and then washed with cold water (20 mL, ice−water), filtered through Celite, and washed with cold NH_4Cl (0.5 M, ice−water, 10 mL). The organic layer containing the kenimine was separated, dried over $MgSO_4$, and used without further purification in the next step.

General Procedure for the Synthesis of α-Benzyloxy β-Lactams 7 and 10. A solution of (benzyloxy)acetyl chloride (2.05 mL, 13 mmol) in CH_2Cl_2 (15 mL) was added dropwise to a stirred solution containing the corresponding imine (10 mmol) prepared as above and triethylamine (3.24 mL, 23.3 mmol) in dry CH_2Cl_2 under nitrogen 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 rt. The mixture was diluted with CH_2Cl_2 (25 mL) and washed with water (25 mL), 0.1 M HCl (25 mL), and saturated solution of $NaHCO_3$ (25 mL). The organic layer was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to give the crude β-lactam, which was purified by column chromatography (silica gel 200 mesh, EtOAc−hexanes (1:10) as eluent).

General Procedure for the Preparation of α-Hydroxy β-Lactams 8. A suspension of the corresponding α-benzyloxy β-lactam (10 mmol), NH_4HCO_2 (3.89 g, 61.7 mmol), and 10% Pd on carbon (3.5 g) was refluxed with stirring in methanol (20 mL) for 1 h. The mixture was filtered through Celite, poured into H_2O (50 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to afford the corresponding α-hydroxy β-lactams **8**.

(3*S*,4*S*)-1-Benzyl-4-[(1*S*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-3-hydroxy-4-methylazetidin-2-one (8a): yield, 97%; mp: 103−104 °C; $[\alpha]_D^{25} = -3.5$ (c = 0.2, CH_2Cl_2); IR (KBr) 3334, 1727 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.31−7.28 (m, 5H); 4.61 (d, 1H, J = 15.3 Hz); 4.29 (s, 1H);4.29 (d, 1H, J = 15.3 Hz); 4.20 (q, 1H, J = 6.4 Hz); 1.20 (d, 3H, J = 6.4 Hz); 1.13 (s, 9H). ^{13}C NMR ($CDCl_3$, δ) 169.5, 137.3, 128.6, 128.4, 128.3, 128.2, 127.5, 82.6, 72.3, 68.3, 44.7, 25.9, 18.8, 18.0, 17.5, −3.27, −4.3. Anal. Calcd for $C_{19}H_{31}NO_3Si$: C, 65.28; H, 8.96; N, 4.01. Found: C, 65.40; H, 8.95; N, 3.99.

(3*S*,4*S*)-1-Benzyl-4-[(1*S*)-1-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl]-3-hydroxy-4-methylazetidin-2-one (8b): yield, 90%; mp: 143 °C; $[\alpha]_D^{25} = +25.0$ (c = 1, CH_2Cl_2); IR (NaCl, film) 3267, 1750 cm^{-1}. ^1H NMR ($CDCl_3$, δ) 7.32−7.25 (m, 5H); 4.80 (d, 1H, J = 15.2 Hz); 4.38 (s_b, 1H); 4.24 (d, 1H, J = 15.2 Hz); 4.09 (d, 1H, J = 2.4 Hz); 1.88−1.82 (m, 1H); 1.15 (s, 3H); 1.07 (d, 3H, J = 4.2 Hz); 1.02 (s, 9H); 0.91 (d, 3H, J = 7.2 Hz); 0.18 (s, 3H); 0.19 (s, 3H). ^{13}C NMR ($CDCl_3$, δ) 170.6, 138.0, 128.6, 128.4, 128.3, 128.4, 82.1, 80.1, 70.2, 45.6, 30.6, 26.5, 22.4, 18.6, 17.6, 17.3, −2.2, −3.9. Anal. Calcd for $C_{21}H_{35}NO_3Si$: C, 66.79; H, 9.36; N, 3.71. Found: C, 67.01; H, 9.35; N, 3.70.

