tance of W. K. Rule and M. McDonald in performing amino acid analyses and M. John in sequencing peptides is gratefully acknowledged.

Registry No. 1, 118869-37-7; 3·HCl, 2462-35-3; 4, 122520-32-5; 5, 5680-86-4; 6·TFA, 122520-34-7; 7, 122539-48-4; 8·TFA, 122520-36-9; 9·TFA, 122520-38-1; 9·HF, 122520-43-8; 10·TFA, 122520-40-5; 11·TFA, 122520-42-7; BOC-Trp-OH, 13139-14-5; BOC-Trp-Leu-Obzl, 72755-34-1; H-Trp-Leu-OBzl·TFA, 122520-45-0; Z-Glu(OBzl)-Trp-Leu-OBzl, 122520-46-1.

The Reformatsky Type Reaction of Gilman and Speeter in the Preparation of Valuable β-Lactams in Carbapenem Synthesis: Scope and Synthetic Utility

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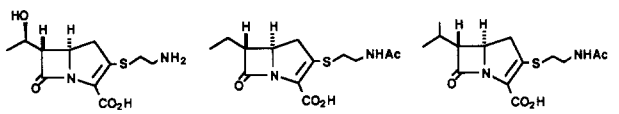
The preparation of appropriately substituted 3-alkyl β-lactams from the Reformatsky type reaction of Gilman and Speeter is described. Treatment of Schiff bases derived from α-methylcinnamaldehyde and amines with ethyl α-bromobutyrate or ethyl α-bromoisovalerate in the presence of zinc dust followed by an ozonolysis–Baeyer–Villiger sequence of the resulting β-lactams afforded 3-alkyl-4-acetoxy β-lactams as synthetic intermediates for the synthesis of PS-5 and PS-6 carbapenem compounds. The reaction between cinnamylideneamines and these α-bromoesters under Gilman and Speeter's conditions also works well to provide the expected 3-alkyl-4-styryl β-lactams suitable for further chemical manipulations by known methods. As expected, application of this procedure to the synthesis of 3-unsubstituted β-lactams starting from methyl bromoacetate was inefficient. However, activation of zinc dust by trimethylchlorosilane provided an exceedingly efficient route to 3-unsubstituted β-lactams in 70–95% yields except those derived from cinnamylideneamines. Treatment of the lithium enolate of 1-(4-methoxyphenyl)-4-(α-methylstyryl)azetidin-2-one with acetaldehyde or methyl acetate afforded the corresponding trans derivatives as synthetic precursors of (±)-thienamycin. A new diastereoselective entry for the synthesis of optically active carbapenem compounds is also described.

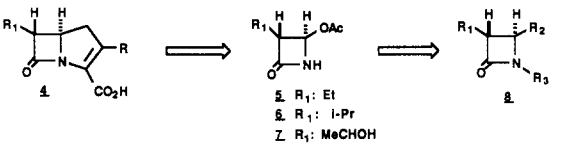
Since the discovery of novel biologically active β-lactam antibiotics[1] such as thienamycin **1** and the closely related carbapenems PS-5 **2** and PS-6 **3**, intense effort has been



1 **2** **3**

focused in the development of suitable methods for their total synthesis.[2] These compounds and related structures comprise a new family of streptomycete metabolites characterized by the presence of the 7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic acid system carrying an exocyclic (aminoethyl)thio substituent at C_3 of the pyrroline ring and alkyl side chains at the α-position adjacent to the β-lactam carbonyl. The novel chemical features and potent antibacterial properties of these new bicyclic β-lactams, together with the reported low-yield fermentation processes as compared to those in other noted β-lactam antibiotics, have made carbapenems attractive target molecules for many research groups.[3]

The main strategies toward carbapenem synthesis usually involve first the construction of an appropriately substituted monocyclic β-lactam **8** with the correct stereochemistry at C_3–C_4 of the β-lactam ring, followed by chemical manipulations at N_1 and C_4 and subsequent ring closure to form the bicyclic ring system **4** in the last step of the synthesis.[3,4] 4-Acetoxyazetidin-2-ones **5**–**7** are recognized as the most useful intermediates for this type of carbapenem synthesis, because the acetoxy group can



4 **5** R_1: Et; **6** R_1: i-Pr; **7** R_1: MeCHOH; **8**

(1) For reviews on β-lactam antibiotics, see: (a) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vol. 1–3. (b) *Recent Advances in The Chemistry of β-Lactam Antibiotics*; Brown, A. G., Roberts, S. M., Eds.; The Royal Society of Chemistry: Burlington House, London, 1984. (c) *Topics in Antibiotic Chemistry*; Sammes, P. G., Ed.; Ellis Horwood: New York, 1980; Vol. 3–4. (d) Southgate, R.; Elson, S. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, Ch., Eds.; Springer-Verlag: New York, 1985; p 1. (e) Dürckheimer, W.; Blumbach, J.; Latrell, R.; Sheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180.

(2) For a recent review on the synthesis of Thienamycin see: Georg, G. I. In *Studies in Natural Product Chemistry*; Rahman, A-ur, Ed.; Elsevier Science: Amsterdam; in press. For leading references on total synthesis of PS-5 and PS-6 see: (a) Ohta, T.; Sato, N.; Kimuna, T.; Nozoe, S. *Tetrahedron Lett.* **1988**, *29*, 4305. (b) Gennari, C.; Cozzi, P. G. *J. Org. Chem.* **1988**, *53*, 4015. (c) Bonini, C.; Fabio, R. *Tetrahedron Lett.* **1988**, *29*, 815. (d) Cainelli, G.; Panuzio, M. *J. Am. Chem. Soc.* **1988**, *110*, 6879.

(3) For reviews on the synthesis of carbapenems, see: (a) Ratcliffe, R. W.; Albers-Schonberg, G. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M.; Eds.; Academic: New York, 1982; Vol. 2, p 227. (b) Hoppe, D. *Nachr. Chem., Tech. Lab.* **1982**, *30*, 24. (c) Kametani, T.; Fukumoto, K.; Ihara, M. *Heterocycles* **1982**, *17*, 463. (d) Shibuya, M. *J. Synth. Org. Chem. Jpn.* **1983**, *41*, 62. (e) Labia, R.; Morin, C. *J. Antibiot.* **1984**, *37*, 1103. (f) Nagahara, T.; Kametani, T. *Heterocycles* **1987**, *25*, 729. (g) 1-β-Methylcarbapenems: Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29.

(4) Christensen, B. G.; Salzmann, T. N. In *Handbook of Experimental Pharmacology*; Demain, A. L., Solomon, N. A., Eds.; Springer-Verlag: New York, 1983; Vol. 67/I, p 329.

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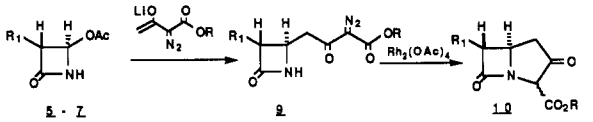
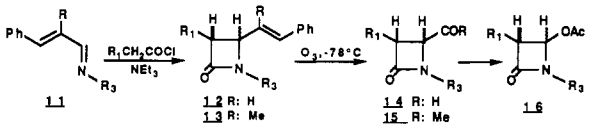
be replaced by a variety of nucleophiles.[5] The most direct access to 4-acetoxyazetidin-2-ones is the addition of chlorosulfonyl isocyanate (CSI) to the corresponding vinyl acetate.[6] Following this approach, Kametani and coworkers[7] were the first to accomplish the total synthesis of antibiotic PS-5 by reaction between 3-ethyl-4-acetoxyazetidin-2-one (5) and the lithium enolate of *tert*-butyl α-diazoacetylacetate followed by the carbene insertion reaction developed by the Merck group[8] (eq 1). The same



(1)

authors[9] reported the synthesis of antibiotic PS-6 starting from the corresponding 4-acetoxyazetidin-2-one 6, and later other groups have used an analogous approach for the preparation of other related β-lactam building blocks[10] including the thienamycin precursor 7.[11] However, apart from the low yields reported and the lack of stereoselectivity in the cycloaddition step, CSI is reactive toward several functional groups and such a process is not usually feasible.[12] Consequently, the development of short and highly stereocontrolled methods for the synthesis of 4-acetoxyazetidin-2-ones or β-lactams containing leaving groups at the C_4 position of the β-lactam ring becomes of crucial importance in β-lactam chemistry.

