A Study on the Asymmetric Synthesis of β-Lactams through Double Stereodifferentiating Cycloaddition Reactions

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The cycloaddition reaction of chiral aminoketenes, generated from their corresponding acid chlorides and triethylamine, with chiral imines is evaluated as the most direct approach for the construction of cis-β-lactams with the absolute stereochemistry at the C_3 and C_4 positions being controlled by the ketene partner, independently of the absolute stereochemistry of the imine component.

The β-lactam skeleton is the key structural element of the most widely employed class of antibacterial agents, the β-lactam antibiotics.[1] As a consequence, a plethora of methods for the production of β-lactams are now available, and the topic has been reviewed on more than one occassion.[2] In particular, the [2 + 2] cycloaddition reaction of ketenes to imines, known as the Staudinger reaction,[3] has acquired central importance for the asymmetric construction of the azetidinone ring, from both academic and industrial standpoints.[4,5] Over the past years, this reaction has been extensively developed by using a combination of either chiral ketenes and achiral imines or achiral ketenes and chiral imines, generally providing good yields and excellent diastereoselectivity.[5] One example is the cycloaddition reaction of Evans−Sjögren ketenes, generated from chiral oxazolidinylacetic acid chlorides and triethylamine, with achiral imines to form optically active β-lactams with high levels of asymmetric induction, typically ≥96% de.[6] This exceptional quality of stereochemical control imparted by the oxazolidinone moiety has also been demonstrated in the reaction of (4(*S*)-phenyloxazolidinyl)ketene with imines derived from achiral aldehydes and either (*R*)- or (*S*)-α-amino esters (eq 1) in which the sense of the asymmetric induction is entirely dictated by the configuration of the starting ketene.[6g] On the other hand, impressive results have also been obtained in the cycloaddition reaction of achiral ketenes with chiral imines, especially when the chirality is induced by the aldehyde component.[7] By this means, virtually complete control of the level of reaction diastereoselection has been achieved using imines derived from both 1(*S*)-[8] and 1(*R*)-glyceraldehyde acetonide[9] (eq 2). Subsequent to these findings, work in this laboratory and others has also documented the utility of O-protected α-hydroxy-substituted acetaldehydes as effective tools for the asymmetric synthesis of β-lactams.[10] However, the question of the stereochemical outcome when a homochiral ketene reacts with homochiral alde-

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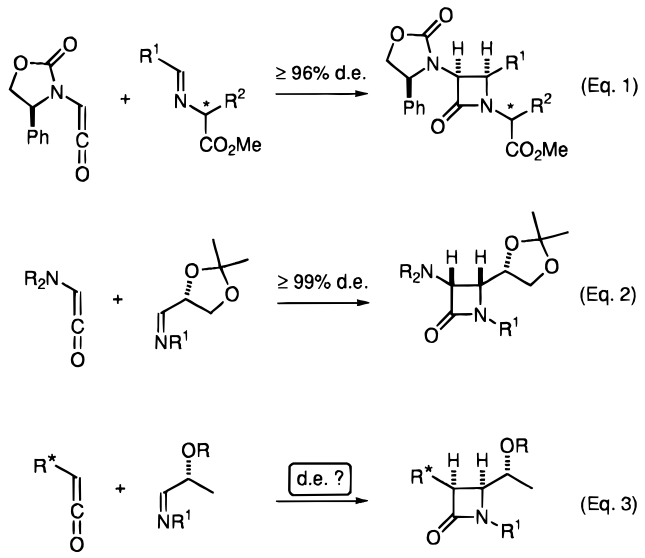
hyde-derived imines still remains unclear.[11] In particular, by understanding the stereochemical control elements involved in such processes, it would be possible to delineate a convergent access to β-lactams with the stereochemistry being controlled by the ketene partner[12] (eq 3). In particular, diastereomeric β-lactams similar to those provided by reactions in eq 2, but with the same stereochemistry at the exocyclic stereogenic center, would be accessible for the first time. As a consequence, the approach would extend the scope of β-lactam chemistry[1] and the chemistry employing β-lactams as the synthetic building blocks of non-β-lactam products.[13] Herein we disclose our studies addressing these issues.



Results and Discussion

For the study we elected to use the Evans−Sjögren ketenes derived from the acid chlorides **1** and **2** and the imines **3**, **4**, and **5** as representative examples (Figure 1). In all cases, the ketenes were generated by adding triethylamine to a solution of the corresponding oxazolidinylacetic acid chlorides **2** in methylene chloride at −78 °C (Scheme 1), the respective imines were then added to the preformed ketenes, and the mixture was allowed to react for 2 h at 0 °C and then at room temperature overnight. These reactions were selected for development in view of the existing precedents concerning the synthesis of *O*-2-isocephems,[14] a particular class of nuclear analogues of cephalosporins with promising therapeutic activity. In other terms, the success of our hypothesis would imply a single-step access to monocylic β-lactams as precursors of the bicyclic structures depicted in Figure 2. We have adopted the terminology "matched-mismatched" introduced by Masamune[15] and, accordingly,

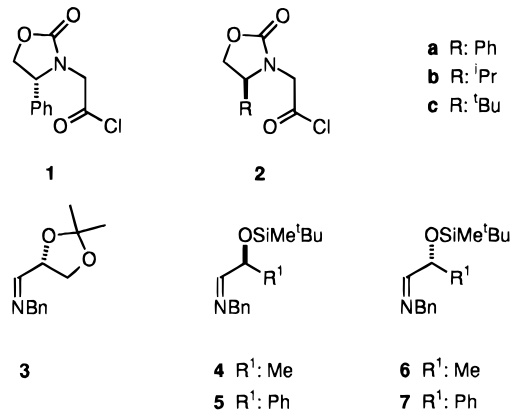
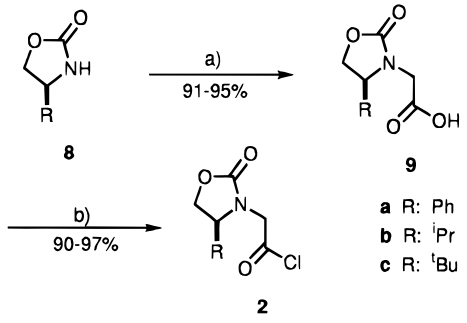


Figure 1.

Scheme 1[a]



[a] Reagents and conditions: (a) NaH, THF, $BrCH_2CO_2Me$, 2 h, 0 °C, then NaOH, H_2O, THF, 2 h, rt; (b) ClCOCOCl, CH_2Cl_2, DMF cat., 1 h, rt.

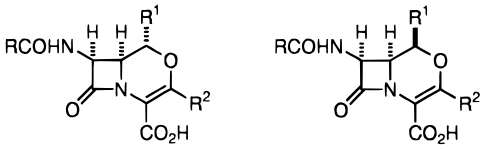


Figure 2.

when both chiral reagents creating two new stereocenters (x,y) display the same or opposite induction sense, the interactions are termed "x,y-matched" and "x,y-mismatched", respectively.

Reaction of Chiral Aminoketenes with Chiral Imines Derived from Chiral α-Oxy Aldehydes and Achiral Amines. The 3,4-Matched and 3,4-Mismatched Cases. Although the concept of double asymmetric induction has been extensively applied to a wide array of important reactions, hitherto the interaction of two chiral reactants in [2 + 2] cycloaddition reactions involving ketenes remains an unexplored area.[15,16] There-

(11) For a recent paper dealing with the reaction of achiral ketenes with imines derived from chiral aldehydes and chiral amines, see: (a) Niu, C.; Miller, M. J. *Tetrahedron Lett.* **1995**, *36*, 497. (b) Niu, C.; Petterson, T.; Miller, M. J. *J. Org. Chem.* **1996**, *61*, 1014.

(12) For details on the mechanism of the Staudinger reaction, see: (a) ref 4a. (b) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784. (b) Sordo, J. A.; González, J.; Sordo, T. L. *J. Am. Chem. Soc.* **1992**, *114*, 6249. (c) Palomo, C.; Cossío, F. P.; Cuevas, C.; Lecea, B.; Mielgo, A.; Roman, P.; Luque, A.; Martínez-Ripoll, M. *J. Am. Chem. Soc.* **1992**, *114*, 9360. (d) Cossío, F. P.; Ugalde, J. M.; López, X.; Lecea, B.; Palomo, C. *J. Am. Chem. Soc.* **1993**, *115*, 995. (e) Yamabe, S.; Minato, T.; Osamura, Y. *J. Chem. Soc., Chem. Commun.* **1993**, 450.

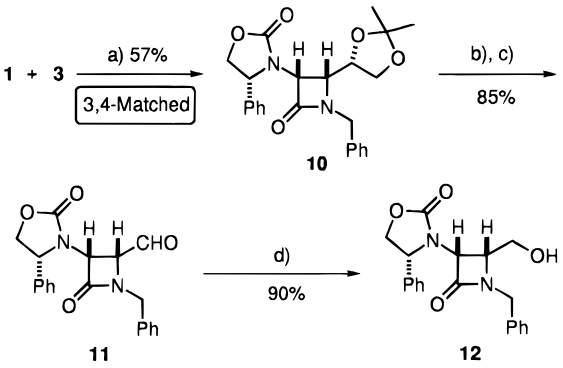
(13) For detailed information on this topic, see: (a) Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755. (b) Ojima, I. *Acc. Chem. Res.* **1995**, 383. (c) Hesse, M. In *Ring enlargement in Organic Chemistry*; VCH: Weinheim, 1991. (d) Hegedus, L. S. *Acc. Chem. Res.* **1995**, *28*, 299.

(14) For representative synthetic strategies to *O*-2-isocephems, see: (a) Tenneson, S. M.; Belleu, B. *Can. J. Chem.* **1980**, *58*, 1605. (b) Doyle, T. W.; Douglas, J. L.; Bellau, B.; Conway, T. T.; Ferrari, C. F.; Horning, D. E.; Lim, G.; Luh, B. Y.; Martel, A.; Menard, M.; Morris, M. L.; Misiek, M. *Can. J. Chem.* **1980**, *58*, 2508. (c) Hakimelahi, G. H. *Helv. Chim. Acta* **1982**, *65*, 1378. (d) Hrytsak, M.; Durst, T. *Heterocycles* **1987**, *26*, 2393. (e) Mastarelz, H.; Vinet, V. *J. Chem. Soc., Chem. Commun.* **1987**, 1283. (f) Nitta, H.; Hatanaka, M.; Ishimura, T. *J. Chem. Soc., Chem. Commun.* **1987**, 51. (g) Nitta, H.; Hatanaka, M.; Ueda, I. *J. Chem. Soc., Perkin Trans. 1* **1990**, 432. (h) Tsubouchi, H.; Tsuji, K.; Yasumura, K.; Tada, N.; Nishitami, S.; Minamikawa, J.; Ishikawa, H. *Tetrahedron: Asymmetry* **1994**, *5*, 441. See also ref 11b and references therein.

(15) Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

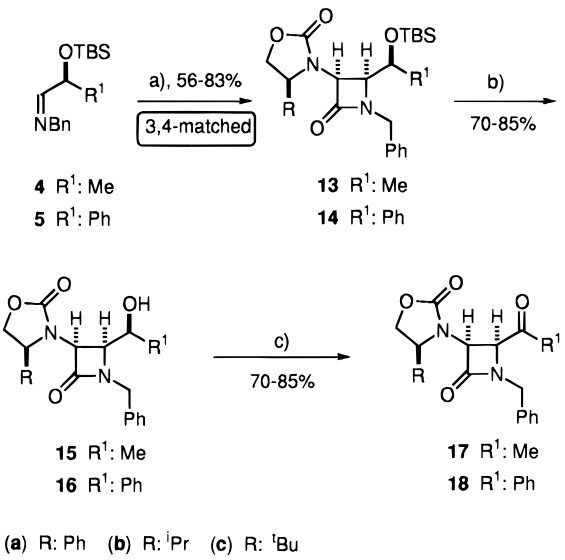
(16) For a study on double asymmetric induction in the ester enolate−imine condensation, see: Annunziata, R.; Benaglia, M.; Chiovato, A.; Cinquini, M.; Cozzi, F. *Tetrahedron* **1995**, *51*, 10025.