(3*S*,4*S*)-1-Benzyl-4-[(1*S*)-1-[(*tert*-butyldimethylsilyl)oxy]-2-phenylethyl]-3-hydroxy-4-methylazetidin-2-one (8c): yield, 92%; mp: 152−153 °C. $[\alpha]_D^{25} = +2.3$ (c = 1.0, CH_2Cl_2); IR (NaCl, film) 3373, 1735 cm^{-1}. ^1H NMR ($CDCl_3$, δ) 7.37−7.22 (m, 10H); 4.77 (d, 1H, J = 4.6 Hz); 4.64 (d, 1H, J = 15.2 Hz); 4.53 (d, 1H, J = 4.6 Hz); 4.47 (dd, 1H, J = 3.7, 7.6 Hz); 4.03 (d, 1H, J = 15.2 Hz); 3.13 (dd, 1H, J = 3.7, 14.3 Hz); 2.70 (dd, 1H, J = 7.6, 14.Hz); 1.23 (s, 3H); 0.95 (s, 9H); 0.06 (s, 3H); −0.53 (s, 3H). ^{13}C NMR ($CDCl_3$, δ) 169.5, 139.0, 137.5, 128.8, 128.7, 128.4, 128.4, 127.6, 126.4, 82.3, 78.5, 68.3, 45.2, 41.3, 26.1, 18.5, 18.1, −3.8, −4.7. Anal. Calcd for $C_{25}H_{35}NO_3Si$: C, 70.53; H, 8.30; N, 3.29. Found: C, 70.54; H, 8.31; N, 3.29.

(3*S*,4*S*)-1-Benzyl-4-[(1*S*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-3-hydroxy-4-ethylazetidin-2-one (8d): yield, 95%; syrup; $[\alpha]_D^{25} = +6.0$ (c = 1.0, CH_2Cl_2); IR (NaCl, film) 3280, 1724 cm^{-1}. ^1H NMR ($CDCl_3$, δ) 7.36−7.26 (m, 10H); 4.88 (d, 1H, J = 12.1 Hz); 4.71 (d, 1H, J = 12.1 Hz); 4.67 (d, 1H, J = 10.1 Hz); 4.32 (s, 1H); 4.28 (d, 1H, J = 10.1 Hz); 4.27 (q, 1H, J = 6.3 Hz); 1.67 (q, 2H, J = 7.5 Hz); 1.23 (d, 3H, J = 6.3 Hz); 0.92 (s, 9H); 0.57 (t, 3H, J = 7.5 Hz); 0.09 (s, 3H); 0.04 (s, 3H). ^{13}C NMR ($CDCl_3$, δ) 168.6, 137.1, 137.0, 128.5, 128.4, 127.8, 127.4, 127.3, 80.1, 71.2, 70.1, 44.7, 44.8, 25.8, 24.5, 19.1, 17.9, 8.0, −2.8, −4.5. Anal. Calcd for $C_{20}H_{33}NO_3Si$: C, 48.58; H, 6.73; N, 2.83. Found: C, 48.73; H, 6.79; N, 2.86.

(3*R*,4*S*)-1-Benzyl-3-(benzyloxy)-4-[(1*R*)-1,2-dihydroxyethyl]-4-methylazetidin-2-one (11). A solution of the β-lactam **10** (3.81 g, 10 mmol) in THF (95 mL) and H_2O (15 mL) containing *p*-toluenesulfonic acid (0.65 g, 3.4 mmol) was refluxed for 15 h, and then the organic solvent was evaporated under reduced pressure. To the resulting mixture was added saturated aqueous solution of $NaHCO_3$ (30 mL) and extracted three times with EtOAc (25 mL). The organic solvent was

(44) For a more detailed experimental information on this subject, see: Palomo, C.; Aizpurua, J. M.; Galarza, R.; Mielgo, A. *J. Chem. Soc., Chem. Commun.* **1996**, 633.

(45) For a recent study documenting this aspect, see: Ruhland, B.; Bhandari, A.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 253.