Several groups have shown that the annelation of cinnamylidene Schiff bases 11 with an activated acetic acid is a convenient procedure for the construction of appropriately substituted azetidin-2-ones (eq 2). Ozonolysis of

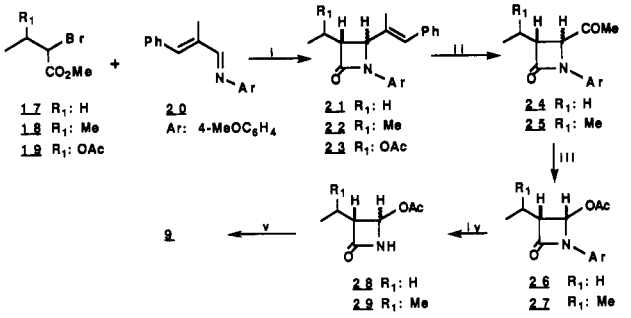


(2)

the styryl moiety and further elaboration of the resulting carbonyl group have provided entries to several monocyclic and bicyclic β-lactam compounds.[1] Following this approach, we[13] and others[14] have recently described a concise method for preparing 4-acetoxyazetidin-2-ones **16** that involves the preparation of a β-lactam **13** with a 4-(α-methylstyryl) group as latent carbonyl functionality followed by a Baeyer–Villiger oxidation of the resulting methyl ketone **15**. The reaction works especially well with electron-withdrawing substituents at the α-position of the acid choride. Unfortunately, the first step of the method was not effective for the direct preparation of 3-alkyl-4-(α-methylstyryl) β-lactams nor for the corresponding 3-unsubstituted ones.[15]

Among other methods for the synthesis of substituted monocyclic β-lactams,[16] the Reformatsky type reaction of Gilman and Speeter[17] is of potential value not only for the

Scheme I[a]



[a] Reagents and conditions: i, Zn, I_2, benzene or toluene, reflux; ii, O_3, −78 °C, CH_2Cl_2, then Me_2S; iii, *m*-CPBA, benzene, reflux; iv, cerium(IV) ammonium nitrate (CAN), CH_3CN–H_2O; v, ref 9.

Table I. Preparation of β-Lactams 21 and 22 under Different Conditions[a]

product	catalyst	solvt	time, h	yield,[b] %
21, R_1: H	I_2	benzene	2.5	60 (30/60)
	I_2	toluene	2.5	72 (35/65)
	$HgCl_2$	toluene	8	80 (20/80)
	I_2	dioxane	2.5	96 (60/40)
	I_2	THF	4	77 (55/45)
22, R_1: Me	I_2	toluene	30	90 (15/85)
	I_2	toluene	2.5	89 (15/85)
	$HgCl_2$	dioxane	2.5	85 (30/70)
	I_2	THF	6	80 (55/45)
	$HgCl_2$	toluene	14	75 (17/83)

[a] Reactions conducted on 10 mmol scale; 1.2:1:0.12 bromo ester **17** and **18**, imine **20**, and I_2 or $HgCl_2$, respectively. [b] Yields based on weight of isolated product by column chromatography; the number in parentheses indicated the cis/trans ratio determined by NMR spectroscopy.

(5) For comprehensive reviews, see: (a) ref 3c and 3f. (b) Davies, D. E.; Storr, R. C. In *Comprehensive Heterocyclic Chemistry*; Lwowski, W., Ed.; Pergamon: New York, 1984; Vol. 7, p 237.

(6) Claus, K.; Grimm, D.; Prossel, G. *Liebigs Ann. Chem.* **1974**, 539.

(7) Kametani, T.; Honda, T.; Nakayama, A.; Fukumoto, K. *Heterocycles* **1980**, *14*, 1967.

(8) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 31.

(9) Kametani, T.; Honda, T.; Nakayama, A.; Sasaki, Y.; Mochizuki, T.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2228. For a related approach, see: Favara, D.; Omodei-Salé, A.; Consonni, P.; Depaoli, A. *Tetrahedron Lett.* **1982**, *23*, 3105.

(10) (a) Cecchi, R.; Favara, D.; Omodei-Salé, A.; Depaoli, A.; Cousonni, P. *Gazz. Chim. Ital.* **1984**, *114*, 225. (b) Bateson, J. H.; Quinn, A. M.; Smale, T C.; Southgate, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2219. (c) Buynak, J. O.; Narayana Rao, M.; Pajouhesh, H.; Yegna Chandrasekaran, R.; Finn, K.; Meester, P.; Chu, S. C. *J. Org. Chem.* **1985**, *50*, 4245. (d) Buynak, J. D.; Narayana Rao, M. *J. Org. Chem.* **1986**, *51*, 1571. (e) Buynak, J. D.; Mathew, J.; Narayana Rao, M.; Haley, E.; Georg, C.; Siriwardane, U. *J. Chem. Soc., Chem. Commun.* **1987**, 735.

(11) (a) Ohasti, T.; Kan, K.; Sada, I.; Miyama, A.; Watanaba, K. EP O 167 155 Al, **1986**; *Chem. Abstr.* **1986**, *105*, 60469f. (b) Buynak, J. D.; Narayana Rao, M. *J. Chem. Soc., Chem. Commun.* **1986**, 941.

(12) For reviews on CSI, see: (a) Rasmussen, J. K.; Hassner, A. *Chem. Rev.* **1976**, *76*, 389. (b) Dhar, D. N.; Murthy, K. S. K. *Synthesis* **1986**, 437. (c) Kamai, A.; Sattur, P. B. *Heterocycles* **1987**, *26*, 1051.

(13) (a) Aizpurua, J. M.; Cossio, F. P.; Lecea, B.; Palomo, C. *Tetrahedron Lett.* **1986**, 4359. (b) Arrieta, A.; Lecea, B.; Cossio, F. P.; Palomo, C. *J. Org. Chem.* **1988**, *53*, 3784, and references therein.

(14) Georg, G. I.; Kant, J.; He, P.; Ly, A. M.; Lampe, L. *Tetrahedron Lett.* **1988**, *29*, 2409.

(15) Some exceptions have been recently described for the preparation of 3-alkyl β-lactams from the acid chloride–imine approach: (a) Alcaide, B.; Dominguez, G.; Escobar, G.; Parreno, V.; Plumet, J. *Heterocycles* **1986**, *24*, 1579. (b) Ernst, B.; Bellus, D. DE 36 20467 Al; *Chem. Abstr.* **1987**, *106*, 176045q. (c) Tschaen, D. M.; Fuentes, L. M.; Lynch, J. E.; Laswell, W. L.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 2779.

(16) For reviews, see: (a) Mukerjee, A. K.; Srivastava, R. C. *Synthesis* **1973**, 373. (b) Bose, A. K.; Manhas, M. S. *Lect. Heterocycl. Chem.* **1976**, *3*, 43. (c) Isaacs, N. S. *Chem. Soc. Rev.* **1976**, *76*, 181. (d) Mukerjee, A. K.; Singh, A. K. *Tetrahedron* **1978**, *34*, 1731. (e) Koppel, G. A. In *Small Ring Heterocycles-Azetidines, β-Lactams, Diazetidines and Diaziridines*; Hassner, A., Ed.; Wiley: New York, 1983; Chapter 2. (f) Hanessian, S.; Sahoo, S. P.; Couture, C.; Wyss, H. *Bull. Soc. Chim. Belg.* **1984**, *93*, 571. (g) Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49.