Scheme 2[a]



[a] Reagents and conditions: (a) NEt_3, CH_2Cl_2, −78 °C → rt, 20 h; (b) *p*-TosOH, THF, H_2O; (c) $NaIO_4$, Me_2CO, H_2O; (d) $NaBH_4$, MeOH.

Scheme 3[a]

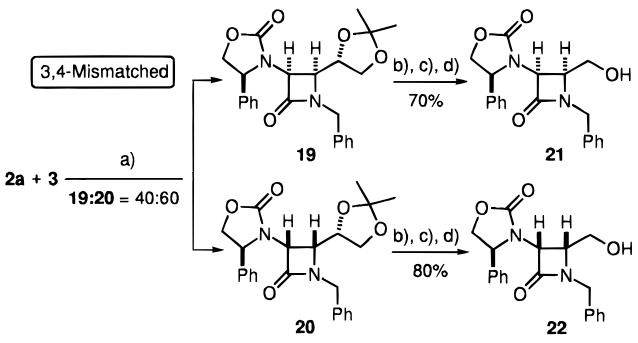


[a] Reagents and conditions: (a) **2**, NEt_3, CH_2Cl_2, −78 °C → rt, 20 h; (b) $^nBu_4NF$, THF; (c) $(Cl_3CO)_2CO$/DMSO, NEt_3, CH_2Cl_2, −78 °C.

fore, our study began with the simplest case, that is the reaction of the ketene generated from **1** as above with the imine **3** (Scheme 2) in which the sense of asymmetric induction of both chiral templates was matched, and as a result, 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 the resulting *β*-lactam product **10** was unequivocally established by removal of the acetonide protecting group, followed by oxidative cleavage of the resulting glycol and subsequent reduction of the 4-formyl *β*-lactam **11** into the 4-hydroxymethyl derivative **12**, whose absolute configuration has been previously established.[6d] Similarly (Scheme 3), the imine **4** upon exposure to acid chlorides **2a**, **2b**, and **2c** and triethylamine led to the formation of *β*-lactams **13a**, **13b**, and **13c** in 56%, 58%, and 83% yields, respectively, as single diastereomers. The same stereochemical result was produced when **2a** reacted with the imine **5** to produce the cycloadduct **14a** in 65% isolated yield. For reasons which will be outlined later, each *β*-lactam **13a**−**c** and **14a** was subjected to *O*-desilylation to give **15a**−**c** and **16a**, respectively. These *β*-lactam products, upon Swern oxidation, afforded the corresponding ketones **17a**−**c** and **18a**.

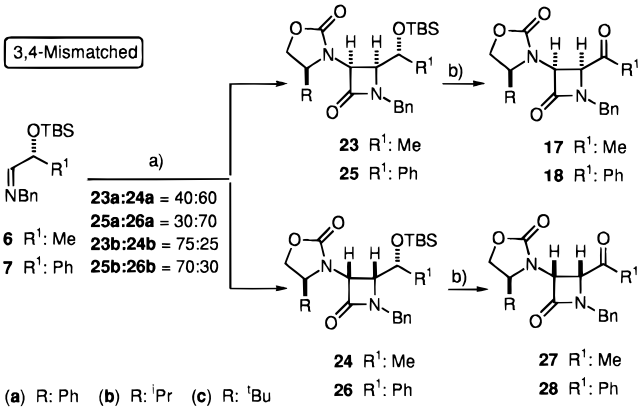
The next step of our study was to confront the sense

Scheme 4[a]



[a] Reagents and conditions: (a) NEt_3, CH_2Cl_2, −78 °C → rt, 20 h; (b) *p*-TosOH, THF, H_2O; (c) $NaIO_4$, Me_2CO, H_2O; (d) $NaBH_4$, MeOH.

Scheme 5[a]



[a] Reagents and conditions: (a) **2**, NEt_3, CH_2Cl_2, −78 °C → rt, 20 h; (b) $^nBu_4F$, THF, then $(Cl_3CO)_2CO$, DMSO, NEt_3, 70−75%.

of induction of the ketene derived from **2a** with the imine **3**. In this case, both chiral templates were mismatched and the result was the formation of a mixture of *β*-lactams **19** and **20** in a 40:60 ratio, respectively, as determined by ^1H NMR (Scheme 4). The absolute configuration of these adducts was established again by their conversion into the corresponding 4-hydroxymethyl derivatives **21** and **22**, respectively. Compound **22** had been previously obtained by an independent route,[12c] and **21** was identified as the enantiomer of **12**. With this result in hand, we subjected imine **6** to treatment with **2a** and triethylamine (Scheme 5), and the stereochemical result was the same as that achieved with the imine **3**; namely, a mixture of *β*-lactams **23a** and **24a** (52% yield) was produced in a 40:60 ratio, respectively. A somewhat better stereochemical outcome was attained when the imine **7** was employed in this reaction to give *β*-lactams **25a** and **26a** (67% yield) in a 30:70 ratio, respectively.

Each pair of diastereomers was separated by column chromatography or by preparative HPLC and correlated with those obtained in the matched case, *vide supra*. As shown in Scheme 5, compounds **23a** and **25a**, upon elaboration of the C_4 substituent, led to the carbonyl derivatives **17a** and **18a**, identical in all respects to those previously obtained from **13a** and **14a** (Scheme 3), respectively. Moreover, since adducts **27a** and **28a** showed identical coupling constants ($J_{cisC3-C4} \approx 5$ Hz) to those of **17a** and **18a**, their absolute stereochemistry should be as depicted.

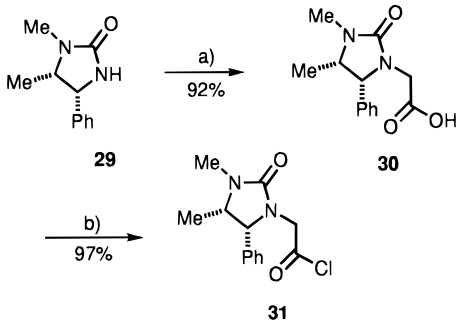
In view of the recent methods for recovering[6e,f] and/or

cleaving[17] oxazolidinone chiral auxiliaries, we next evaluated the behavior of ketenes derived from **2b** and **2c** in such a cycloaddition process with the aim of establishing whether bulkier groups at the C_3 position of the oxazolidinone moiety might exert some influence in directing the stereochemical course of the reaction.[18] In an effort to verify this argument, we subjected imine **6** to treatment with **2b** and **2c** under the same conditions as above. In the first case, a mixture of cycloadducts **23b** and **24b** (52% yield) was produced in a 75:25 ratio, thus indicating that, indeed, by increasing the size of the substituent on the ketene partner, it is possible to control the reaction diastereoselectivity. Likewise, the imine **7**, upon treatment with **2b**, gave **25b**/**26b** (63% yield) in a 70:30 ratio, respectively. Surprisingly, when **2c** was used, derived from the bulkier amino acid *tert*-leucine and imines **6** and **7**, only the anti-Evans β-lactams **24c** (80% yield) and **26c** (82% yield) were produced without traces of the corresponding diastereomeric products.

The absolute configurations of **23b** and **25b** were established by chemical correlation with the corresponding ketones **17b** and **18b**, which were identical to those obtained from the respective combinations in a matched relationship (see Scheme 3). As expected, adducts **24b** and **26b** upon desilylation and subsequent oxidation gave the corresponding diastereomeric ketones **27b** and **28b**, respectively. Finally, compounds **23b** and **24c** were submitted to single-crystal X-ray analyses to further confirm unambiguously the sense of asymmetric induction observed for these reactions.[19]

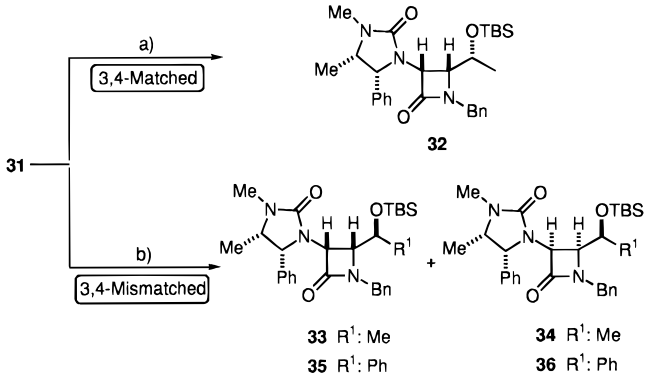
The imidazolidinone **29** has proven to be useful for asymmetric transformations,[20] including [4 + 2] cycloadditions.[21] Therefore, we also examined its behavior in [2 + 2] cycloadditions. The primary aim was to evaluate whether an additional stereogenic center on the chiral inductor could influence the stereochemical outcome of the cycloaddition. First, the corresponding acid chloride **31** was prepared (Scheme 6) from the acid **30** and

Scheme 6[a]



[a] Reagents and conditions: (a) NaH, THF, $BrCH_2CO_2Me$, 2 h, 0 °C, then NaOH, H_2O, THF, 2 h, rt; (b) ClCOCOCl, CH_2Cl_2, DMF cat., 1 h, rt.

Scheme 7[a]



[a] Reagents and conditions: (a) **6**, NEt_3, CH_2Cl_2, −78 °C → rt, 20 h; (b) **4** or **5**, NEt_3, CH_2CL_2, −78 °C → rt, 20 h.

subjected to treatment with the imine **6**. As Scheme 7 illustrates, the result was, as to be expected by the matched relationship between both components, the formation of the β-lactam **32** whose relative configuration was determined by X-ray analysis.[22] Once we had established that the sense of asymmetric induction exerted by this imidazolidinone inductor was the same as that observed for the above oxazolidinone derivatives, we investigated the reaction of **31** with imines **4** and **5** in which each reactant was in a mismatched relationship. While in the latter case a mixture of β-lactams **35**/**36** in a 70:30 ratio was produced,[23] in the former case only the β-lactam product **33**, with stereochemistry dictated by the ketene partner, was obtained in a de higher than 95%.

Reaction of Chiral Aminoketenes with Chiral Imines Derived from Chiral α-Oxy Aldehydes and Chiral Amines. The 1,3,4-Matched and 1,4-Matched-

(17) Fisher, J. W.; Dunigan, J. M.; Hatfield, L. D.; Hoying, R. C.; Ray, J. E.; Thomas, K. L. *Tetrahedron Lett.* **1993**, *34*, 4755.

(18) A semiempirical SCF-MO AM1 study carried out by us indicated that the stereochemistry observed for the reaction of chiral Evans−Sjögren ketenes with achiral imines, and particularly those involving the (trimethylsilyl)methyl moiety, is governed by the relative orientation adopted by the phenyl group in the corresponding transition state. While our theoretical work was in progress, an anticipated paper by Cossio from this laboratory documented the same observation, see: Cossío, F. P.; Arrieta, A.; Lecea, B.; Ugalde, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 2085.

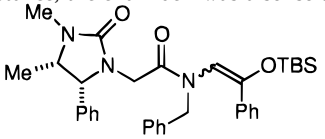
(19) Crystal data for compound **23b**: $C_{24}H_{38}N_2O_4Si$, M_r = 446.65, triclinic, space group *P*1, a = 14.258(4), b = 15.172(3), and c = 6.256(1) Å, α = 93.40(2), β = 95.45(2), and γ = 71.70(2)°, V = 1278.5(5) Å^{-3}, Z = 2, D_c = 1.160 g cm^{-3}, T = −100 °C, Mo Kα radiation, λ = 0.710 69 Å, μ = 0.1217 mm^{-1}. The structure, with two symmetry-independent molecules, was solved by direct methods and refined on F by full-matrix least-squares methods to give R = 0.0384, wR = 0.0335, and S = 1.477 using 556 refined parameters and 5113 observed reflections with $I > 2\sigma(I)$ from the 6094 collected with 5° < 2θ < 55°. For compound **24c**: $C_{25}H_{40}N_2O_4Si$, M_r = 460.68, orthorhombic, space group $P2_12_12_1$, a = 12.532(2), b = 33.796(2), and c = 6.389(4) Å, V = 2706(1) Å^{-3}, Z = 4, D_c = 1.131 g cm^{-3}, T = 10 °C, Mo Kα radiation, λ = 0.710 69 Å, μ = 0.1169 mm^{-1}. The structure was solved by direct methods and refined on F by full-matrix least-squares methods to give R = 0.0427, wR = 0.0368, and S = 1.530 using 341 refined parameters and 3298 observed reflections with $I > 3\sigma(I)$ from the 10 662 collected with 5° < 2θ < 60°. For each structure, the enantiomorph was fixed by the known *R* configuration of the (silyloxy)ethyl group. The atomic coordinates have been deposited at the Cambridge Crystallographic Data Centre.[27]

(20) For some examples, see: (a) Cardillo, G.; D'Amico, A.; Orena, M.; Sandri, S. *J. Org. Chem.* **1988**, *53*, 2354. (b) Cardillo, G.; Simone, A.; Gentilucci, L.; Sabatino, P.; Tomasini, C. *Tetrahedron Lett.* **1994**, *35*, 5051. (c) Drewes, S. E.; Malissar, D. G. S.; Roos, G. H. P. *Tetrahedron: Asymmetry* **1992**, *3*, 515. (d) Drewes, S. E.; Malissar, D. G. S.; Roos, G. H. P. *Chem. Ber.* **1991**, *124*, 2913.