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

dried over $MgSO_4$ and evaporated under reduced pressure to give the title compound: yield, 85%; syrup; $[\alpha]_D^{25} = +74.2$ (c = 1, CH_2Cl_2); IR (NaCl, film) 3600−3200, 1730 cm^{-1}. ^1H NMR ($CDCl_3$, δ) 7.38−7.24 (m, 10H); 4.98 (d, 1H, J = 11.6 Hz); 4.70 (d, 1H, J = 11.6 Hz); 4.52 (d, 1H, J = 15.2 Hz); 4.37 (d, 1H, J = 15.2 Hz); 4.29 (s, 1H); 3.86 (dd, 1H, J = 3.5, 7.2 Hz); 3.65 (dd, 1H, J = 3.5, J = 12.2 Hz); 3.53 (dd, 1H, J = 7.2, J = 12.2 Hz); 1.10 (s, 3H). ^{13}C NMR ($CDCl_3$, δ) 166.8, 136.8, 136.4, 128.7, 128.4, 128.2, 128.1, 127.7, 88.0, 74.0, 73.6, 66.4, 62.4, 44.4, 18.3. Anal. Calcd for $C_{20}H_{27}NO_4$: C, 65.96; H, 7.28; N, 4.81. Found: C, 65.83; H, 7.23; N, 4.78.

(3*R*,4*S*)-1-Benzyl-3-(benzyloxy)-4-carboxy-4-methylazetidin-2-one (12). Sodium periodate (6.42 g, 30 mmol) was added to a solution of the β-lactam **10** (3.41 g, 10 mmol) in acetone (100 mL) and H_2O (65 mL), and a white precipitate was formed. Then, $KMnO_4$ (0.79 g, 5 mmol) was added to the reaction mixture, and an exothermic reaction occurred. After stirring 20 min at room temperature, the reaction mixture was cooled at 0 °C, and an aqueous solution of $NaHSO_3$ (40%) was added until decoloration. The mixture was extracted with EtOAc (4 × 25 mL), and the extract dried over $MgSO_4$ and evaporated under reduced pressure to give the title compound which was purified by column chromatography (silica gel 200 mesh, EtOAc-hexanes (1:2) as eluent): yield, 70%; syrup; $[\alpha]_D^{25} = +20.4$ (c = 1, CH_2Cl_2); IR (NaCl, film) 3380−3367, 1747 cm^{-1}. ^1H NMR ($CDCl_3$, δ) 7.37−7.27 (m, 10H); 6.30 (s_b, 1H); 4.88 (d, 1H, J = 15.2 Hz); 4.76 (d, 1H, J = 11.6 Hz); 4.70 (d, 1H, J = 11.6 Hz); 4.65 (s, 1H); 4.14 (d, 1H, J = 15.2 Hz); 1.29 (s, 3H). ^{13}C NMR ($CDCl_3$, δ) 175.2, 165.7, 136.2, 135.6, 128.7, 128.6, 128.5, 128.1, 127.9, 89.3, 73.4, 44.6, 68.0, 44.7, 19.8. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 69.84; H, 6.02; N, 4.22.

General Procedure for the Synthesis of β-Lactams 21, 22, and 35. Oxalyl chloride (1.30 mL, 15 mmol) was added carefully to a stirred solution of the corresponding β-(dimethylphenylsilyl)alkanoic acid or (4*S*)-(2-oxo-4-phenyl-3-oxazolidinyl)acetic acid (12 mmol) in CH_2Cl_2 (36 mL) cooled at 0 °C, followed by slow addition of anhydrous DMF (0.05 mL, cat.). After 1 h stirring at rt, the mixture was evaporated at reduced pressure to afford the corresponding acid chloride. This compound was redissolved in CH_2Cl_2 (15 mL) and added dropwise to a mixture containing 4 Å molecular sieves (2 g), the corresponding imine **18** or **34** (10 mmol), and triethylamine (3.32 mL, 24 mmol) in methylene chloride (25 mL) at 0 °C. The mixture was refluxed overnight under nitrogen, the molecular sieves were filtered off, and the filtrate was washed successively with 1 M HCl (25 mL), saturated solution of $NaHCO_3$ (25 mL), and water (25 mL). The organic layer was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to give the crude β-lactam, which was purified by column chromatography (silica gel 200 mesh, EtOAc−hexanes (1:8) as eluent). Analytical samples were available by crystallization from hexanes or by preparative HPLC.