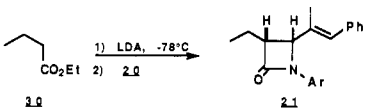
(17) Gilman, H.; Speeter, M. *J. Am. Chem. Soc.* **1943**, *65*, 2255. (b) Luche, J. L.; Kagan, H. B. *Bull. Soc. Chim. Fr.* **1969**, 3500; **1971**, 2260. (c) Dardoize, F.; Moreau, J. L.; Gaudemar, M. *Comptes Rendus* **1969**, *C268*, 2228; *Bull. Soc. Chim. Fr.* **1972**, 3841; *Ibid.* **1973**, 1668. (d) Piotrowska, K.; Mostowicz, D. *J. Chem. Soc., Chem. Commun.* **1981**, 41. (e) Mochalin, V. B.; Khenkina, T. V. *J. Org. Chem. (USSR)* **1982**, *18*, 583. (f) Bellassoued, M.; Arous-Chtara, R.; Gaudemar, M. *J. Organomet. Chem.* **1982**, *231*, 185. (g) Moreau, J. L.; Gaudemar, M. *C. R. Acad. Sci., Ser 2* **1985**, *300*, 399. (h) Taguchi, T.; Kitagawa, O.; Suda, Y.; Ohkawa, S.; Hashimoto, A; Iitaka, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 5291. (i) For a recent study on zinc enolates see: Dekker, J.; Schouten, A.; Budzelaar, P. H. M.; Boersma, J.; Van Der Kerk, G. J. M.; Spek, A. L.; Duisenberg, A. J. M. *J. Organomet. Chem.* **1987**, *320*, 1.

ready accessibility of starting materials but also for the direct preparation of β-lactams with 3-alkyl side chains and for the possibility to control the stereoselectivity of the reaction. Surprisingly, the Reformatsky type reaction between α-bromoesters and imines has received very little attention within the context of β-lactam antibiotic synthesis. Presumably, this fact may be due to the low yields often produced in the azetidinone ring formation, specially in those derived from bromoacetic esters.[18] Bergbreiter and Newcomb[19] introduced a variant of this reaction by using lithium enolates of esters, and then Hart,[20] Georg,[21] and other workers[2] have successfully applied such an approach to the synthesis of carbapenem compounds. Other conceptually similar approaches involved ketene silyl acetals,[22] boron enolates,[23] and Sn(II) enolates,[24] which upon treatment with Schiff bases afforded β-amino esters that then were cyclized to the corresponding β-lactams. Recently we have applied the Gilman and Speeter reaction to the synthesis of appropriately substituted β-lactams for the preparation of 4-acetoxyazetidin-2-ones as carbapenem building blocks.[25] Herein we report details of our study that demonstrate the synthetic utility of the α-bromo ester–imine condensation in β-lactam chemistry.

Results and Discussion

As we have previously reported,[25] our general strategy for the synthesis of 3-alkyl-4-acetoxyazetidin-2-ones involves the synthesis of precursors of type **21–23** with a 4-alkenyl group, followed by the ozonolysis–Baeyer–Villiger sequence depicted in Scheme I. The key to our synthesis was the high-yield preparation of the precursor **21** by means of the Reformatsky type reaction of Gilman and Speeter between methyl α-bromobutyrate **17** and the Schiff base **20** derived from *p*-anisidine and α-methylcinnamaldehyde. Thus, under the conditions indicated in Table I, β-lactam **21** was obtained in 80% yield as a 1:4 mixture of the corresponding cis and trans isomers without formation of side products. This result contrasts with the formation of 3,4-dihydro-2-pyridones from enolates of substituted acetates and 1-azabutadienes, reported by Komatsu and co-workers.[26] Subsequent elaboration of the styryl group in **21** and further N-dearylation[27] provided an easy access to the 3-ethyl-4-acetoxyazetidin-2-one **28** as intermediate for the preparation of (±)-PS-5 carbapenem antibiotic **2**.

Similarly, preparation of **22** has also been studied to synthesize the (±)-PS-6 carbapenem precursor **29**. Thus, compound **20** was treated with methyl α-bromoisovalerate (**18**) in the presence of zinc dust and iodine as catalyst in refluxing toluene to afford **22** in 90% yield as a 1:5.5 mixture of cis and trans isomers, respectively (Table I), from which the trans isomer could be separated by column chromatography. The stereochemistry of the product **22** was determined on the basis of its ^{1}H NMR spectral data. Thus, the proton at C_4 in the cis isomer shows as a doublet at 4.63 ppm (J = 5.7 Hz) while the corresponding one in the trans isomer appears at 4.30 ppm (J = 2.4 Hz). In general, the C_4–H proton in a trans isomer appears at higher field than the corresponding C_4–H proton in the respective cis isomer. In subsequent experiments to carry out the best stereoselective control of the β-lactam ring formation following Kagan's observations,[17b] we examined both the ester group and the solvent influence. In the first case, we found that the use of bulky esters did not lead to the formation of the expected β-lactam **22**, and in the second case reaction between **18** and **20** in a more polar solvent, such as dioxane, gave an approximately 1:2 mixture of the cis and trans isomers of **22**. When the imine **20** was treated with the Reformatsky reagent of **17** in the same solvent, the β-lactam **21** was obtained in 96% yield as a 1.5:1 mixture of cis and trans isomers (Table I). For comparison (eq 3), when the lithium enolate of ethyl bu-



(3)

tyrate (**30**) was subjected to treatment with the imine **20** under the same conditions reported by Bergbreiter,[19] the corresponding cis β-lactam **21** was produced in 70% isolated yield and only traces of the corresponding trans isomer were detected by ^{1}H NMR analysis of the crude reaction mixture. With hexamethylphosphoric triamide (HMPA) as cosolvent, the ratio of isomers was inverted, giving **21** in 70% yield as a 1:2.5 mixture of cis and trans isomers, respectively.

At this stage we attempted a more direct access to 4-acyl-β-lactams starting from imines derived from pyruvaldehyde[28] and phenylglyoxal;[15a] however, we did not observe any β-lactam formation. Apparently, a carbonyl group at the imine carbon seems to be incompatible with the reaction conditions employed.[29] Therefore, we explored the sequence of reactions depicted in Scheme I to synthesize the carbapenem precursor **29**. Low-temperature ozonolysis of the trans isomer of **22** with dimethyl sulfide workup[30] gave the methyl ketone **25** in 58% yield. Subsequent Baeyer–Villiger oxidation of *trans*-**25** with *m*-chloroperbenzoic acid (*m*-CPBA) in a molar ratio 1:3 respectively in boiling benzene for 2.5 h afforded a mixture of *trans*-**27** together with the starting product **25** (41% conversion) as was expected from earlier experiments carried out on trans **24**.[25a] Further oxidation of this mixture under the same conditions as above gave the trans isomer of **27** in 46% yield as the only reaction product. Oxidative removal of the N-aryl substituent by ammonium cerium(IV) nitrate (CAN) yielded the expected N-unsubstituted *trans*-4-acetoxy-3-isopropylazetidin-2-one (**29**) as intermadiate for the synthesis of (±)-PS-6 carbapenem antibiotic **3**.

Since a trans azetidinone of type **9** is formed from either cis or trans azetidinones **28** or **29**,[7,9] we examined our

(18) (a) Furukawa, M.; Okawara, T.; Noguchi, Y.; Terawaki, Y. *Chem. Pharm. Bull.* **1978**, *26*, 260. (b) Bose, A. K.; Gupta, K.; Manhas, M. S. *J. Chem. Soc., Chem. Commun.* **1984**, 86.

(19) Gluchowski, C.; Cooper, L.; Bergbreiter, D. E.; Newcomb, M. J. *J. Org. Chem.* **1980**, *45*, 3413.

(20) Ha, D. C.; Hart, D. J. *J. Antibiotics* **1987**, *40*, 309, and references therein.

(21) Georg, G. I.; Kant, J. *J. Org. Chem.* **1988**, *53*, 692, and references therein.

(22) For leading references, see: (a) ref 2b. (b) Gennari, C.; Schimperna, G.; Venturini, I. *Tetrahedron* **1988**, *44*, 4221. (c) Colvin, E. W.; McGarry, D.; Nugent, M. J. *Tetrahedron* **1988**, *44*, 4157.

(23) For leading references, see: (a) Shibasaki, M.; Ishida, Y.; Iwasaki, G.; Iimori, T. *J. Org. Chem.* **1987**, *52*, 3489. (b) Mori, M.; Kagechika, K.; Tohjima, K.; Shibasaki, M. *Tetrahedron Lett.* **1988**, *29*, 1409.