(21) Orena, M.; Porzi, G.; Sandri, S. *J. Chem. Res., Synop.* **1992**, 42.

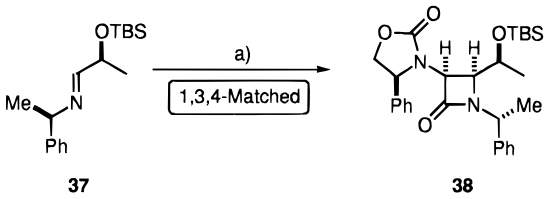
(22) Crystal data for compound **32**: $C_{29}H_{41}N_3O_3Si$, M_r = 507.74, orthorhombic, space group $P2_12_12_1$, a = 11.879(4), b = 26.427(7), and c = 9.052(4) Å, V = 2842(2) Å^{-3}, Z = 4, D_c = 1.187 g cm^{-3}, T = −100 °C, Mo Kα radiation, λ = 0.710 69 Å, μ = 0.1161 mm^{-1}. The structure was solved by direct methods and refined on F by full-matrix least-squares methods to give R = 0.0428, wR = 0.0375, and S = 1.501 using 325 refined parameters and 3315 observed reflections with $I > 2\sigma(I)$ from the 4324 collected with 5° < 2θ < 55°. The enantiomorph was fixed by the known *R* configuration of the (silyloxy)ethyl group. The atomic coordinates have been deposited at the Cambridge Crystallographic Data Centre.[27]

(23) In this instance, the enamide I was also isolated.



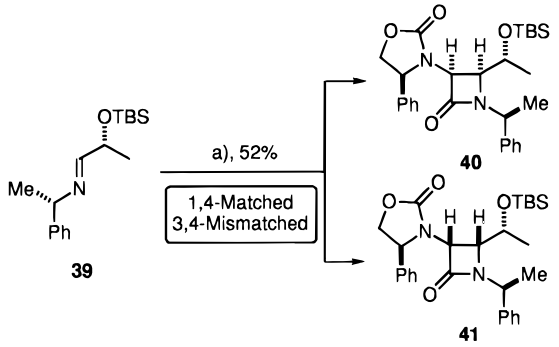
I

Scheme 8[a]



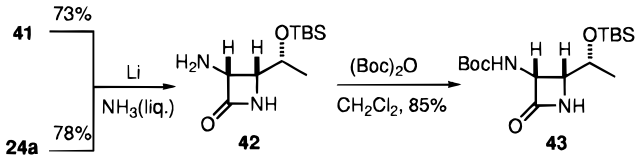
[a] Reagents and conditions: (a) **2a**, NEt_3, CH_2Cl_2, −78 °C → rt, 20 h, 57%.

Scheme 9[a]



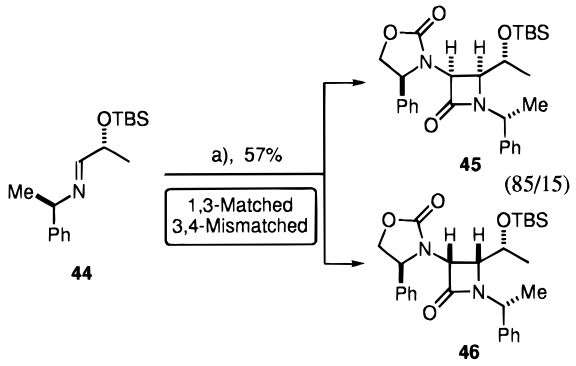
[a] Reagents and conditions: (a) **2a**, NEt_3, CH_2Cl_2, −78 °C → rt, 20 h.

Scheme 10



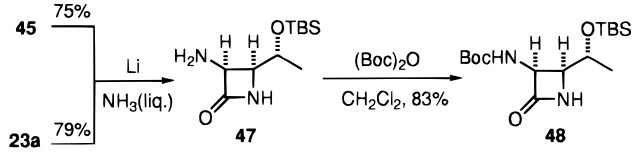
3,4-mismatched Cases. In addition to this double asymmetric induction we also sought information about the behavior of a third chiral component on these reactions. For this purpose, we elected to use imines derived from lactaldehyde and 1-phenylethylamine for which both enantiomers are commercially available and cheap. According to the known induction sense of this amine in β-lactam synthesis,[24] we first checked the fully matched reaction between the Evans−Sjögren acid chloride **2a** and the imine **37** (Scheme 8). By this means, the β-lactam **38** was obtained as the single reaction product. Next, the partially matched case shown in Scheme 9 was examined. Thus, in this experiment, the sense of asymmetric induction establishes a matched relationship between the α-oxy aldehyde and the amine component of the imine partner and a mismatched relationship with respect to the ketene partner. As a result, a mixture of β-lactams **40**/**41** was obtained in a 30:70 ratio, thus indicating that the additional stereogenic center of the amine component slightly reinforces the sense of asymmetric induction exerted by the aldehyde component. The major anti-Evans adduct **41** was separated by crystallization from ethanol and the minor β-lactam **40** by preparative HPLC. Correlation of the stereochemical course of these reactions was established by conversion of both **41** and **24a** (Scheme 10) into the β-lactam **42** which was isolated as the *N*-Boc derivative **43**. The most interesting stereochemical variant is, however, the reaction depicted in Scheme 11, in this

Scheme 11[a]



[a] Reagents and conditions: (a) **2a**, NEt_3, CH_2Cl_2, −78 °C → rt, 20 h.

Scheme 12



reaction, the matched relationship between the amine component of the imine **44** and the ketene partner affords an Evans-selective reaction. Thus, under these conditions, a mixture of the Evans adduct **45** and the anti-Evans adduct **46** was obtained in a ratio of 85:15, respectively. Both compounds were then separated by low-pressure column chromatography, and the major isomer was subjected to the conditions depicted in Scheme 12. The resulting β-lactam **47**, which was *N*-Boc protected as **48**, was identical to that obtained from the β-lactam **23a**.[25]

The above results indicate that the concept of double asymmetric induction can be applied to [2 + 2] cycloadditions of ketenes with imines with, in some instances, reasonable success. However, to facilitate a more versatile entry to β-lactams with stereochemistry dictated by the ketene partner, we examined alternative approaches to the required products. Since in the cycloaddition reaction of the Evans−Sjögren ketene with α-oxy aldehyde derived imines **4** and **5** in a 3,4-matched relationship only one β-lactam product was always formed (see Scheme 3), we expected that reduction of the corresponding 4-acyl β-lactams **17** and **18** would be highly stereoselective owing to the steric bulk of the substituent at the C_3 position. To confirm this, we first subjected the 4-acetyl β-lactam **17a** to treatment with $NaBH_4$, but unfortunately, no selectivity was observed. In fact, Miller and co-workers[26] also showed the same lack of stereoselectivity in the reduction of closely related 4-acetyl β-lactams. However, the reduction of **17a** carried out by means of L-Selectride proceeded to give the desired carbinol **51** as virtually a single diastereomer. Likewise, **18a** furnished **52** without detectable amounts of the corresponding epimeric carbinol. In view of these results, we also considered another way to obtain the correspond-

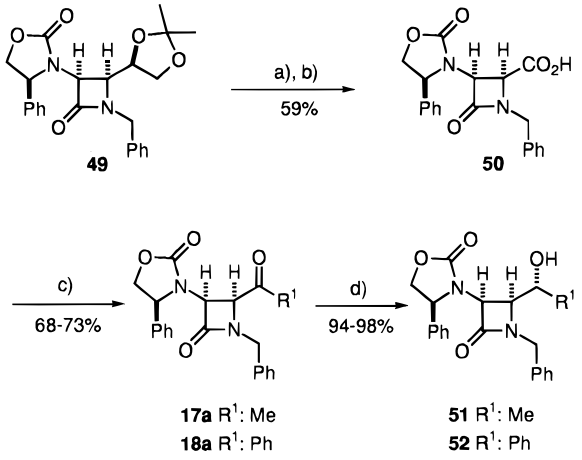
(24) (a) Ojima, I.; Suga, S.; Abe, R. *Chem. Lett.* **1980**, 853. (b) Alcaide, B.; Dominguez, G.; Escobar, G.; Parreno, M.; Plumet, J. *Heterocycles* **1986**, *24*, 1579. (c) Thomas, R. C. *Tetrahedron Lett.* **1989**, *46*, 1579.

(25) For an enolate−imine condensation route to these β-lactams with relative trans stereochemistry at the C_3−C_4 positions, see: Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *Tetrahedron* **1996**, *52*, 1685.

(26) Farouz, F.; Miller, M. J. *Tetrahedron Lett.* **1991**, *32*, 3305.

(27) The author has deposited atomic coordinates for these structures 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.

Scheme 13[a]



[a] Reagents and conditions: (a) *p*-TosOH, THF, H_2O; (b) $NaIO_4$, $KMnO_4$, Me_2CO, H_2O, rt, 6 h; (c) Cl_2SO, CH_2Cl_2, reflux, 3 h, then R^1MgX (1.3 equiv), THF, −40 °C → rt; (d) L-Selectride, THF, −60 °C, 1 h.

ing 4-acyl β-lactams that would be more general in scope. As Scheme 13 illustrates, the 4-carboxy β-lactam **50**, easily available from the β-lactam **49**, fulfills this criterion. For example, the coupling reaction of the acid chloride derived from **50** with both methylmagnesium bromide and phenylmagnesium bromide as representative Grignard reagents provided the ketones **17a** and **18a** in 75% and 70% yields, respectively, and, most satisfactorily, without overaddition products. Therefore, both approaches developed here, the cycloaddition reaction and the diastereoselective reduction of 4-acyl β-lactams, are complementary and open a way to the synthesis of 1(*R*)- and 1(*S*)-hydroxyalkyl β-lactams with the same cis stereochemistry between the C_3 and C_4 positions.

Experimental Section

Melting points were determined on a capillary apparatus and are uncorrected. Proton nuclear magnetic resonance (300 MHz) spectra and ^{13}C NMR 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 ± 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 using a UV detector (254 nm). Flash chromatography was executed with Merck kiesegel 60 (230−400 mesh) using mixtures of ethyl acetate and hexane as eluants. Acetonitrile and hexane were dried and purified by distillation. Tetrahydrofuran was distilled over sodium and benzophenone (indicator). Methylene chloride was shaken with concentrated sulfuric acid, dried over potassium carbonate, and distilled. Commercially available compounds were used without further purification. Compound **9a** was prepared according to a literature procedure.[6d]

General Procedure for the Preparation of Carboxylic Acids 9b, 9c, and 30. General Procedure A. Methyl bromoacetate (4.68 mL, 50 mmol) was added dropwise at 0 °C under a nitrogen atmosphere to a suspension of the corresponding oxazolidinone (50 mmol) and sodium hydride (1.2 g, 50 mmol) in dry THF (75 mL). The resulting mixture was allowed to stir at 0 °C for 2 h. Then, a solution of NaOH in water/THF (10 g, 100 mL of water, 125 mL of THF) was added, and the mixture was allowed to stir at room temperature for 2 h. Finally the mixture was acidified with concd HCl and extracted with methylene chloride (3 × 100 mL). The organic extracts were combined and dried over $MgSO_4$. Concentration in vacuo afforded the desired compound **9b** or **9c**, which was utilized in the next step without further purification.