(3*S*)-1-[Bis(trimethylsilyl)methyl]-4,4-dimethyl-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (35a): yield, 70%; mp: 101−103 °C; $[\alpha]_D^{25} = +55.4$ (c = 1.0, CH_2Cl_2); IR (KBr) 1737 cm^{-1}. ^1H NMR ($CDCl_3$, δ) 7.44−7.34 (m, 5H); 5.12 (dd, 1H, J = 6.0, 9.1 Hz); 4.71 (t, 1H, J = 9.1 Hz); 4.25 (dd, 1H, J = 6.0, 9.1 Hz); 4.10 (s, 1H); 1.78 (s, 1H); 1.30 (s, 3H); 1.04 (s, 3H); 0.12 (s, 9H); −0.06 (s, 9H). ^{13}C NMR ($CDCl_3$, δ) 161.4, 158.3, 138.7, 128.9, 128.7, 127.7, 71.3, 66.7, 61.8, 58.9, 34.7, 23.3, 21.9, 0.43, −0.1. MS (m/z, rel int) 418 (0.5), 403 (33), 345 (40), 345 (62), 104 (63), 73 (100). Anal. Calcd for $C_{21}H_{34}N_2O_3Si_2$: C, 60.24; H, 8.18; N, 6.69. Found: C, 60.22; H, 8.11; N, 6.74.

(3*S*)-1-[Bis(trimethylsilyl)methyl]-4,4-diethyl-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (35b): yield, 69%; mp: 101−102 °C; $[\alpha]_D^{25} = +57.1$ (c = 1.0, CH_2Cl_2); IR (KBr) 1759, 1738 cm^{-1}. ^1H NMR ($CDCl_3$, δ) 7.39 (s, 5H); 4.99 (dd, 1H, J = 6.7, 9.0 Hz); 4.67 (t, 1H, J = 8.8Hz); 4.16 (dd, 1H, J = 6.5Hz, J = 8.7Hz); 3.83 (s, 1H); 2.06 (s, 1H); 1.88−1.39 (m, 2H), 0.98−0.84 (m, 2H), 0.13 (s, 9H); 0.09 (s, 9H). ^{13}C NMR ($CDCl_3$, δ) 162.5, 158.2, 138.4, 129.4, 129.2, 127.6, 71.7, 68.7, 66.2, 60.0, 37.4, 26.9, 24.2, 9.2, 8.9, 1.0, 0.4 . Anal. Calcd for $C_{23}H_{38}N_2O_3Si_2$: C, 61.85; H, 8.59; N, 6.27. Found: C, 61.76; H, 8.41; N, 6.41.

(3*S*)-1-[Bis(trimethylsilyl)methyl]-4,4-dipropyl-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (35c): yield, 70%; mp: 195−197 °C; $[\alpha]_D^{25} = +65.5$ (c = 1.0, CH_2Cl_2); IR (KBr) 1757, 1740 cm^{-1}. ^1H NMR ($CDCl_3$, δ) 7.39 (s, 5H); 5.05 (dd, 1H, J = 6.1, 9.1 Hz); 4.67 (t, 1H, J = 8.7 Hz); 4.18 (dd, 1H, J = 6.0, 8.7 Hz); 3.92 (s, 1H); 2.03 (s, 1H); 1.40−1.24 (m, 8H), 1.0−0.88 (m, 6H), 0.13 (s, 9H); 0.05 (s, 9H). ^{13}C NMR ($CDCl_3$, δ) 162.6, 158.2, 138.8, 129.3, 129.1, 127.8, 71.2, 68.0, 66.7, 59.7, 37.2, 34.7, 17.9, 17.5, 14.6, 14.3, 1.0, 0.4. Anal. Calcd for $C_{25}H_{42}N_2O_3Si_2$: C, 63.25; H, 8.94; N, 5.90. Found: C, 63.02; H, 8.67; N, 6.13.