(24) Yamada, T.; Suzuki, H.; Mukaiyama, T. *Chem. Lett.* **1987**, 293.

(25) (a) Odriozola, J. M.; Cossío, F. P.; Palomo, C. *J. Chem. Soc., Chem. Commun.* **1988**, 809. (b) Cossío, F. P.; Odriozola, J. M.; Oiarbide, M.; Palomo, C. *J. Chem. Soc., Chem. Commun.* **1989**, 74.

(26) Komatsu, M.; Yamamoto, S.; Ohshiro, Y.; Agawa, T. *Heterocycles* **1985**, *23*, 677.

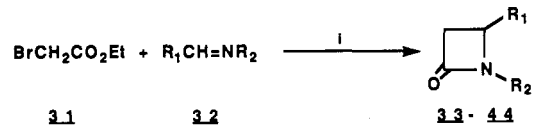
(27) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

(28) Alcaide, B.; Escobar, G.; Perez-Ossorio, R.; Plumet, J.; Rodriguez, I. M. *An. Quim., Ser. C* **1985**, 81.

(29) Georg, G. I.; Kant, J.; Gill, H. S. *J. Am. Chem. Soc.* **1987**, *109*, 1129.

(30) Pappas, J. J.; Keaveney, W. P.; Gaucher, E.; Berger, M. *Tetrahedron Lett.* **1966**, 4273.

Scheme II[a]



31 32 33-44

[a] Reagents and conditions: i, Zn, TMCS, benzene, 2.5 h.

Table II. Trimethylchlorosilane-Catalyzed Reaction between Ethyl Bromoacetate (31) and Schiff Bases 32[a]

entry	product	R_1	R_2	yield,[b] %	mp, °C
a	**33**	Ph	Ph	82	154–155
b	**34**	Ph	4-MeOPh	80	83–84
c	**35**	4-MePh	4-MeOPh	80	97–99
d	**36**	4-MeOPh	4-MeOPh	78	157–159
e	**37**	4-ClPh	4-MeOPh	80	132–133
f	**38**	*t*-PhCH=CH	4-MeOPh	58	139–142
g	**39**	*t*-PhCH=CH	Ph	49	oil
h	**40**	*c*-PhCH=CH	4-MeOPhCH$_2$	49	oil
i	**41**	*t*-PhCH=C(Me)	4-MePh	95	81–83
j	**42**	*t*-PhCH=C(Me)	Ph	80	113–116
k	**43**	*c*-PhCH=C(Me)	4-MeOPhCH$_2$	70	oil
l	**44**	*c*-EtCH=C(Me)	4-MeOPh	61	85–87

[a] Reactions conducted on 10 mmol scale; 1.2:1:0.5 bromo ester **31**, imine **32**, and TMCS, respectively. [b] Yields based on weight of isolated product by column chromatography.

methodology starting from a mixture of the corresponding cis and trans isomers of **22** to improve the overall chemical yield. Thus, ozonolysis of the crude mixture of cis and trans isomers of **22** in methylene chloride at −78 °C afforded the expected mixture of cis and trans isomers of **25**. However, when this mixture was then treated with *m*-CPBA under the described conditions, only the trans isomer of **25** gave the expected 4-acetoxy β-lactam **27** and no traces of the corresponding starting *cis*-4-acetyl β-lactam **25** were detected in the crude reaction mixture. This result seems to indicate that the cis isomer of **25** (R_1 = Me) was unstable to the above reaction conditions. For example, we found that when pure *cis*-**25** was subjected to treatment with *m*-CPBA for 2.5 h under the above conditions, no reaction but extensive degradation took place and the starting product was recovered in only 48% yield. When the same reaction was performed on *cis*-**24** (R_1 = H), only a 15% conversion was achieved after 2.5 h in refluxing benzene. Further treatment of this mixture with more *m*-CPBA (molar ratio 1:3) under the same conditions as above gave a 30% conversion to *cis* **26** together with degradation products. These results indicated that Baeyer–Villiger oxidation on N-substituted 4-acetyl β-lactams is sensitive to the steric constraints imposed by the 3-alkyl substituents in a cis disposition to the acetyl group.[13b] Attempted isomerization[31] of cis β-lactams **24** and **25** into the corresponding *trans*-4-acetyl β-lactams by either 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBA) at room temperature in methylene chloride as solvent resulted in recovered starting cis β-lactams. The Baeyer–Villiger oxidation on the corresponding N-unsubstituted *cis*-4-acetyl β-lactams would be an alternative route to *cis*-4-acetoxyazetidin-2-ones in these cases.[14,32]

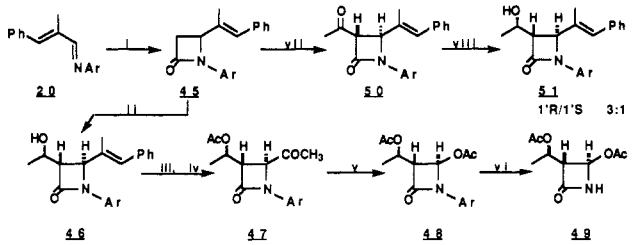
The next question we examined was the preparation of the corresponding thienamycin precursor **23**. Unfortunately, reaction between **19** and the Schiff base **20** under the same conditions as those used for the preparation of **21** and **22** gave a complex mixture of degradation products, probably by an easy elimination of the acetoxy group in the starting product **19** or in the β-aminoester intermediate that should be formed in the reaction process.[17] Therefore, we sought an alternative method to introduce the hydroxyethyl side chain present in thienamycin **1**.

3-Unsubstituted β-lactams are recognized as valuable starting materials for the introduction of several groups at the α-position of the β-lactam carbonyl.[10b,33] Consequently, we rationalized that we could utilize this methodology for the preparation of a wide variety of functionalized β-lactams, including thienamycin precursors, via a common starting material. Since the acid chloride–imine approach,[34] as well as the ester enolate–imine method,[19] has proven to be unsuccessful for the direct preparation of 3-unsubstituted β-lactams,[35] we decided to explore the Reformatsky type reaction between ethyl bromoacetate (**31**) and Schiff bases **32** (Scheme II). Our finding[25b] is that activation of zinc by trimethylchlorosilane (TMCS)[36] was exceedingly effective in promoting the Gilman and Speeter reaction between ethyl bromoacetate and Schiff bases, providing an easy direct access to the corresponding 3-unsubstituted β-lactams **33–44**. As shown in Table II, the procedure can be applied to a variety of *N*-aryl- and *N*-benzylaldimines. Furthermore, it is interesting to note that under usual Gilman and Speeter conditions,[18b] the reaction proceeded slowly and the yields of β-lactams were 20–50%. Exceptionally, we found that under TMCS catalysis, cinnamylideneamines (entries f–h) afforded relatively low yields of the expected 3-unsubstituted β-lactams. Efforts to improve the yields by using polar solvents such as dioxane and tetrahydrofuran (THF) were unfruitful, and increasing the amount of either ethyl bromoacetate (**31**) or trimethylchlorosilane did not improve the yields of the expected β-lactams. However, when the method was applied to imines derived from α-methylcinnamaldehyde (entries i–k), the corresponding β-lactams were obtained in high yields.