General Procedure B. Methyl bromoacetate (4.68 mL, 50 mmol) was added dropwise at 0 °C under a nitrogen atmosphere to a suspension of the imidazolidinone **29** (9.6 g, 50 mmol) and sodium hydride (1.2 g, 50 mmol) in dry THF (75 mL). The resulting mixture was allowed to stir at 0 °C for 2 h. Then, a solution of NaOH in water/THF (10 g, 100 mL of water, 125 mL of THF) was added, and the mixture was allowed to stir at room temperature for 2 h. Finally the mixture was acidified with concd HCl and extracted with methylene chloride (3 × 100 mL). The organic extracts were combined and dried over $MgSO_4$. Concentration in vacuo afforded the desired compound **30**, which was utilized in the next step without further purification.

[(4*S*)-2-Oxo-4-isopropyloxazolidin-3-yl]acetic Acid (9b). The title compound was prepared from 4(*S*)-isopropyloxazolidin-2-one (**8b**) following general procedure A; yield 95%. An analytical sample was purified by column chromatography (70−230 mesh, methylene chloride as eluant): white low-melting solid. $[\alpha]^{25}_D = +62.6°$ ($c = 1.0$, CH_2Cl_2); IR (NaCl): ν 3620−2520 cm^{-1} (OH); 1740 cm^{-1} (C═O); 1735 (C═O); ^1H NMR ($CDCl_3$, δ ppm): 8.92 (s_b, 1H); 4.34 (dd, 1H, $J = 8.7$ Hz, $J = 6.3$ Hz); 4.31 (d, 1H, $J = 18.0$ Hz); 4.10 (t, 1H, $J = 6.3$ Hz); 4.03−3.97 (m, 1H); 3.67 (d, 1H, $J = 18.0$ Hz); 2.04−1.92 (m, 1H); 0.89 (d, 1H, $J = 6.1$ Hz); 0.85 (d, 1H, $J = 6.2$ Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 171.1, 159.5, 63.8, 59.4, 43.3, 27.4, 17.5, 14.5. Anal. Calcd for $C_8H_{13}NO_4$ (187.19): C, 51.33; H, 6.99; N, 7.48. Found: C, 50.99; H, 7.01; N, 7.39.

[(4*S*)-4-*tert*-Butyl-2-oxooxazolidin-3-yl]acetic Acid (9c). The title compound was prepared from (4*S*)-4-*tert*-buthyloxazolidin-2-one (**8c**) following general procedure A: yield 91%; white solid recrystallized from methylene chloride/hexane; mp 162−164 °C (CH_2Cl_2, hexane). $[\alpha]^{25}_D = +34.4°$ ($c = 1.0$, CH_2Cl_2). IR (KBr): ν 3550−2400 cm^{-1} (OH); 1747 cm^{-1} (C═O); 1736 (C═O). ^1H NMR ($CDCl_3$, δ ppm): 8.91−8.72 (s_b, 1H); 4.52 (d, 1H, $J = 18.4$ Hz); 4.42 (t, 1H, $J = 9.0$ Hz); 4.22 (dd, 1H, $J = 4.7$ Hz, $J = 9.0$ Hz); 3.95 (d, 1H, $J = 18.4$ Hz); 3.74 (dd, 1H, $J = 4.7$ Hz, $J = 9.0$ Hz); 0.98 (s, 9H). ^{13}C NMR ($CDCl_3$, δ ppm): 172.9, 160.6, 65.5, 64.2, 46.8, 34.5, 25.5. Anal. Calcd for $C_9H_{15}NO_4$ (201.22): C, 53.72; H, 7.51; N, 6.96. Found: C, 53.68; H, 7.32; N, 7.09.

[(4*R*,5*S*)-1,5-Dimethyl-2-oxo-4-phenylimidazolidin-3-yl]-acetic Acid (30). The title compound was prepared from (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one (**29**) following general procedure B: yield 92%; white solid recrystallized from ethyl acetate/hexane; mp 168−170 °C (AcOEt, hexane). $[\alpha]^{25}_D = -34.0°$ ($c = 1.0$, MeOH). IR (KBr): ν 2892−2858 cm^{-1} (OH); 1760 cm^{-1} (C═O); 1748 (C═O). ^1H NMR ($CDCl_3$, δ ppm): 7.38−7.14 (m, 5H); 6.94−6.62 (s_b, 1H); 4.94 (d, 1H, $J = 9.1$ Hz); 4.35 (d, 1H, $J = 18.1$ Hz); 3.95−3.86 (m, 1H); 3.37 (d, 1H, $J = 18.1$ Hz); 2.81 (s, 3H); 0.74 (d, 3H, $J = 6.6$ Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 172.5, 161.6, 134.9, 128.7, 128.4, 128.0, 62.3, 55.8, 43.7, 28.7, 14.5. Anal. Calcd for $C_{13}H_{16}N_2O_3$ (248.28): C, 62.89; H, 6.49; N, 11.28. Found: C, 62.57; H, 6.31; N, 11.04.

General Procedure for β-Lactam Formation. Triethylamine (6.36 mL, 45 mmol) was added at −78 °C to a solution of the corresponding acyl choride **1**, **2a**, **2b**, **2c**, or **31** (30 mmol) in dry methylene chloride (90 mL). After 15 min, a solution of the corresponding imine (33 mmol) in dry toluene was added dropwise at the same temperature and the resulting mixture was stirred under nitrogen atmosphere at 0 °C for 2 h and at room temperature overnight. Then, the reaction mixture was successively washed with water (100 mL), 0.1 N HCl (100 mL), and a saturated solution of $NaHCO_3$ (100 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure to give the corresponding crude β-lactam, which was further purified by column chromatography and then by preparative HPLC when necessary.

***cis*-(3*R*,4*R*)-1-Benzyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-[(4*R*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (10).** The title compound was prepared from the acid chloride **1** and the imine **3** following the general procedure. The crude β-lactam was purified by colum chromatography (silica gel 70−230 mesh, methylene chloride/hexane 1:2 as

eluant): white solid recrystallized from ethanol; yield 57%; mp 176−178 °C (ethanol). $[\alpha]^{25}_D = -88.6°$ ($c = 1.0$, CH_2Cl_2). IR (KBr): υ 1751 cm^{-1} (C═O); 1741 cm^{-1} (CO). ^1H NMR (DMSO-d_6 at 90 °C, δ ppm): 7.46−7.19 (m, 10H); 4.99 (dd, 1H, J = 5.0 Hz, J = 8.9 Hz); 4.74 (t, 1H, J = 8.9 Hz); 4.50−4.44 (m, 2H); 4.23−4.15 (m, 2H); 4.05−3.97 (m, 2H); 3.66−3.60 (m, 2H); 1.23 (s, 3H); 1.17 (s, 3H). ^{13}C NMR (DMSO-d_6 at 90 °C, δ ppm): 163.3, 156.9, 138.6, 136.1, 128.9, 128.6, 128.1, 127.8, 127.1, 126.9, 108.6, 75.5, 70.2, 65.6, 61.0, 59.8, 59.1, 45.1, 26.3, 24.9. Anal. Calcd for $C_{24}H_{26}N_2O_5$ (422.48): C, 68.23; H, 6.20; N, 6.63. Found: C, 68.07; H, 6.12; N, 6.43.

***cis*-(3*S*,4*S*)-1-Benzyl-4-[(1*S*)-[(*tert*-butyldimethylsilyl)-oxy]ethyl]-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (13a).** The title compound was prepared from the acid chloride **2a** and the imine **4** following the general procedure. The crude β-lactam was purified by column chromatography (silica gel 70−230 mesh, methylene chloride/hexane 1:2 as eluant): white solid recrystallized from ethanol; yield 56%; mp 172−174 °C (ethanol). $[\alpha]^{25}_D = +125.4°$ ($c = 1.0$, CH_2Cl_2). IR (KBr): υ 1751 cm^{-1} (C═O); 1748 cm^{-1} (CO). ^1H NMR (DMSO-d_6 at 90 °C, δ ppm): 7.45−7.15 (m, 10H); 5.00 (dd, 1H, J = 5.0 Hz, J = 8.9 Hz); 4.72 (t, 1H, J = 15.4 Hz); 4.42 (d, 1H, J = 5.3 Hz); 4.18 (d, 1H, J = 15.4 Hz); 4.15 (dd, 1H, J = 5.0 Hz, J = 8.9 Hz); 4.02−3.93 (m, 1H); 3.49 (dd, 1H, J = 5.3 Hz, J = 9.0 Hz); 1.09 (d, 3H, J = 6.1 Hz); 0.85 (s, 9H); 0.04 (s, 3H); −0.20 (s, 3H). ^{13}C NMR (DMSO-d_6 at 90 °C, δ ppm): 164.1, 156.9, 138.5, 135.9, 128.8, 128.5, 128.1, 127.1, 126.9, 126.8, 69.9, 68.8, 62.7, 59.7, 59.1, 45.1, 25.5, 20.3, 17.2, −4.5, −4.7. Anal. Calcd for $C_{27}H_{36}N_2O_4Si$ (480.68): C, 67.47; H, 7.55; N, 5.83. Found: C, 67.39; H, 7.38; N, 5.92.

***cis*-(3*S*,4*S*)-1-Benzyl-4-[(1*S*)-[(*tert*-butyldimethylsilyl)-oxy]ethyl]-3-[(4*S*)-2-oxo-4-isopropyloxazolidin-3-yl]azetidin-2-one (13b).** The title compound was prepared from the acid chloride **2b** and the imine **4** following the general procedure. The crude β-lactam was purified by flash column chromatography (silica gel 230−240 mesh, ethyl acetate/hexane 1:3 as eluant): white solid recrystallized from ethanol; yield 58%; mp 233−234 °C (ethanol). $[\alpha]^{25}_D = +97.0°$ ($c = 1.0$, CH_2Cl_2). IR (KBr): υ 1764 cm^{-1} (C═O); 1737 cm^{-1} (CO). ^1H NMR ($CDCl_3$, δ ppm): 7.36−7.22 (m, 5H); 4.89 (d, 1H, J = 14.7 Hz); 4.43−4.11 (m, 4H); 4.22 (d, 1H, J = 14.7 Hz); 3.91−3.71 (m, 1H); 3.47 (dd, 1H, J = 5.1 Hz, J = 9.3 Hz); 2.08−2.00 (m, 1H); 1.04 (d, 3 Hz, J = 5.9 Hz); 1.01 (d, 3H, J = 6.8 Hz); 0.94 (s, 9H); 0.92 (d, 3H, J = 7.1 Hz); 0.14 (s, 3H); 0.13 (s, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 164.8, 157.9, 135.9, 128.7, 128.4, 127.6, 69.2, 63.1, 62.2, 59.8, 59.6, 45.9, 28.6, 25.9, 20.9, 17.9, 13.7, −4.2, −4.4. Anal. Calcd for $C_{24}H_{38}N_2O_4Si$ (446.66): C, 64.54; H, 8.57; N, 6.27. Found: C, 64.39; H, 8.45; N, 6.15.