(3*S*,4*R*)-1-[Bis(trimethylsilyl)methyl]-4-ethyl-4-methyl-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (35d): yield, 80%; mp: 124−126 °C; $[\alpha]_D^{25} = +59.5$ (c = 0.34, CH_2Cl_2); IR (KBr) 1758, 1750 cm^{-1}. ^1H NMR ($CDCl_3$, δ) 7.45−7.40 (m, 5H); 5.22 (dd, 1H, J = 6.8, 9.2 Hz); 4.71 (t, 1H, J = 9.0 Hz); 4.30 (dd, 1H, J = 5.8, 8.8Hz); 4.20 (s, 1H); 1.85 (s, 1H); 1.41−1.28 (m, 2H), 1.31 (s, 3H); 0.89 (t, 3H); 0.18 (s, 9H); 0.06 (s, 9H). ^{13}C NMR ($CDCl_3$, δ) 162.0, 159.5, 139.4, 129.3, 129.1, 127.9, 71.5, 67.4, 65.4, 59.2, 35.3, 28.5, 19.8, 9.2, 0.9, 0.3. MS (m/z, rel int) 271 (1.3), 198 (70), 73 (100), 59 (49), 45 (22). Anal. Calcd for $C_{22}H_{36}N_2O_3Si_2$: C, 61.05; H, 8.40; N, 6.47. Found: C, 60.96; H, 8.20; N, 6.61.

(3*S*,4*R*)-1-[Bis(trimethylsilyl)methyl]-4-methyl-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]-4-(2-phenylethyl)azetidin-2-one (35e): yield, 60%; mp: 120−123 °C; $[\alpha]_D^{25} = +16.1$ (c = 1.0, CH_2Cl_2); IR (KBr) 1759, 1751 cm^{-1}. ^1H NMR ($CDCl_3$, δ) 7.37−7.12 (m, 10H); 5.22 (dd, 1H, J = 8.2, 6.3 Hz); 4.70 (t, 1H, J = 8.9 Hz); 4.25 (s, 1H); 4.22 (dd, 1H, J = 8.9, 6.2 Hz); 2.68−2.60 (m, 2H); 1.87 (s, 1H); 1.71-1.57 (m, 2H); 1.42 (s, 3H); 0.17 (s, 9H); −0.02 (s, 9H). ^{13}C NMR ($CDCl_3$, δ) 162.0, 159.6, 141.2, 139.9, 129.2, 128.9, 128.5, 128.2, 128.0, 126.0, 71.8, 67.8, 64.8, 59.1, 36.3, 35.5, 30.2, 20.5, 0.9, 0.4. Anal. Calcd for $C_{28}H_{40}N_2O_3Si_2$: C, 66.08; H, 7.94; N, 5.50. Found: C, 66.15; H, 8.01; N, 5.36.

(3*S*,4*R*)-1-[Bis(trimethylsilyl)methyl]-4-methyl-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (35f): yield, 49%; mp: 142−144 °C; $[\alpha]_D^{25} = +91.1$ (c = 1.0, CH_2Cl_2); IR (KBr) 1740 cm^{-1}. ^1H NMR ($CDCl_3$, δ) 7.43 (m, 5H); 5.08 (dd, 1H, J = 6.2, 8.9 Hz); 4.73 (t, 1H, J = 8.9 Hz); 4.52 (d, 1H, J = 4.8 Hz); 4.23 (dd, 1H, J = 6.2, 9.0 Hz); 3.67 (m, 1H); 2.12 (s, 1H); 1.10 (d, 3H, J = 6.3 Hz); 0.82 (s, 9H); 0.04 (s, 9H). ^{13}C NMR ($CDCl_3$, δ) 162.3, 158.4, 138.5, 129.1, 129.0, 127.6, 71.2, 60.4, 59.4, 56.7, 38.0, 13.8, -0.1, −0.2. MS (m/z, rel int) 390 (3.2), 204 (21), 104 (71), 73 (100). Anal. Calcd for $C_{20}H_{32}N_2O_3Si_2$: C, 59.36; H, 7.97; N, 6.92. Found: C, 59.02; H, 8.09; N, 6.98.