For synthetic purposes, the imine **20** was subjected to treatment with **31** under these conditions, and the β-lactam **45** was obtained in 95% yield (Scheme III). The β-lactam thus prepared was treated with lithium diisopropylamide (LDA) at −78 °C in THF as solvent, and the resulting solution quenched with 4-fold excess of acetaldehyde[33c] to furnish the expected *trans*-3-(1-hydroxyethyl) β-lactam **46** as an equimolar mixture of diastereoisomers epimeric about the hydroxyl group, which were not separated. The trans relationship of the C-3 and C-4 substituents on the β-lactam ring was determined by ^{1}H NMR spectroscopy ($J_{3,4} \approx 2$ Hz). To test our methodology, the mixture of epimers of **46**, after protection of the hydroxyl group as an acetoxy derivative, was subjected to low-temperature ozonolysis with dimethyl sulfide workup to give the

(31) Bose, A. K.; Narayanan, C. S.; Manhas, M. S. *J. Chem. Soc., Chem. Commun.* **1970**, 975.
(32) Shiozaki, M.; Ishida, N.; Hiraoka, T.; Yanagisawa, H. *Tetrahedron Lett.* **1981**, *22*, 5205.
(33) For leading references, see: (a) ref 3c,f. (b) Hamlet, A. B.; Durst, T. *Can. J. Chem.* **1983**, *61*, 411. (c) Ogilvie, W. W.; Durst, T. *Can. J. Chem.* **1988**, *66*, 304.
(34) Mujean, A.; Chuche, J. *Tetrahedron Lett.* **1976**, 2905.
(35) For a two-step synthesis of 3-unsubstituted β-lactams by the acid chloride–imine approach, see: Manhas, M. S.; Hedge, V. R.; Wagle, D. R.; Bose, A. K. *J. Chem. Soc., Perkin Trans 1* **1985**, 2045.
(36) (a) Picotin, G.; Migianic, P. *J. Org. Chem.* **1987**, *52*, 4796. (b) Tamaru, Y.; Nakamura, T.; Sakaguchi, H.; Ochiai, H.; Yoshida, Z. *J. Chem. Soc., Chem. Commun.* **1988**, 610. (c) For other methods used for activation of organozinc reagents, see: Erdik, E. *Tetrahedron* **1987**, *43*, 2203.

Scheme III[a]



[a] Reagents and conditions: i, Zn, $ClSiMe_3$, **31**, benzene; ii, LDA, −78 °C, THF, then CH_3CHO; iii, $ClCOCH_3$, pyridine, CH_2Cl_2; iv, O_3, −78 °C, CH_2Cl_2, then Me_2S; v, MCPBA, benzene, reflux; vi, CAN, CH_3CN–H_2O; vii, LDA, −78 °C, THF, then CH_3CO_2Me; viii, K-Selectride, THF, KI, 4 h. Room temperature. Ar: 4-$MeOC_6H_4$.

Table III. Hydride Reduction of Ketone 50[a]

reagent	additive or catalyst	solvt	time, h	ratio[b] 1*R*/1*S*	yield, %
K-Selectride[b]	KI	Et_2O	29	3:1	60[i]
K-Selectride[b]	$MgCl_2$	Et_2O	18	3:1	56[i]
(^{t}BuO)$_3$LiAlH[c]		THF	2[d]	1:1	97
(2-^{t}Bu-6-$MeC_6H_3O)_3$LiAlH[e]		Et_2O/THF	21	1:1	60[i]
Me_2PhSiH[f]	TASF	THF	70	1:4	50[i]
Me_2PhSiH[f]	TASF	HMPA	23	1:8	90
Me_2PhSiH[g]		F_3CCO_2H	22[d]	1:1	90

[a] Reactions carried out at room temperature unless noted otherwise. [b] See ref 37. [c] Brown, H. C.; McFarlin, R. F. *J. Am. Chem. Soc.* **1956**, *78*, 252; **1958**, *80*, 5372. See also: *Org. Synth.* **1973**, *5*, 692. [d] Reaction carried out at 0 °C. [e] See: Haubenstock, H. *J. Org. Chem.* **1975**, *40*, 926. [f] See ref 38a. [g] See ref 38b. [h] Determined by 300-MHz ^{1}H NMR (H_3) of the product mixture before chromatography. [i] *A* ≈ 30% yield of the starting product was recovered by column chromatography.

trans-4-acetyl β-lactam **47** in 54% overall yield from **45**. Treatment of **47** with *m*-CPBA (molar ratio 1:3) under refluxing benzene afforded a mixture of *trans*-**48** together with the starting product **47**. Further oxidation as above provided the β-lactam **48** as sole isolated product in 57% yield, which upon N-dearylation furnished the expected *trans*-4-acetoxyazetidin-2-one **49** in 68% yield as an oil.

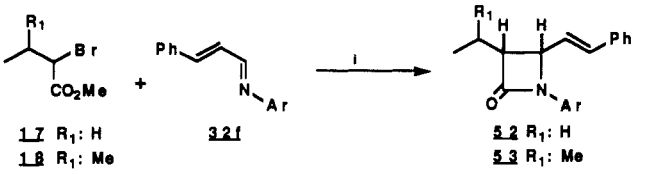
To obtain the desired stereochemistry in the β-lactam side chain, we then examined the reduction of the ketone **50** by means of potassium tri-*sec*-butylborohydride (K-Selectride) according to Bouffard's procedure.[37] Thus, the ketone **50** obtained from the lithium enolate of **45** and quenching the resulting solution with 4-fold excess of methyl acetate was subjected to treatment with K-Selectride (1:2.4 molar ratio) in the presence of KI for 4 h. After this time, TLC analysis indicated partial transformation, and further equivalents of K-Selectride were added. After the reaction mixture stirred overnight, the expected carbinol **51** was obtained together with its epimer in a ratio 3:1, respectively. Although we have not been able to improve this stereochemical ratio, other hindered hydrides such as lithium tris-(*tert*-butoxy)aluminum hydride and lithium tris(2-*tert*-butyl-6-methylphenoxy)aluminum hydride were found to be less efficient than K-Selectride for carrying out the best stereoselective reduction (Table III). We also have examined the recently described hydrosilane–fluoride method for the direct reduction of α-keto amides reported by Hiyama and Fujita[38a] and have found that reduction of ketone **50** by dimethylphenylsilane under tris(diethylamino)sulfonium difluorotrimethylsiliconate (TASF) catalysis afforded the *S* epimer of **51** as the main product, as was expected by the observations of those authors. However, when the reaction was examined under acid catalysis,[38b] no stereoselection was produced and an equimolar mixture of both epimers was obtained in 90% yield.

Similarly to the above approach, the trans β-lactams **21** and **22** were obtained in good yields after quenching the lithium enolate of the β-lactam **45** with the corresponding alkyl iodide. Particularly in the case of isopropyl iodide, a better yield was obtained when the reaction was performed in the presence of hexamethylphosphoric triamide. These trans β-lactam compounds can be further elaborated according to the above described methodology to give the corresponding *trans*-PS-5 **28** and *trans*-PS-6 **29** precursors. It is interesting to note that this procedure only leads to trans isomers. Therefore, it appears to be superior to the earlier route in terms of overall yield and stereocontrol.

Next, to determine the scope of the Reformatsky type reaction of Schiff bases derived from cinnamaldehyde, we concentrated our study (Scheme IV) on the reaction between the Schiff base **32f** and α-substituted esters **17** and **18** (Table IV). Gaudemar and Moreau[17g] found that condensation of ethyl α-bromoisobutyrate with cinnamylideneamines gives the corresponding β-amino esters, β-lactams, and dihydropyridones or mixtures of these products. We have found, however, that reaction between the Schiff base **32f** and **17** in the presence of zinc dust and iodine or TMCS as catalysts afforded the desired β-lactam **52** in excellent yield as sole reaction product. Similarly, **32f** upon treatment with **18** gave a high yield of the corresponding β-lactam **53**. In both cases, the stereoisomer ratio was determined by integration of the corresponding signals due to the C_4–H protons for the cis and the trans isomers, respectively. As expected, when the reaction was carried out in toluene as solvent, the trans isomer was the major product, and in a more polar solvent, such as dioxane, the trans/cis ratio decreased. From a synthetic point of view, these compounds can be appropriately elaborated by known methods,[20,21] providing an easy access to the carbapenems (±)-PS-5 and (±)-PS-6, respectively.

Finally, we examined the Reformatsky type reaction of Gilman and Speeter between α-bromo esters and the Schiff

Scheme IV[a]



[a] Reagents and conditions: i, Zn, reflux, catalyst, solvent (see Table IV).