***cis*-(3*S*,4*S*)-1-Benzyl-4-[(1*S*)-[(*tert*-butyldimethylsilyl)-oxy]ethyl]-3-[(4*S*)-4-*tert*-butyl-2-oxooxazolidin-3-yl]azetidin-2-one (13c).** The title compound was prepared from the acid chloride **2c** and the imine **4** following the general procedure. The crude β-lactam was purified by flash column chromatography (silica gel 230−240 mesh, ethyl acetate/hexane 1:4 as eluant): white solid recrystallized from ethanol; yield 83%; mp 198−200 °C (ethanol). $[\alpha]^{25}_D = +47.3°$ ($c = 1.0$, CH_2Cl_2). IR (KBr): υ 1762 cm^{-1} (C═O); 1734 cm^{-1} (CO). ^1H NMR ($CDCl_3$, δ ppm): 7.41−7.26 (m, 5H); 4.87 (d, 1H, J = 14.8 Hz); 4.52−4.32 (m, 2H); 4.28−4.21 (m, 1H); 4.27 (d, 1H, J = 5.2 Hz); 4.24 (d, 1H, J = 14.8 Hz); 3.52 (dd, 1H, J = 5.2 Hz, J = 9.2 Hz); 3.34−3.20 (s_b, 1H); 1.07 (d, 3H, J = 6.1 Hz); 1.02 (s, 9H); 0.93 (s, 9H); 0.12 (s, 6H). ^{13}C NMR ($CDCl_3$, δ ppm): 165.5, 157.3, 136.2, 128.7, 128.6, 127.5, 66.1, 65.3, 63.9, 61.7, 45.8, 35.8, 25.9, 25.7, 20.9, 17.8, −4.2, −4.3. Anal. Calcd for $C_{25}H_{40}N_2O_4Si$ (460.69): C, 65.18; H, 8.75; N, 6.08. Found: C, 64.90; H, 8.57; N, 5.99.

***cis*-(3*S*,4*S*)-1-Benzyl-4-[(1*S*)-[(*tert*-butyldimethylsilyl)-oxy]benzyl]-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (14a).** The title compound was prepared from the acid chloride **2a** and the imine **5** following the general procedure. The crude β-lactam was purified by flash column chromatography (silica gel 230−240 mesh, ethyl acetate/hexane 1:2 as eluant): white solid recrystallized from ethanol; yield 65%; mp 175−177 °C (ethanol). $[\alpha]^{25}_D = +176.7°$ ($c = 1.0$, CH_2Cl_2). IR (KBr): υ 1762 cm^{-1} (C═O); 1744 cm^{-1} (CO). ^1H NMR ($CDCl_3$, δ ppm): 7.51−7.16 (m, 13H); 7.01−6.98 (m, 2H); 5.30 (d, 1H, J = 8.8 Hz); 4.93 (d, 1H, J = 15.2 Hz); 4.39 (d, 1H, J = 15.2 Hz); 4.15 (t, 1H, J = 8.6 Hz); 4.04 (dd, 1H, J = 5.2 Hz, J = 8.8 Hz); 3.85 (t, 1H, J = 8.6 Hz); 3.70 (d, 1H, J = 5.2 Hz); 2.71−2.62 (m, 1H); 0.78 (s, 9H); 0.00 (s, 3H); −0.30 (s, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 164.9, 156.9, 141.0, 136.3, 129.4, 129.2, 128.8, 128.6, 128.1, 127.7, 127.6, 127.4, 127.0, 75.9, 70.4, 63.7, 59.8, 58.5, 45.6, 25.8, 17.9, −4.4, −4.5. Anal. Calcd for $C_{32}H_{38}N_2O_4Si$ (542.75): C, 70.81; H, 7.06; N, 5.16. Found: C, 70.69; H, 6.95; N, 5.03.

***cis*-(3*S*,4*S*)-1-Benzyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (19).** The title compound was prepared from the acid chloride **2a** and the imine **3** following the general procedure. The crude β-lactam was purified by column chromatography (silica gel 70−230 mesh, methylene chloride/hexane 1:2 as eluant) and the title compound was separated from the anti-Evans isomer by preparative HPLC (ethyl acetate as eluant, 10 mL/min, t_R = 10.05 min): white solid recrystallized from ethanol; yield 26%; mp 166−168 °C (ethanol). $[\alpha]^{25}_D = +100.2°$ ($c = 1.0$, CH_2Cl_2). IR (NaCl): υ 1754 cm^{-1} (C═O); 1750 cm^{-1} (CO). ^1H NMR ($CDCl_3$, δ ppm): 7.45−7.22 (m, 10H); 4.99 (t, 1H, J = 8.6 Hz); 4.65 (t, 1H, J = 8.6 Hz); 4.46 (d, 1H, J = 15.6 Hz); 4.32 (d, 1H, J = 15.6 Hz); 4.32 (m, 1H): 4.19 (d, 1H, J = 5.1 Hz); 4.17 (t, 1H, J = 8.6 Hz); 3.53−3.46 (m, 2H); 3.36 (dd, 1H, J = 5.1 Hz, J = 8.6 Hz); 1.39 (s, 3H); 1.28 (s, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 164.5, 157.5, 136.5, 135.2, 129.3, 128.8, 128.0, 127.8, 127.6, 127.3, 109.0, 74.0, 70.5, 67.7, 61.4, 60.6, 60.4, 45.3, 26.7, 25.0. Anal. Calcd for $C_{24}H_{26}N_2O_5$ (422.48): C, 68.23; H, 6.20; N, 6.63. Found: C, 68.10; H, 6.13; N, 6.37.

***cis*-(3*S*,4*S*)-1-Benzyl-4-[(1*R*)-[(*tert*-butyldimethylsilyl)-oxy]ethyl]-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (23a).** The title compound was prepared from the acid chloride **2a** and the imine **6** following the general procedure and separated from the anti-Evans isomer by flash column chromatography (silica gel 230−400 mesh, methylene chloride/hexane 1:2 as eluant): syrup purified by preparative HPLC (ethyl acetate as eluant, 10 mL/min, t_R = 9.80 min); yield 21%. $[\alpha]^{25}_D = +73.61°$ ($c = 1.0$, CH_2Cl_2). IR (NaCl): υ 1757 cm^{-1} (C═O); 1752 cm^{-1} (CO). ^1H NMR ($CDCl_3$, δ ppm): 7.49−7.17 (m, 10H); 4.91 (dd, 1H, J = 7.5 Hz, J = 9.0 Hz); 4.78 (d, 1H, J = 15.2 Hz); 4.66 (t, 1H, J = 9.0 Hz); 4.32−4.27 (m, 1H0; 4.18 (dd, 1H, J = 7.5 Hz, J = 9.0 Hz); 4.13 (d, 1H, J = 5.1 Hz); 3.33 (dd, 1H, J = 5.1 Hz, J = 8.3 Hz); 3.33 (dd, 1H, J = 5.1 Hz, J = 8.3 Hz); 1.16 (d, 3H, J = 6.2 Hz); 0.90 (s, 9H); 0.11 (s, 3H); 0.10 (s, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 165.8, 157.5, 137.3, 135.4, 129.6, 129.4, 128.8, 128.1, 127.6, 127.4, 70.5, 67.6, 64.4, 60.7, 60.2, 46.0, 26.0, 22.3, 18.1, −3.0, −3.7.

***cis*-(3*S*,4*S*)-1-Benzyl-4-[(1*R*)-[(*tert*-butyldimethylsilyl)-oxy]ethyl]-3-[(4*S*)-2-oxo-4-isopropyloxazolidin-3-yl]azetidin-2-one (23b).** The title compound was prepared from the acid chloride **2b** and the imine **6** following the general procedure and separated from the anti-Evans isomer by flash column chromatography (silica gel 230−400 mesh, ethyl acetate/hexane 1:4 as eluant): white solid recrystallized from ethanol; yield 39%; mp 110−112 °C (ethanol). $[\alpha]^{25}_D = +25.7°$ ($c = 1.0$, CH_2Cl_2). IR (KBr): υ 1751 cm^{-1} (C═O); 1749 cm^{-1} (CO). ^1H NMR ($CDCl_3$, δ ppm): 7.37−7.25 (m, 5H); 4.83 (d, 1H, J = 15.4 Hz); 4.34−4.31 (m, 1H); 4.33 (d, 1H, J = 5.3 Hz); 4.26 (t, 1H, J = 9.0 Hz); 4.16 (dd, 1H, J = 5.0 Hz, J = 9.0 Hz); 4.14 (d, 1H, J = 15.4 Hz); 3.78 (ddd, 1H, J = 3.5 Hz, J = 5.0 Hz, J = 9.0 Hz); 3.44 (dd, 1H, J = 5.3 Hz, J = 8.1 Hz); 2.18−2.08 (m, 1H); 1.21 (d, 3H, J = 6.2 Hz); 1.02 (d, 3H, J = 6.8 Hz); 0.89 (d, 3H, J = 6.9 Hz); 0.84 (s, 9H); 0.05 (s, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 166.2, 157.8, 135.5, 128.8, 128.1, 127.6, 67.2, 64.2, 63.0, 60.1, 59.8, 46.1, 27.6, 25.8, 22.2, 17.9, 17.5, 13.4, −3.2, −4.1. Anal. Calcd for $C_{24}H_{38}N_2O_4Si$ (446.66): C, 64.54; H, 8.57; N, 6.27. Found: C, 64.31; H, 8.35; N, 6.04.

***cis*-(3*R*,4*R*)-1-Benzyl-4-[(1*R*)-[(*tert*-butyldimethylsilyl)-oxy]ethyl]-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (24a).** The title compound was prepared from the acid chloride **2a** and the imine **6** following the general procedure and separated from the Evans isomer by column chromatography (silica gel 70−230 mesh, methylene chloride/hexane 1:2 as eluant): white solid recrystallized from ethanol; yield 31%; mp 148−150 °C (ethanol). $[\alpha]^{25}_D = +21.4°$ ($c = 1.0$, CH_2Cl_2). IR (KBr): υ 1761 cm^{-1} (C═O); 1753 cm^{-1} (CO). ^1H NMR ($CDCl_3$, δ ppm): 7.40−7.21 (m, 10H); 4.88 (t, 1H, J = 8.6 Hz);

4.81 (d, 1H, J = 14.8 Hz); 4.65 (t, 1H, J = 8.6 Hz); 4.52−4.47 (m, 1H); 4.32−4.26 (m, 2H); 4.18 (d, 1H, J = 14.8 Hz); 3.30 (dd, 1H, J = 5.6 Hz, J = 8.8 Hz); 0.96 (d, 3H, J = 6.1 Hz); 0.93 (s, 9H); 0.16 (s, 3H); 0.15 (s, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 165.0, 157.9, 136.2, 135.9, 129.7, 129.2, 128.6, 128.5, 127.9, 127.6, 69.9, 68.1, 63.2, 62.3, 60.7, 45.8, 26.0, 21.5, 17.9, −4.1, −4.3. Anal. Calcd for $C_{27}H_{36}N_2O_4Si$ (480.68): C, 67.47; H, 7.55; N, 5.83. Found: C, 67.20; H, 7.45; N, 5.43.

***cis*-(3*R*,4*R*)-1-Benzyl-4-[(1*R*)-[(*tert*-butyldimethylsilyl)-oxy]ethyl]-3-[(4*S*)-2-oxo-4-isopropyloxazolidin-3-yl]azetidin-2-one (24b).** The title compound was prepared from the acid chloride **2b** and the imine **6** following the general procedure and separated from the Evans isomer by flash column chromatography (silica gel 230−400 mesh, ethyl acetate/hexane 1:4 as eluant): white solid recrystallized from ethanol; yield 13%; mp 115−117 °C (ethanol). $[\alpha]^{25}_D = -48.7°$ (c = 1.0, CH_2Cl_2). IR (KBr): υ 1750 cm^{-1} (C═O); 1747 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$, δ ppm): 7.37−7.24 (m, 5H); 4.89 (d, 1H, J = 14.7 Hz); 4.81 (d, 1H, J = 5.1 Hz); 4.25 (t, 1H, J = 8.7 Hz); 4.21−4.14 (m, 3H); 3.81−3.75 (m, 1H); 3.51 (dd, 1H, J = 5.1 Hz, J = 8.1 Hz); 2.55−2.42 (m, 1H); 1.11 (d, 3H, J = 6.1 Hz); 0.94 (s, 9H); 0.91 (d, 3H, J = 6.8 Hz); 0.90 (d, 3H, J = 7.0 Hz); 0.14 (s, 3H); 0.13 (s, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 165.3, 157.9, 135.4, 128.8, 128.3, 127.8, 69.2, 63.5, 62.3, 62.1, 60.7, 46.0, 28.7, 25.9, 21.6, 18.5, 18.0, 14.5, −4.1, −4.2. Anal. Calcd for $C_{24}H_{38}N_2O_4Si$ (446.66): C, 64.54; H, 8.57; N, 6.27. Found: C, 64.28; H, 8.43; N, 6.12.