(3*S*,4*R*)-1-[Bis(trimethylsilyl)methyl]-4-methyl-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (35g): yield, 49%; oil; $[\alpha]_D^{25} = +30.2$ (c = 1.0, CH_2Cl_2); IR (NaCl, film) 1743, 1737 cm^{-1}. ^1H NMR ($CDCl_3$, δ) 7.38−7.14 (m, 10H); 4.94 (m, 1H); 4.65 (t, 1H, J = 8.8 Hz); 4.58 (d_b, 1H); 4.18 (dd, 1H, J = 8.8, 5.9Hz); 3.50 (m, 1H); 2.64 (t, 2H, J = 7.8 Hz); 2.04 (s, 1H); 1.85−1.50 (m, 2H); 0.05 (s, 9H); 0.04 (s, 9H). ^{13}C NMR ($CDCl_3$, δ) 162.7, 158.4, 140.7, 138.6, 129.2, 129.0, 128.4, 128.1, 127.5, 126.0, 71.1, 60.5, 59.2, 38.6, 32.1, 29.8, −0.1, −0.2. MS (m/z, rel int) 219 (36), 73 (100), 59 (35). Anal. Calcd for $C_{27}H_{38}N_2O_3Si_2$: C, 65.54; H, 7.74; N, 5.66. Found: C, 65.23; H, 7.99; N, 5.63.

General Procedure for the Deprotection of *N*-[Bis(trimethylsilyl)methyl] β-Lactams 35 and 39: Method A: To a solution of the corresponding β-lactam (5 mmol) in dry MeOH (40 mL) or acetonitrile (30 mL)/water (12.5 mL) was added cerium(IV) ammonium nitrate (10.96 g, 20 mmol) at room temperature, and the suspension was stirred at the same temperature for 2−3 h. The reaction mixture was taken up over water (50 mL) and extracted with EtOAc (3 × 80 mL). The organic layer was washed successively with aqueous $NaHCO_3$ (100 mL, saturated solution), aqueous $NaHSO_3$ (3 × 50 mL, 40%), aqueous $NaHCO_3$ (100 mL, saturated solution), and aqueous NaCl (100 mL, saturated solution). Drying and evaporation of solvents yielded fairly pure *N*-formyl β-lactams (e.g: **37**) which was dissolved in a mixture of acetone (8.5 mL),

aqueous $NaHCO_3$ (8.5 mL, saturated solution), and Na_2CO_3 (0.14 g, 0.5 mmol). After stirring at room temperature for 2 h, the suspension was filtered through a pad of silica gel and washed with acetone (25 mL) and the resulting solution evaporated under reduced pressure to afford *N*-H-*β*-lactams **38** or **40** which were purified by crystallization in EtOAc/hexanes. **(3*S*)-3-[(Benzyloxycarbonyl)amino]-4,4-dimethylazetidin-2-one (40):** yield, 70%; mp: 118−119 °C; $[\alpha]_D^{25} = +38.9$ ($c = 1.0$, CH_2Cl_2); IR (KBr) 3340, 3218, 1721 cm^{-1}, 1696 cm^{-1} . ^1H NMR ($CDCl_3$, δ) 7.31 (s, 5H); 6.55 (s, 1H); 6.24 (d, 1H, $J = 8.1$ Hz); 5.07 (s, 2H); 4.56 (d, 1H); 1.23 (s, 3H); 1.22 (s, 3H). ^{13}C NMR ($CDCl_3$, δ) 166.7, 156.0, 136.0, 128.4, 128.1, 127.9, 67.0, 65.7, 58.4, 26.2, 22.3. MS (*m*/*z*, rel int) 205 (3), 91 (100), 58 (77). Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.88; H, 6.51; N, 11.28. Found: C, 63.03; H, 6.59; N, 11.35.

Method B: To a solution of the corresponding *β*-lactam (5 mmol) in dry MeOH (40 mL) was added cerium(IV) ammonium nitrate (10.96 g, 20 mmol) at room temperature, and the suspension was stirred at reflux temperature for 3 h. Workup as in method A afforded pure *N*-H-*β*-lactams **38**.

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Supporting Information Available: A listing of physical and spectroscopic data of compounds **5**, **6**, **7a**−**d**, **10**, **21a**,**b**, **22a**,**b**, **26a**−**c**, **28**, **29**, **32a**−**c**, **39**, as well as the X-ray crystallographic data of **22b** and **37d** (9 pages). This material is contained in 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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