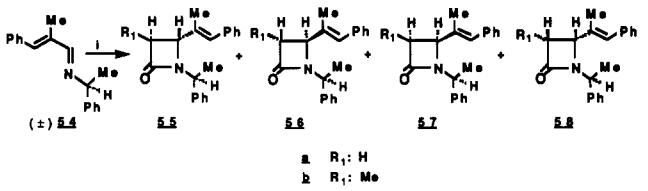
Table IV. Preparation of β-Lactams 52 and 53 under Different Conditions[a]

product	solvt	time, h	yield,[b] %
52	toluene	13	85 (37/63)
	toluene	13	82 (45/55)[c]
	toluene	2.5	80 (35/60)
	dioxane	2.5	80 (52/48)
53	toluene	24	92 (28/72)
	toluene	2.5	90 (25/75)
	dioxane	2.5	85 (38/62)

[a] Reactions conducted on 10 mmol scale, 1.2:1:0.12 bromo ester **17** and **18**, imine **32f**, I_2, respectively. [b] Yields based on weight of isolated product by column chromatography; the number in parentheses indicates the cis/trans ratio determined by NMR spectroscopy. [c] Trimethylchlorosilane as catalyst.

(37) Bouffard, F. A.; Christensen, B. G. *J. Org. Chem.* **1981**, *46*, 2208.
(38) (a) Fujita, M.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 5405. (b) Fujita, M.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 5415.

Scheme V[a,b]



[a] All β-lactams prepared are racemic mixtures. Only one enantiomer of each compound is drawn. [b] Reagents and conditions: i, 17 or 18, Zn, I_2, reflux, solvent, 2.5 h (see Table V).

Table V. Diastereoisomeric Racemic 2-Azetidinones from α-Bromo Esters and the Imine (±)-54[a]

product	R_1	solvt[b]	yield,[c] %	ratio of diastereoisomers,[d] % 55	56	57	58	trans/cis ratio, %
a	Et	benzene	35	49	17	27	7	66/34
		toluene	42	46	17	29	8	63/37
b	*i*-Pr	benzene	65	69	6	25		75/25
		toluene	50	55	12	33		67/33

[a] All β-lactams prepared are racemic mixtures. Only one enantiomer is drawn in the figure. [b] Reactions conducted on 10 mmol scale. The ratio 17 or 18:54 and I_2 was 1.2:1:0.12, respectively. [c] Total yield of 2-azetidinone material isolated by column chromatography. [d] Determined by 300-MHz ^1H NMR spectroscopy.

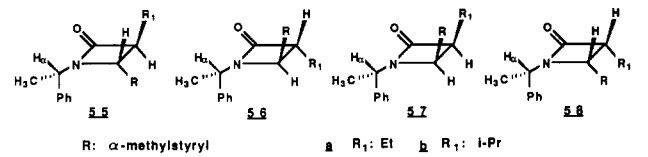


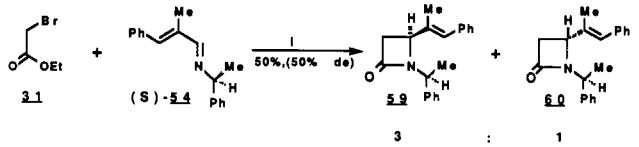
Figure 1. Preferred conformations for the β-lactams **55–58**. Only one enantiomer of each compound is drawn.

base **54** derived from α-methylcinnamaldehyde and racemic α-phenylethylamine to determine the diastereoselectivity of the reaction (Scheme V). Our results are reported in Table V. We have found that when the imine **54** was allowed to react with bromo esters **17** and **18** under usual Gilman and Speeter conditions, a diastereoisomeric mixture of the corresponding racemic cis and trans β-lactams **55–58** was obtained in yields in the range 35–65%. As shown in Table V, increasing the size of the R_1 substituent from Et to *iPr* improves the chemical yield and increases the ratio between **55/56** (trans) and **57/58** (cis) isomers, while the total trans/cis ratio remains practically unaffected. No great changes were observed when the reaction was carried out in either benzene or toluene as solvents.

Although these isomers were not separated, the determination of their relative configuration of diastereoisomers **55–58** was based on the data reported on related molecules by Belzecki and Rogalska[39] concerning the ^1H NMR chemical shift of the quadruplet corresponding to the exocyclic methine proton H_α attached to the nitrogen N-1. Figure 1 shows the preferred conformations according to these authors, and Table VI shows the chemical shifts of H_α observed by us in these isomers. As can be seen in the data listed in Table VI, the H_α proton cis to the α-methylstyryl substituent (compounds **56** and **57**) are shifted to higher field, and the H_α proton trans to the C-4 substituent (compounds **55** and **58**) to the lower field. It is interesting to note that this result together with our previous ones on related structures[13b] constitutes an extension

(39) Rogalska, E.; Belzecki, C. *J. Org. Chem.* **1984**, *49*, 1397.

Scheme VI[a]



[a] Reagents and conditions: i, Zn, TMCS (cat.), benzene, reflux, 2 h.

of the Barrow and Spotwood's observations on *N*-benzyl β-lactams.[40]

The results obtained encouraged us to perform the reaction between the chiral imine **54**, prepared from α-methylcinnamaldehyde and (*S*)-(−)-α-methylbenzylamine, and ethyl bromoacetate (Scheme VI) under the optimized conditions found by us for achiral 3-unsubstituted β-lactams. In this way we have obtained the epimeric 2-azetidinones **59** and **60** in 50% yield and in a 3:1 ratio after purification by column chromatography. The stereochemical assignement of both epimers was determined following the aforementioned observations. Since these compounds can be separated[39] and further elaborated,[24,41] this procedure constitutes a new diastereoselective entry for the preparation of optically active carbapenem compounds.

Conclusion

From the results reported here the Reformatsky type reaction of Gilman and Speeter has been found to be an efficient method for the preparation of appropriately substituted 3-alkyl β-lactams as well as the corresponding 3-unsubstituted ones. These compounds upon further chemical elaborations have provided entries to various carbapenem precursors in good yields. The methodology is experimentally simple and allows a highly stereoselective synthesis of valuable β-lactams for carbapenem synthesis, which may be readily extended to further applications.

Experimental Section

Melting points were determined on either Büchi SMP-20 or Mettler FP61 instruments and are uncorrected. Proton nuclear magnetic resonance spectra were recorded on a Varian VXR 300 spectrometer. All chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane. Significant ^1H NMR data are tabulated in order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons, coupling constant(s) in hertz. Infrared (IR) spectra were recorded on a Shimadzu IR-435 spectrophotometer, calibrated with the 1602-cm^{-1} band of a polystyrene film. Ozonization reactions were carried out by using a Fisher 502 ozone generator. Microanalytical data were obtained in these laboratories. Analytical thin-layer chromatography (TLC) analyses were carried out with Merck F-254 silica gel plates. The Schiff bases were prepared by literature methods.[42] All β-lactams prepared are racemic mixtures except those derived from (*S*)-(−)-1-phenylethylamine. All the other starting materials used in this work were comercially available in 98% or higher purity and were used without further purification. Hexane and EtOAc were purified by distillation. CH_2Cl_2, benzene, and THF were respectively distilled over P_4O_{10} and Na/benzophenone.

3-Ethyl-4-(α-methylstyryl)-1-(4-methoxyphenyl)azetidin-2-one (21). A mixture of *N*-(α-methylcinnamylidene)-*p*-anisidine (**20**,[14b] 2.51 g, 10 mmol), zinc dust (0.78 g, 12 mmol), *dl*-methyl

(40) Barrow, K. D.; Spotswood, T. M. *Tetrahedron Lett.* **1965**, 3325.
(41) (a) Teutsch, G.; Bonnet, A. *Tetrahedron Lett.* **1984**, *25*, 1561. (b) Shibasaki, M.; Ishida, Y.; Iwasaki, G.; Limori, T. *J. Org. Chem.* **1987**, *52*, 3489.
(42) Sandler, R. S.; Karo, W. In *Organic Functional Group Preparations*; Academic Press: New York, 1986; Vol. 2, p 291.

Table VI. ^{1}H NMR Data of Exocyclic Methine of Compounds 55–58[a]

	$\delta(H_\alpha)$, ppm				$J(H_\alpha$–$CH_3)$, Hz			
compd	55	56	57	58	55	56	57	58
a	4.91	4.29	4.46	4.79	7.2	6.9	6.9	7.2
b	4.91	4.30	4.46		7.2	6.3	7.2	

[a] Measured on a 300-MHz spectrometer in $CDCl_3$/TMS.