***cis*-(3*R*,4*R*)-1-Benzyl-4-[(1*R*)-[(*tert*-butyldimethylsilyl)-oxy]ethyl]-3-[(4*S*)-4-*tert*-butyl-2-oxooxazolidin-3-yl]azetidin-2-one (24c).** The title compound was prepared from the acid chloride **2c** and the imine **6** following the general procedure. The crude β-lactam was purified by flash column chromatography (silica gel 230−400 mesh, ethyl acetate/hexane 1:4 as eluant): white solid recrystallized from ethanol; yield 80%. $[\alpha]^{25}_D = -31.6°$ (c = 1.0, CH_2Cl_2). IR (KBr): υ 1766 cm^{-1} (C═O); 1739 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$, δ ppm): 7.34−7.26 (m, 5H); 4.88 (d, 1H, J = 14.9 Hz); 4.83 (m, 1H); 4.45 (d, 1H, J = 9.3 Hz); 4.30 (d, 1H, J = 14.9 Hz); 4.21 (d, 1H, J = 5.2 Hz); 4.19 (dd, 1H, J = 5.1 Hz, J = 9.3 Hz); 3.53 (dd, 1H, J = 5.2 Hz, J = 9.3 Hz); 3.48 (dd, 1H, J = 5.1 Hz, J = 9.3 Hz); 1.2 (d, 3H, J = 6.0 Hz); 0.94 (s, 9H); 0.92 (s, 9H); 0.17 (s, 3H); 0.14 (s, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 165.5, 159.4, 136.1, 128.7, 128.5, 127.5, 68.8, 68.3, 65.5, 65.1, 63.6, 45.6, 34.5, 26.0, 25.2, 22.3, 17.9, −4.1, −4.5. Anal. Calcd for $C_{25}H_{40}N_2O_4Si$ (460.69): C, 65.18; H, 8.75; N, 6.08. Found: C, 64.97; H, 8.62; N, 5.93.

***cis*-(3*S*,4*S*)-1-Benzyl-4-[(1*R*)-[(*tert*-butyldimethylsilyl)-oxy]benzyl]-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (25a).** The title compound was prepared from the acid chloride **2a** and the imine **7** following the general procedure. The crude β-lactam was purified by flash column chromatography (silica gel 230−400 mesh, ethyl acetate/hexane 1:2 as eluant). The title compound was then separated from the anti-Evans isomer by preparative HPLC (ethyl acetate/hexane 2:1 as eluant, 10 mL/min, t_R = 12.82 min): syrup; yield 20%. $[\alpha]^{25}_D = +3.59°$ (c = 1.0, CH_2Cl_2). IR (NaCl): υ 1780 cm^{-1} (C═O); 1730 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$, δ ppm): 7.44−6.92 (m, 15H); 4.66 (d, 1H, J = 5.9 Hz); 4.65 (d, 1H J = 15.2 Hz); 4.48 (d, 1H, J = 2.6 Hz); 4.48 (t, 1H, J = 8.8 Hz); 4.24 (dd, 1H, J = 6.6 Hz, J = 8.8 Hz); 4.02 (d, 1H, J = 15.2 Hz); 3.96 (dd, 1H, J = 6.6 Hz, J = 8.8 Hz); 3.48 (dd, 1H, J = 2.6 Hz, J = 5.8 Hz); 0.85 (s, 9H); −0.01 (s, 3H); −0.25 (s, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 164.8, 157.0, 140.1, 137.8, 135.4, 129.3, 128.9, 128.7, 128.4, 128.3, 128.1, 127.4, 126.8, 126.5, 75.6, 70.6, 62.2, 61.1, 58.9, 45.5, 25.8, 18.0, −4.5, −5.0.

***cis*-(3*S*,4*S*)-1-Benzyl-4-[(1*R*)-[(*tert*-butyldimethylsilyl)-oxy]benzyl]-3-[(4*S*)-2-oxo-4-isopropyloxazolidin-3-yl]azetidin-2-one (25b).** The title compound was prepared from the acid chloride **2b** and the imine **7** following the general procedure and was separated from the anti-Evans isomer by flash column chromatography (silica gel 230−400 mesh, ethyl acetate/hexane 1:7 as eluant): white solid recrystallized from ethanol; yield 44%; mp 212−214 °C (ethanol). $[\alpha]^{25}_D = -31.0°$ (c = 0.8, CH_2Cl_2). IR (KBr): υ 1752 cm^{-1} (C═O); 1748 cm^{-1} (CO). ^{1}H NMR (DMSO-d_6 at 90 °C, δ ppm): 7.41−7.22 (m, 10H); 5.37 (d, 1H, J = 8.8 Hz); 4.77 (d, 1H, J = 15.6 Hz); 4.63 (d, 1H, J = 5.4 Hz); 4.46 (d, 1H, J = 15.6 Hz); 4.26 (t, 1H, J = 8.7 Hz); 4.16 (dd, 1H, J = 5.4 Hz, J = 8.8 Hz); 3.86 (t, 1H, J = 8.7 Hz); 3.62−3.55 (m, 1H); 1.58−1.34 (m, 1H); 0.76 (s, 9H); 0.52 (d, 3H, J = 6.7 Hz); 0.37 (d, 3H, J = 6.4 Hz); −0.06 (s, 3H); −0.30 (s, 3H). ^{13}C NMR (DMSO-d_6 at 90 °C, δ ppm): 165.3, 157.3, 140.2, 135.9, 128.0, 127.9, 127.2, 127.0, 126.7, 75.4, 64.2, 62.7, 62.0, 61.0, 45.1, 28.8, 25.3, 17.8, 14.8, −4.9, −5.1. Anal. Calcd for $C_{29}H_{40}N_2O_4Si$ (508.73): C, 68.47 H, 7.92; N, 5.51. Found: C, 68.31; H, 7.85; N, 5.47.

***cis*-(3*R*,4*R*)-1-Benzyl-4-[(1*R*)-[(*tert*-butyldimethylsilyl)-oxy]benzyl]-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (26a).** The title compound was prepared from the acid chloride **2a** and the imine **7** following the general procedure and was separated from the Evans isomer by flash column chromatography (silica gel 230−400 mesh, ethyl acetate/hexane 1:2 as eluant): white solid recrystallized from ethanol; yield 47%; mp 189−191 °C (ethanol). $[\alpha]^{25}_D = -24.3°$ (c = 1.0, CH_2Cl_2). IR (KBr): υ 1765 cm^{-1} (C═O); 1746 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$, δ ppm): 7.52−7.22 (m, 11H); 7.09−7.04 (m, 2H); 6.18−6.15 (d, 2H); 5.75 (d, 1H, J = 9.0 Hz); 4.99 (d, 1H, J = 14.9 Hz); 4.86 (dd, 1H, J = 8.3 Hz, J = 11.1 Hz); 4.50 (d, 1H, J = 14.9 Hz); 4.48 (t, 1H, J = 8.3 Hz); 3.97 (dd, 1H, J = 5.7 Hz, J = 9.0 Hz); 3.82 (d, 1H, J = 5.7 Hz); 3.77 (dd, 1H, J = 8.3 Hz, J = 11.1 Hz); 0.87 (s, 9H); 0.07 (s, 3H); −0.20 (s, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 166.2, 158.3, 141.4, 136.1, 134.1, 130.0, 129.7, 129.6, 129.2, 129.1, 127.4, 127.3, 75.8, 70.2, 64.2, 62.8, 59.8, 45.5, 25.9, 17.9, −4.4, −4.5. Anal. Calcd for $C_{32}H_{38}N_2O_4Si$ (542.75): C, 70.81; H, 7.06; N, 5.16. Found: C, 71.03; H, 7.34; N, 5.56.

***cis*-(3*R*,4*R*)-1-Benzyl-4-[(1*R*)-[(*tert*-butyldimethylsilyl)-oxy]benzyl]-3-[(4*S*)-4-*tert*-butyl-2-oxooxazolidin-3-yl]azetidin-2-one (26c).** The title compound was prepared from the acid chloride **2c** and the imine **7** following the general procedure. The crude β-lactam was purified by flash column chromatography (silica gel 230−400 mesh, ethyl acetate/hexane 1:4 as eluant): white solid recrystallized from ethanol; yield 82%; mp 228−230 °C (ethanol). $[\alpha]^{25}_D = -21.0°$ (c = 1.0, CH_2Cl_2). IR (KBr): υ 1765 cm^{-1} (C═O); 1736 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$, δ ppm): 7.40−7.23 (m, 10H); 5.79 (d, 1H, J = 9.0 Hz); 4.95 (d, 1H, J = 14.9 Hz); 4.51 (d, 1H, J = 14.9 Hz); 4.33 (t, 1H, J = 9.2 Hz); 4.18 (dd, 1H, J = 5.5 Hz, J = 9.0 Hz); 4.12 (d, 1H, J = 5.5 Hz); 3.99 (dd, 1H, J = 5.3 Hz, J = 9.2 Hz); 3.29 (dd, 1H, J = 5.3 Hz, J = 9.2 Hz); 0.79 (s, 9H); 0.32 (s, 9H); −0.02 (s, 3H); −0.29 (s, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 166.3, 159.7, 140.9, 1363, 128.7, 128.5, 128.3, 128.1, 127.5, 76.0, 68.3, 65.1, 63.5, 45.6, 33.5, 25.9, 24.5, 18.0, −4.4. Anal. Calcd for $C_{30}H_{42}N_2O_4Si$ (522.76): C, 68.93; H, 8.10; N, 5.36. Found: C, 69.03; H, 7.84; N, 5.18.

***cis*-(3*R*,4*R*)-1-Benzyl-4-[(1*R*)-[(*tert*-butyldimethylsilyl)-oxy]ethyl]-3-[(4*R*,5*S*)-1,5-dimethyl-2-oxo-4-phenylimidazolidin-3-yl]azetidin-2-one (32).** The title compound was prepared from the acid chloride **31** and the imine **6** following the general procedure. The crude β-lactam was purified by flash column chromatography (silica gel 230−400 mesh, ethyl acetate/hexane 1:4 as eluant): white solid recrystallized from ethanol; yield 85%; mp 176−178 °C (ethanol). $[\alpha]^{25}_D = -88.8°$ (c = 1.0, CH_2Cl_2). IR (KBr): υ 1757 cm^{-1} (C═O); 1697 cm^{-1} (N−CO−N). ^{1}H NMR ($CDCl_3$, δ ppm): 7.35−7.28 (m, 10H); 4.82 (d, 1H, J = 8.5 Hz); 4.75 (d, 1H, J = 15.4 Hz); 4.38−4.28 (m, 1H); 4.33 (d, 1H, J = 15.4 Hz); 4.33 (d, 1H, J = 5.2 Hz); 3.95−3.86 (m, 1H); 3.54 (dd, 1H, J = 5.2 Hz); 2.75 (s, 3H); 1.19 (d, 3H, J = 6.1 Hz); 0.99 (s, 9H); 0.82 (d, 3H, J = 6.3 Hz); 0.16 (s, 3H); 0.14 (s, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 166.3, 161.4, 136.3, 136.1, 128.6, 128.5, 128.2, 127.4, 69.7, 62.8, 62.1, 61.4, 56.8, 45.7, 29.0, 25.9, 20.7, 17.8, 15.1, −4.4, −4.5. Anal. Calcd for $C_{29}H_{41}N_3O_3Si$ (507.75): C, 68.60; H, 8.14; N, 8.28. Found: C, 68.79; H, 8.06; N, 7.74.