2-bromobutyrate (17, 1.38 mL, 12 mmol), and a catalytic amount of $HgCl_2$ in toluene (20 mL) was refluxed under nitrogen for 8 h. The resulting mixture was cooled at room temperature and poured into an aqueous solution of NH_4Cl (20 mL, saturated solution) and 25% NH_4OH (20 mL). Then methylene chloride (20 mL) was added, and the organic layer was separated, washed with 0.1 N HCl (20 mL) and water (20 mL), and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave a residue which was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane 1:2 as eluant) to give 2.57 g (80%) of a 1:4 mixture of cis and trans isomers of **21**. The cis isomer was separated by trituration in hexane and further crystallization from ethanol: mp 99–100 °C (EtOH); IR (KBr) ν 1730 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.39–7.22 (m, 7 H, Ar), 6.84 (d, 2 H, J = 9 Hz, Ar), 6.49 (s_{br}, 1 H, CH), 4.59 (d, 1 H, J = 6 Hz, CH), 3.76 (s, 3 H, OCH_3), 3.39 (ddd, 1 H, J = 8.7 Hz, J' = 7.2 Hz, J'' = 6 Hz, CH), 1.92 (d, 3 H, J = 1.2 Hz, CH_3), 1.87–1.74 (m, 1 H, CH_2), 1.67–1.53 (m, 1 H, CH_2), 1.10 (t, 3 H, J = 7.2 Hz, CH_3). Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.46; H, 7.08; N, 4.23. The trans isomer was isolated as an oil: IR (KBr) ν 1739 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.45–7.23 (m, 7 H, Ar), 6.85 (d, 2 H, J = 9 Hz, Ar), 6.69 (s_{br}, 1 H, CH), 4.24 (d, 1 H, J = 2.1 Hz, CH), 3.73 (s, 3 H, OCH_3), 3.06 (td, 1 H, J = 7.2 Hz, J' = 2.1 Hz, CH), 2.00–1.78 (m, 5 H, CH_3, CH_2), 1.12 (t, 3 H, J = 7.5 Hz, CH_3).

3-Isopropyl-4-(α-methylstyryl)-1-(4-methoxyphenyl)azetidin-2-one (22). A mixture of imine **20** (2.51 g, 10 mmol), zinc dust (0.78 g, 12 mmol), *dl*-methyl 2-bromoisovalerate (**18**, 1.73 mL, 12 mmol), and I_2 (0.3 g, 1.2 mmol) in toluene (20 mL) was refluxed under nitrogen for 2.5 h. Following the above workup, a 1:5.5 mixture of cis and trans isomers of **22** was obtained which was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane 1:4 as eluant) to give the cis/trans isomers of **22**, yield 3 g, (89%). Crystallization from ethanol gave the cis isomer of **22**: mp 124–127 °C (EtOH); IR (KBr) ν 1728 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.42–7.24 (m, 7 H, Ar), 6.84 (d, 2 H, J = 9 Hz, Ar), 6.65 (s_{br}, 1 H, Ar), 4.63 (d, 1 H, J = 5.7 Hz, CH), 3.75 (s, 3 H, OCH_3), 3.17 (dd, 1 H, J = 11.1 Hz, J' = 5.7 Hz, CH), 2.19–2.07 (m, 1 H, CH), 1.94 (d, 3 H, J = 1.2 Hz, CH_3), 1.23 (d, 3 H, J = 6.6 Hz, CH_3), 0.94 (d, 3 H, J = 6.6 Hz, CH_3). Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.17. Found: C, 78.78; H, 7.51; N, 4.31. The trans isomer was crystallized in hexane: mp 76–78 °C (hexane); IR (KBr) ν 1736 cm^{-1} (C=O), ^{1}H NMR ($CDCl_3$) δ 7.43–7.23 (m, 7 H, Ar), 6.84 (d, 2 H, J = 9 Hz, Ar), 6.70 (s_{br}, 1 H, Ar), 4.30 (d, 1 H, J = 2.4 Hz, CH), 3.75 (s, 3 H, OCH_3), 2.91 (dd, 1 H, J = 8.1 Hz, J' = 2.4 Hz, CH), 2.21–2.10 (m, 1 H, CH), 1.86 (d, 3 H, J = 1.2 Hz, CH_3), 1.17 (d, 3 H, J = 6.6 Hz, CH_3), 1.08 (d, 3 H, J = 6.6 Hz, CH_3). Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.17. Found: C, 79.02; H, 7.63; N, 4.32.

3-Ethyl-1-(4-methoxyphenyl)-4-styrylazetidin-2-one (52). A mixture of cinnamylidene-*p*-anisidine (**32f**, 2.37 g, 10 mmol), zinc dust (0.78 g, 12 mmol), *dl*-methyl 2-bromobutyrate (**17**, 1.38 mL, 12 mmol), and I_2 (0.3 g, 1.2 mmol) in toluene (20 mL) was refluxed under nitrogen for 2.5 h. Following the above workup a 1:2 mixture of cis and trans isomers of **52** was obtained which was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane 1:5 as eluant): yield 2.46 g (80%); IR (KBr) ν 1729 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.41–7.22 (m, 21 H, Ar), 6.83–6.71 (m, 9 H, Ar), 6.31–6.20 (m, 3 H, Ar), 4.67 (dd, 1 H, J = 7.9 Hz, J' = 6 Hz, CH), 4.27 (dd, 2 H, J = 8.4 Hz, J' = 1.8 Hz, CH), 3.71 (s, 9 H, OCH_3), 3.34 (td, 1 H, J = 7.8 Hz, J' = 6 Hz, CH), 3.02 (td, 2 H, J = 7.3 Hz, J' = 1.8 Hz, CH), 1.97–1.59 (m, 6 H, CH_2), 1.11–1.01 (m, 9 H, CH_3). Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.24; H, 6.80; N, 4.56.

3-Isopropyl-1-(4-methoxyphenyl)-4-styrylazetidin-2-one (53). A mixture of imine **32f** (2.37 g, 10 mmol), zinc dust (0.78 g, 12 mmol), *dl*-methyl 2-bromoisovalerate (**18**, 1.73 mL, 10 mmol), and I_2 (0.3 g, 1.2 mmol) in toluene (20 mL) was refluxed under nitrogen for 2.5 h. Following the above workup a 1:3 mixture of cis and trans isomers of **53** was obtained which was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane 1:4 as eluant) to give the pure β-lactam **53**, yield 2.89 g (90%). The trans isomer was separated by crystallization from CH_2Cl_2/hexane: mp 95–97 °C (CH_2Cl_2/hexane); IR (KBr) ν 1730 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.40–7.25 (m, 7 H, Ar), 6.83 (d, 2 H, J = 9.3 Hz, Ar), 6.77 (d, 1 H, J = 15.9 Hz, Ar), 6.28 (dd, 1 H, J = 15.9 Hz, J' = 8.4 Hz, Ar), 4.34 (dd, 1 H, J = 8.4 Hz, J' = 2.4 Hz, CH), 3.75 (s, 3 H, OCH_3), 2.89 (dd, 1 H, J = 8.4 Hz, J' = 2.4 Hz, CH), 2.21–2.09 (m, 1 H, CH), 1.14 (d, 3 H, J = 6.6 Hz, CH_3), 1.06 (d, 3 H, J = 6.6 Hz, CH_3). Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.31; H, 7.27; N, 4.35. The cis isomer was separated by crystallization from ethanol: mp 139–142 °C (EtOH); IR (KBr) ν 1730 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.40–6.75 (m, 10 H, Ar), 6.30 (dd, 1 H, J = 15.9 Hz, J' = 8.4 Hz, Ar), 4.69 (dd, 1 H, J = 8.4 Hz, J' = 5.7 Hz, CH), 3.74 (s, 3 H, OCH_3), 3.13 (dd, 1 H, J = 11.1 Hz, J' = 5.7 Hz, CH), 2.18–2.06 (m, 1 H, CH), 1.23 (d, 3 H, J = 6.6 Hz, CH_3), 0.92 (d, 3 H, J = 6.6 Hz, CH_3). Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.37; H, 7.27; N, 4.32.