***cis*-(3*R*,4*R*)-1-Benzyl-4-[(1*S*)-[(*tert*-butyldimethylsilyl)-oxy]ethyl]-3-[(4*R*,5*S*)-1,5-dimethyl-2-oxo-4-phenylimidazolidin-3-yl]azetidin-2-one (33).** The title compound was prepared from the acid chloride **31** and the imine **4** following the general procedure. The crude β-lactam was purified by flash column chromatography (silica gel 230−400 mesh, ethyl acetate/hexane 1:4 as eluant): syrup further purified by preparative HPLC (ethyl acetate as eluant, 10 mL/min, t_R = 14.47 min); yield 80%. $[\alpha]^{25}_D = -25.2°$ (c = 1.0, CH_2Cl_2). IR (NaCl): υ 1766 cm^{-1} (C═O); 1739 cm^{-1} (N−CO−N). ^{1}H NMR ($CDCl_3$, δ ppm): 7.45−7.18 (m, 10H); 4.80 (d, 1H, J = 15.3

Hz); 4.68 (d, 1H, J = 8.9 Hz); 4.45−4.31 (m, 1H); 4.11 (d, 1H, J = 15.3 Hz); 4.09 (d, 1H, J = 5.1 Hz); 3.92−3.78 (m, 1H); 3.29 (dd, 1H, J = 8.1 Hz, J = 5.1 Hz); 2.77 (s, 3H); 1.20 (d, 3H, J = 6.2 Hz); 0.89 (s, 9H); 0.76 (d, 3H, J = 6.5 Hz); 0.07 (s, 3H); 0.06 (s, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 167.4, 160.3, 135.6, 128.4, 128.3, 127.9, 127.2, 67.2, 64.4, 62.9, 61.6, 55.3, 45.7, 28.4, 25.8, 22.1, 17.8, 15.1, −3.2, −4.2.

***cis*-(3*R*,4*R*)-1-Benzyl-4-[(1*R*)-[(*tert*-butyldimethylsilyl)-oxy]benzyl]-3-[(4*R*,5*S*)-1,5-dimethyl-2-oxo-4-phenylimidazolidin-3-yl]azetidin-2-one (35).** The title compound was prepared from the acid chloride **31** and the imine **5** following the general procedure. The crude β-lactam was purified by flash column chromatography (silica gel 230−400 mesh, ethyl acetate/hexane 1:3 as eluant). The title compound was obtained as a syrup after purification by preparative HPLC (ethyl acetate as eluant, 10 mL/min, t_R = 12.48 min): yield 18%. $[\alpha]^{25}_D$ = −57.1° (c = 1.0, CH_2Cl_2). IR (NaCl): υ 1765 cm^{-1} (C=O); 1708 cm^{-1} (N−CO−N). ^{1}H NMR ($CDCl_3$, δ ppm): 7.47−7.08 (m, 13H); 6.61−6.58 (m, 2H); 5.19 (d, 1H, J = 8.8 Hz); 4.74 (d, 1H, J = 9.1 Hz); 4.41 (d, 1H, J = 15.1 Hz); 4.10 (d, 1H, J = 5.0 Hz); 3.92−3.86 (m, 1H); 3.58 (dd, 1H, J = 5.0 Hz, J = 8.8 Hz); 2.81 (s, 3H); 2.44 (d, 1H, J = 15.1 Hz); 0.83 (s, 9H); 0.76 (d, 3H, J = 6.5 Hz); 0.02 (s, 3H); −4.8 (s, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 167.4, 160.5, 142.5, 135.7, 135.5, 128.8, 128.6, 128.3, 128.2, 128.1, 127.1, 72.9, 63.5, 63.3, 62.5, 55.5, 44.3, 28.7, 25.8, 17.9, 15.5, −4.0, −4.9.

***cis*-(3*S*,4*S*)-4-[(1*R*)-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]-1-[(1*R*)-phenylethyl]-azetidin-2-one (38).** The title compound was prepared from the acid chloride **2a** and the imine **37** following the general procedure. The crude β-lactam was purified by flash column chromatography (silica gel 230−400 mesh, ethyl acetate/hexane 1:3 as eluant): white solid recrystallized from ethanol; yield 57%; mp 127−129 °C (ethanol). $[\alpha]^{25}_D$ = +70.1° (c = 1.0, CH_2Cl_2). IR (KBr): υ 1748 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6 at 90 °C, δ ppm): 7.48−7.20 (m, 10H); 5.03 (dd, 1H, J = 5.4 Hz); 4.72 (t, 1H, J = 8.8 Hz); 4.54 (q, 1H, J = 7.0 Hz); 4.45 (d, 1H, J = 5.1 Hz); 4.16 (dd, 1H, J = 5.4 Hz, J = 8.8 Hz); 3.86 (m, 1H); 3.62 (dd, 1H, J = 5.1 Hz, J = 8.4 Hz); 1.50 (d, 3H, J = 7.0 Hz); 1.12 (d, 3H, J = 5.9 Hz); 0.73 (s, 9H); −0.08 (s, 3H); −0.36 (s, 3H). ^{13}C NMR (DMSO-d_6 at 90 °C, δ ppm): 163.8, 158.3, 140.3, 138.1, 129.4, 129.3, 128.1, 127.9, 126.9, 126.7, 70.7, 69.2, 63.9, 59.9, 59.0, 54.7, 25.7, 20.1, 19.3, 17.7, −3.8, −4.8. Anal. Calcd for $C_{28}H_{38}N_2O_4Si$ (494.7): C, 67.98; H, 7.74; N, 5.66. Found: C, 68.03; H, 7.59; N, 5.41.

***cis*-(3*S*,4*S*)-4-[(1*R*)-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]-1-[(1*S*)-phenylethyl]-azetidin-2-one (40).** The title compound was prepared from the acid chloride **2a** and the imine **39** following the general procedure. The crude β-lactam was purified by flash column chromatography (silica gel 230−400 mesh, ethyl acetate/hexane 1:4 as eluant) and the title compound was separated from the anti-Evans isomer by preparative HPLC (ethyl acetate as eluant, 10 mL/min, t_R = 9.48 min): syrup; yield 16%. $[\alpha]^{25}_D$ = +60.7° (c = 1.6, CH_2Cl_2). IR (NaCl): υ 1752 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, δ ppm): 7.48−7.24 (m, 10H); 4.94 (dd, 1H, J = 7.0 Hz, J = 9.0 Hz); 4.67 (t, 1H J = 9.0 Hz); 4.61 (q, 1H, J = 7.2 Hz); 4.25−4.17 (m, 1H); 4.20 (d, 1H, J = 7.0 Hz, J = 9.0 Hz); 4.13 (d, 1H, J = 5.2 Hz); 3.39 (dd, 1H, J = 5.2 Hz, J = 7.5 Hz); 1.77 (d, 3H, J = 7.2 Hz); 1.03 (d, 3H, J = 6.2 Hz); 0.90 (s, 9H); 0.10 (s, 3H); 0.09 (s, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 165.5, 157.6, 141.4, 137.5, 129.5, 129.3, 128.7, 127.5, 126.6, 71.5, 67.5, 63.8, 60.5, 59.7, 54.6, 25.9, 25.7, 21.9, 19.1, −2.8, −3.4.

***cis*-(3*R*,4*R*)-4-[(1*R*)-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]-1-[(1*S*)-phenylethyl]-azetidin-2-one (41).** The title compound was prepared from the acid chloride **2a** and the imine **39** following the general procedure. The crude β-lactam was purified by flash column chromatography (silica gel 230−400 mesh, ethyl acetate/hexane 1:3 as eluant) and the title compound was separated from the Evans isomer by crystallization from ethanol: white solid; yield 36%; mp 156−158 °C (ethanol). $[\alpha]^{25}_D$ = +80.1° (c = 1.0, CH_2Cl_2). IR (Nujol) υ 1749 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, δ ppm): 7.45−7.18 (m, 10H); 6.19 (q, 1H, J = 7.0 Hz); 4.92 (t, 1H, J = 8.4 Hz); 4.65 (t, 1H, J = 8.4 Hz); 4.51 (d, 1H, J = 5.6 Hz); 4.50−4.43 (m, 1H); 4.27 (t, 1H, J = 8.4 Hz); 3.54 (dd, 1H, J = 5.6 Hz, J = 8.1 Hz); 1.57 (d, 3H, J = 7.0 Hz); 1.06 (d, 3H, J = 6.1 Hz); 0.78 (s, 9H); −0.01 (s, 3H); −0.29 (s, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 164.6, 157.9, 140.8, 136.1, 129.6, 129.1, 128.2, 128.0, 126.7, 126.5, 70.0, 68.4, 64.6, 62.8, 59.8, 54.8, 25.9, 21.2, 19.8, 17.9, −3.8, −4.6. Anal. Calcd for $C_{28}H_{38}N_2O_4Si$ (494.7): C, 67.98; H, 7.74; N, 5.66. Found: C, 67.20; H, 7.65; N, 5.87.

***cis*-(3*S*,4*S*)-4-[(1*R*)-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]-1-[(1*S*)-phenylethyl]-azetidin-2-one (45).** The title compound was prepared from the acid chloride **2a** and the imine **44** following the general procedure and was separated from the anti-Evans isomer by flash column chromatography (silica gel 230−400 mesh, ethyl acetate/hexane 1:9 as eluant): white low-melting point solid; yield 49%. $[\alpha]^{25}_D$ = +2.3° (c = 1.0, CH_2Cl_2). IR (KBr): υ 1746 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, δ ppm): 7.52−7.26 (m, 10H); 4.97 (dd, 1H, J = 7.1 Hz, J = 9.0 Hz); 4.69 (t, 1H, J = 9.0 Hz); 4.49 (q, 1H, J = 7.1 Hz, J = 9.0 Hz); 4.25 (d, 1H, J = 5.2 Hz); 4.23 (dd, 1H, J = 7.1 Hz, J = 9.0 Hz); 4.30−4.08 (m, 1H); 3.53 (dd, 1H, J = 5.2 Hz, J = 7.1 Hz); 1.68 (d, 3H, J = 7.1 Hz); 1.00 (d, 3H, J = 6.2 Hz); 0.94 (s, 9H); 0.12 (s, 3H); 0.11 (s, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 164.7, 157.3, 141.4, 137.1, 129.2, 129.0, 126.3, 127.1, 126.7, 126.2, 70.2, 67.0, 65.8, 60.2, 59.1, 55.6, 26.0, 25.7, 21.1, 20.6, 17.8, −3.5, −4.1. Anal. Calcd for $C_{28}H_{38}N_2O_4Si$ (494.7): C, 67.98; H, 7.74; N, 5.66. Found: C, 67.56; H, 7.60; N, 5.43.

General Procedure for the Preparation of 3-Amino β-Lactams. General Procedure A. A solution of the β-lactam **23a** or **24a** (6 mmol) in THF/*tert*-butyl alcohol (33.4 mL, 10:1) was added to a cold (−78 °C) solution of lithium (0.49 g, 72 mmol) dissolved in liquid amonia (100 mL). The volume ratio of THF/*tert*-butyl alcohol to liquid ammonia was approximately 1:3. After the solution was stirred for 3 min at −78 °C, the excess lithium was quenched with powdered ammonium chloride (12 equiv) and the ammonia was allowed to distill from the reaction. The residual ammonia and solvent were removed *in vacuo*, and the carbamate salt was disolved in water and acidified briefly to pH 3 to effect carbamic decomposition. To isolate the free amine, a pH adjustment to 10 was followed by extraction with methylene chloride (3 × 70 mL) to give the 3-aminoazetidin-2-one.

General Procedure B. A solution of the β-lactam **41** or **45** (6 mmol) in THF/*tert*-butyl alcohol (33.4 mL, 10:1) was added to a cold (−78 °C) solution of lithium (0.62 g, 90 mmol) dissolved in liquid amonia (100 mL). The volume ratio of THF/*tert*-butyl alcohol to liquid ammonia was approximately 1:3. After the solution was stirred for 3 min at −78 °C, the excess lithium was quenched with powdered ammonium chloride (15 equiv) and the ammonia was allowed to distill from the reaction. The residual ammonia and solvent were removed *in vacuo*, and the carbamate salt was disolved in water and acidified briefly to pH 3 to effect carbamic decomposition. To isolate the free amine, a pH adjustment to 10 was followed by extraction with methylene chloride (3 × 70 mL) to give the 3-aminoazetidin-2-one.

***cis*-(3*R*,4*R*)-3-Amino-4-[(1*R*)-[(*tert*-butyldimethylsilyl)-oxy]ethyl]azetidin-2-one (42).** The title compound was prepared from the the β-lactam **24a** following the general procedure A and from **41** following general procedure B and was obtained as a syrup which was utilized in the next step without further purification: yields 78% and 73%, respectively. IR (NaCl): υ 3575−2980 cm^{-1} (NH_2, NH); 1744 (C=O). ^{1}H NMR ($CDCl_3$, δ ppm): 6.11 (s_b, 1H); 4.19 (d, 1H, J = 5.2 Hz); 3.96−3.81 (m, 1H); 3.47 (dd, 1H, J = 5.2 Hz, J = 7.0 Hz); 0.10 (s, 6H). ^{13}C NMR ($CDCl_3$, δ ppm): 171.5, 68.2, 61.1, 59.9, 29.6, 25.7, 17.9, 0.9, −3.6.

***cis*-(3*S*,4*S*)-3-Amino-4-[(1*R*)-[(*tert*-butyldimethylsilyl)-oxy]ethyl]azetidin-2-one (47).** The title compound was prepared from the the β-lactam **23a** following general procedure A and from **45** following general procedure B: white solid recrystallized from hexane; yields 79% and 75%, respectively; mp 96−98 °C (hexane). $[\alpha]^{25}_D$ = −51.3° (c = 0.56, CH_2Cl_2). IR (KBr): υ 3400−3100 cm^{-1} (NH); 1691 (C=O). ^{1}H NMR ($CDCl_3$, δ ppm): 5.96 (s_b, 1H); 4.21 (d, 1H, J = 5.1 Hz); 4.14 (qd, 1H, J = 2.8 Hz, J = 6.5 Hz); 3.57 (dd, 1H, J = 2.8 Hz, J = 5.1 Hz); 1.93 (s_b, 1H); 1.31 (d, 3H, J = 6.5 Hz); 0.88 (s, 9H); 0.07 (s, 9H). ^{13}C NMR ($CDCl_3$, δ ppm): 173.2, 68.8, 63.4, 58.6, 26.2,

20.3, 18.3, −4.1, −4.5. Anal. Calcd for $C_{11}H_{24}N_2O_2Si$ (216.32): C, 54.05; H, 9.89; N, 11.46. Found: C, 53.97; H, 9.75; N, 11.32.

***cis*-(3*R*,4*R*)-1-Benzyl-4-formyl-3-[(4*R*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (11).** *p*-Toluensulfonic acid monohydrate (0.63 g, 3.3 mmol) was added to a solution of the β-lactam **10** (4.22 g, 10 mmol) in THF/water (100 mL, 2:1). The resulting mixture was refluxed for 6 h and then basified with a saturated solution of $NaHCO_3$ to pH 7. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 30 mL). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a residue which was dissolved in acetone/water (90 mL, 13:1). $NaIO_4$ (8.56 g, 40 mmol) was added in one portion to this solution cooled at 0−5 °C, and the resulting suspension was stirred at the same temperature for 1 h 30 min. Then the precipitated salts were filtered off, and the filtrate was concentrated *in vacuo*. The residue was diluted with methylene chloride (20 mL) and washed with water (25 mL). The organic layer was dried over $MgSO_4$, and evaporation of the solvent under reduced pressure gave a crude which was further purified by flash column chromatography (silica gel 230−400 mesh, hexane and then ethyl ether as eluant) to afford a low-melting-point solid: yield 85%. $[\alpha]^{25}_D = -61.4°$ ($c = 0.56$, CH_2Cl_2). IR (KBr): υ 1750 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, δ ppm): 9.40 (d, 1H, $J = 2.2$ Hz); 7.45−7.23 (m, 10H); 4.92 (t, 1H, $J = 8.6$ Hz); 4.63 (t, 1H, $J = 8.6$ Hz); 4.61 (d, 1H, $J = 15.4$ Hz); 4.52 (d, 1H, $J = 15.4$ Hz); 4.48 (d, 1H, $J = 5.7$ Hz); 4.15 (t, 1H, $J = 5.7$ Hz); 4.15 (t, 1H, $J = 8.6$ Hz); 4.03 (dd, 1H, $J = 2.2$ Hz, $J = 5.7$ Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 198.0, 164.0, 157.6, 135.9, 132.2, 129.7, 129.6, 129.5, 129.1, 128.5, 127.5, 71.2, 63.9, 62.0, 60.4, 46.2. Anal. Calcd for $C_{20}H_{18}N_2O_4$ (350.37): C, 68.56; H, 5.18; N, 7.99. Found: C, 68.39; H, 5.04; N, 7.72.

General Procedure for the Preparation of the *cis*-(3*S*,4*S*)-1-Benzyl-4-carboxy-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (50). The same de-acetalization procedure as above was followed starting from β-lactam **49** (2.36 g, 5.6 mmol). Then, $NaIO_4$ (3.2 g, 1.5 mmol) and $KMnO_4$ (0.4 g, 2.5 mmol) were added to a suspension of the crude diol in acetone/water (65 mL/62.5 mL). The resulting mixture was stirred at room temperature for 2 h. Then water (100 mL) was added, and $NaHSO_3$ (40% solution, 35 mL) was added dropwise maintaining the temperature between 0 and 5 °C. The resulting yellow solution was extracted with ethyl acetate (2 × 100 mL). The organic layer was washed with $NaHCO_3$ (saturated solution, 2 × 100 mL), and the aqueous layers were combined, acidified, and extracted with ethyl acetate (2 × 100 mL). The combined organic solutions were dried over $MgSO_4$, and the evaporation of the solvent under reduced pressure gave a crude which was then purified by flash column chromatography (silica gel 230−400 mesh, methylene chloride/hexane 4:1 as eluant and then methylene chloride/methanol 9:1) to afford a low-melting-point white solid: yield 59%. $[\alpha]^{25}_D = +119.2°$ ($c = 1.0$, CH_2Cl_2). IR (KBr): υ 3250−2750 cm^{-1} (OH); 1759 cm^{-1} (CO); 1754 cm^{-1} (CO). ^1H NMR (DMSO-d_6 at 90 °C, δ ppm): 7.49−7.37 (m, 5H); 7.31−7.23 (m, 5H); 4.96 (t, 1H, $J = 8.6$ Hz); 4.70 (d, 1H, $J = 15.5$ Hz); 4.68 (t, 1H, $J = 8.6$ Hz); 4.49 (d, 1H, $J = 5.6$ Hz); 4.31 (d, 1H, $J = 15.5$ Hz); 4.20 (d, 1H, $J = 5.6$ Hz); 4.12 (t, 1H, $J = 8.6$ Hz). ^{13}C NMR (DMSO-d_6 at 90 °C, δ ppm): 170.2, 164.4, 156.9, 137.7, 135.8, 129.3, 129.0, 128.6, 128.0, 127.5, 127.4, 70.5, 60.6, 60.0, 56.0, 44.7. Anal. Calcd for $C_{20}H_{18}N_2O_5$ (366.37): C, 65.57; H, 4.95; N, 7.65. Found: C, 65.32; H, 4.81; N, 7.59.

General Procedure for the Preparation of 4-Acyl β-Lactams. Thionyl chloride (4.5 mL, 6 mmol) was added to a solution of the 4-carboxy β-lactam (3.1 mmol) in dry methylene chloride (15.5 mL). The resulting mixture was refluxed for 3 h, and evaporation of the solvent under reduced pressure gave a solid residue which was then disolved in dry THF (15 mL). A 3.0 M solution in Et_2O of the corresponding magnesium derivative (3.9 mmol) was added dropwise to this solution at −40 °C, and the reaction mixture was stirred for 1 h. Then it was allowed to reach room temperature and stirred for an additional 1 h, after which it was poured into NH_4Cl (saturated solution, 30 mL) and methylene chloride was added. The aqueous layer was separated and extracted with methylene chloride (30 mL). The organic layers were combined, washed with water (30 mL), and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a crude which was further purified by flash column chromatography (230−400 mesh, ethyl acetate/hexane 1:3 as eluant).

General Procedure for the Reduction of 4-Acyl β-Lactams. A 1 M solution of L-Selectride in THF (3.4 mmol) was added via syringe to a solution of the corresponding 4-acyl β-lactam (1.7 mmol) in THF (10 mL) cooled at −78 °C. The resulting mixture was stirred for 1 h at −60 °C, and then water (2 mL) and ethyl ether (50 mL) were added. The mixture was acidified with 6 M HCl, and the organic layer was separated and dried over $MgSO_4$. Evaporation of the solvents under reduced pressure gave the correspondig hydroxy β-lactam.

***cis*-(3*S*,4*S*)-1-Benzyl-4-[(1*R*)-hydroxyethyl]-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (51).** The title compound was prepared from 4-acetyl β-lactam **17a** following the general procedure. The crude β-lactam was purified by flash column chromatography (silica gel 230−400 mesh, ethyl acetate/hexane 1:2 as eluant). A white solid recrystallized from ethanol: yield 94%; mp 183−184 °C (ethanol). $[\alpha]^{25}_D = +136.1°$ ($c = 1.0$, CH_2Cl_2). IR (NaCl): υ 3468 cm^{-1} (OH); 1757 cm^{-1} (CO); 1723 cm^{-1} (CO). ^1H NMR ($CDCl_3$, δ ppm): 7.49−7.08 (m, 10H); 5.13 (dd, 1H, $J = 7.5$ Hz, $J = 9.0$ Hz); 4.72 (t, 1H, $J = 9.0$ Hz); 4.61 (d, 1H, $J = 15.5$ Hz); 4.34 (d, 1H, $J = 4.9$ Hz); 4.24 (dd, 1H, $J = 7.5$ Hz, $J = 9.0$ Hz); 4.14 (d, 1H, $J = 15.5$ Hz); 3.92−3.88 (m, 1H); 3.35 (dd, 1H, $J = 4.9$ Hz, $J = 8.8$ Hz); 2.25−2.11 (s_b, 1H); 1.10 (d, 3H, $J = 6.1$ Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 165.1, 158.3, 137.3, 135.2, 129.3, 129.1, 128.7, 127.7, 127.6, 127.4, 70.9, 65.7, 63.2, 60.4, 60.3, 45.6, 22.0. Anal. Calcd for $C_{21}H_{22}N_2O_4$ (366.42): C, 68.84; H, 6.05 N, 7.64. Found: C, 68.71; H, 5.93; N, 7.42.

***cis*-(3*S*,4*S*)-1-Benzyl-4-[(1*R*)-hydroxybenzyl]-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (52).** The title compound was prepared from 4-benzoyl β-lactam **18a** following the general procedure. The crude β-lactam was purified by flash column chromatography (silica gel 230−400 mesh, ethyl acetate/hexane 1:2 as eluant). A white solid recrystallized from ethanol: yield 98%; mp 175−177 °C (ethanol). $[\alpha]^{25}_D = +145.9°$ ($c = 1.0$, CH_2Cl_2). IR (KBr): υ 3363 cm^{-1} (OH); 1754 cm^{-1} (CO); 1748 cm^{-1} (CO). ^1H NMR (DMSO-d_6, δ ppm): 7.55−7.17 (m, 13H); 6.64 (d, 2H); 5.89 (d_b, 1H); 5.08 (dd, 1H, $J = 6.8$ Hz, $J = 8.8$ Hz); 4.80 (t, 1H, $J = 8.8$ Hz); 4.32 (d, 1H, $J = 4.9$ Hz); 4.19 (d, 1H, $J = 15.4$ Hz); 4.19 (dd, 1H, $J = 6.8$ Hz, $J = 8.8$ Hz); 3.69 (dd, 1H, $J = 4.9$ Hz, $J = 9.1$ Hz); 3.02 (d, 1H, $J = 15.4$ Hz). ^{13}C NMR (DMSO-d_6, δ ppm): 165.3, 157.5, 143.2, 138.5, 135.6, 129.5, 129.1, 128.8, 128.5, 128.3, 127.6, 127.4, 126.6, 71.6, 70.4, 62.2, 60.8, 60.1, 44.5. Anal. Calcd for $C_{26}H_{24}N_2O_4$ (428.49): C, 72.88; H, 5.64; N, 6.54. Found: C, 72.75; H, 5.57; N, 6.38.

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Supporting Information Available: Spectral and analytical data (^1H NMR, ^{13}C NMR, IR, MS) are provided for compounds **12**, **15a−c**, **16a**, **17a−c**, **18a**, **20**, **21**, **22**, **27a**, **27c**, **28a**, **43**, and **48** (6 pages). This material is contained in libraries on microfiche, inmediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current mastahead page for ordering information.

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