4-Acetyl-3-ethyl-1-(4-methoxyphenyl)azetidin-2-one (24). The β-lactam **21** (3.21 g, 10 mmol, cis/trans 1:4) was dissolved in dry CH_2Cl_2 (30 mL), and the solution was cooled to −70 °C. A stream of ozone was passed through the reaction mixture until a pale blue coloration was observed, and then the mixture was purged with nitrogen. A solution of Me_2S (4 mL) in CH_2Cl_2 (8 mL) was added dropwise at −70 °C. When the addition was completed, the bath was removed and the solution was stirred to room temperature. The reaction mixture was washed with H_2O (2 × 200 mL) and with saturated brine (2 × 200 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent gave an oil which was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane 1:2 as eluant) giving the β-lactam **24**, yield 1.48 g (60%) as a 1:4 mixture of cis and trans isomers, respectively. Crystallization from $CHCl_3$/hexane gave pure *cis*-**24**: mp 119–120 °C; IR ($CHCl_3$) ν 1745 (C=O), 1709 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.20 (d, 2 H, J = 9 Hz, Ar), 6.86 (d, 2 H, J = 9 Hz, Ar), 4.58 (d, 1 H, J = 6.3 Hz, CH), 3.78 (s, 3 H, OCH_3), 3.52 (ddd, 1 H, J = 9.15 Hz, J' = 6.6 Hz, J'' = 6.3 Hz, CH), 1.79–1.67 (m, 1 H, *H*CH), 1.65–1.54 (m, 1 H, HC*H*), 1.11 (t, 3 H, J = 7.2 Hz, CH_3). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.45; H, 6.82; N, 5.58. The trans isomer was isolated as an oil: IR ($CHCl_3$) ν 1746 (C=O), 1714 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.22 (d, 2 H, J = 9 Hz, Ar), 6.87 (d, 2 H, J = 9 Hz, Ar), 4.15 (d, 1 H, J = 2.49 Hz, CH), 3.79 (s, 3 H, OCH_3), 3.14 (ddd, 1 H, J = 8.37 Hz, J' = 6 Hz, J'' = 2.49 Hz, CH), 2.20 (s, 3 H, CH_3), 2.03–1.81 (m, 2 H, CH_2), 1.11 (t, 3 H, J = 7.43 Hz, CH_3).

***trans*-4-Acetyl-3-isopropyl-1-(4-methoxyphenyl)azetidin-2-one (25).** Following the above procedure starting from *trans*-3-isopropyl-4-(α-methylstyryl)azetidin-2-one (**22**, 3.35 g, 10 mmol), the title compound was obtained: yield 1.52 g (58%); mp 69–71 °C (EtOH); IR (KBr) ν 1737 (C=O), 1700 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.21 (d, 2 H, J = 9 Hz, Ar), 6.86 (d, 2 H, J = 9 Hz, Ar), 4.19 (d, 1 H, J = 2.7 Hz, CH), 3.78 (s, 3 H, OCH_3), 2.98 (dd, 1 H, J = 8.1 Hz, J' = 2.7 Hz, CH), 2.18 (s, 3 H, CH_3), 2.21–2.13 (m, 1 H, CH), 1.15 (d, 3 H, J = 6.6 Hz, CH_3), 1.07 (d, 3 H, J = 6.6 Hz, CH_3). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 67.85; H, 7.27; N, 5.18.

***trans*-4-Acetoxy-2-ethyl-1-(4-methoxyphenyl)azetidin-2-one (26).** To a solution of *trans*-4-acetyl-2-ethyl-(4-methoxyphenyl)azetidin-2-one (**24**, 2.47 g, 10 mmol) in benzene (75 mL) was added *m*-chloroperbenzoic acid (5.18 g, 30 mmol), and the resulting mixture was stirred under reflux for 2.5 h. Then the mixture was cooled at room temperature, CH_2Cl_2 (100 mL) was

added, and the mixture was washed with 1 N NaOH (3 × 150 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvents under reduced pressure gave a residue which was analyzed by ^1H NMR indicating 50% conversion. The residue was dissolved in benzene (75 mL), *m*-chloroperbenzoic acid (5.18 g, 30 mmol) was added, and the mixture was stirred for an additional 2.5 h. After the same workup as above, a waxy residue was obtained, which was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane 1:1 as eluant) giving the title compound: yield 1.45 g (55%); mp 71–72 °C (EtOH); IR ($CHCl_3$) ν 1753 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.34 (d, 2 H, J = 9 Hz, Ar), 6.87 (d, 2 H, J = 9 Hz, Ar), 6.19 (d, 1 H, J = 1.2 Hz, CH), 3.78 (s, 3 H, OCH_3), 3.17 (td, 1 H, J = 7.2 Hz, J' = 1.2 Hz, CH), 2.13 (s, 3 H, CH_3), 1.93–1.82 (m, 2 H, CH_2), 1.10 (t, 3 H, J = 9 Hz, CH_3). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.34; H, 6.49; N, 5.21.

***trans*-4-Acetoxy-3-isopropyl-1-(4-methoxyphenyl)azetidin-2-one (27).** Following the above procedure starting from *trans*-4-acetyl-3-isopropyl-1-(4-methoxyphenyl)azetidin-2-one (**25**, 2.16 g, 10 mmol) the title compound was obtained: yield 1.28 g (46%); mp 71–73 °C (EtOH); IR (KBr) ν 1746 (C=O); ^1H NMR ($CDCl_3$) δ 7.33 (d, 2 H, J = 9 Hz, Ar), 6.87 (d, 2 H, J = 9 Hz, Ar), 6.36 (d, 1 H, J = 1.2 Hz, CH), 3.78 (s, 3 H, OCH_3), 3.07 (dd, 1 H, J = 7.5 Hz, J' = 1.2 Hz, CH), 2.13 (s, 3 H, CH_3), 2.18–2.09 (m, 1 H, CH), 1.11 (d, 3 H, J = 9 Hz, CH_3), 1.08 (d, 3 H, J = 6.9 Hz, CH_3). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.31; H, 6.91; N, 5.05.

***trans*-4-Acetoxy-3-ethylazetidin-2-one (28).** Ammonium cerium(IV) nitrate (16.4 g, 30 mmol) dissolved in water (50 mL) was added to a cooled (0–5 °C) solution of β-lactam **26** (2.63 g, 10 mmol) in acetonitrile (200 mL). The reaction mixture was stirred at 0–5 °C for 30 min and then poured into water (300 mL). The resulting solution was extracted with AcOEt (4 × 150 mL), and the organic layer washed with aqueous $NaHCO_3$ (120 mL, saturated solution). The aqueous layer was again extracted with AcOEt (60 mL). The combined extracts were washed with 40% $NaHSO_3$ (4 × 200 mL), aqueous $NaHCO_3$ (120 L, saturated solution), and brine (120 mL) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave a residue which was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2 as eluant) to afford the title compound as an oil: yield 1.41 g, (90%); ^1H NMR ($CDCl_3$) δ 6.53 (s_{br}, 1 H, NH), 5.54 (d, 1 H, J = 1.2 Hz, CH), 3.17 (td, 1 H, J = 7.3 Hz, J' = 1.2 Hz, CH), 2.13 (s, 3 H, $OCOCH_3$), 1.88–1.72 (m, 2 H, CH_2), 1.06 (t, 3 H, J = 7.5 Hz, CH_3).

***trans*-4-Acetoxy-3-isopropylazetidin-2-one (29).** Following the above procedure starting from *trans*-4-acetoxy-3-isopropyl-1-(4-methoxyphenyl)azetidin-2-one (**27**, 2.77 g, 10 mmol) the title compound was obtained as an oil: yield 1.47 g (86%); ^1H NMR ($CDCl_3$) δ 7.36 (1 H, s_{br}, NH), 5.61 (d, 1 H, J = 1.2 Hz, CH), 3.00 (dd, 1 H, J = 7.5 Hz, J' = 1.2 Hz, CH), 2.09 (s, 3 H, $OCOCH_3$), 2.08–1.92 (m, 1 H, CH), 1.06 (d, 3 H, J = 6.9 Hz, CH_3), 1.01 (d, 3 H, J = 6.9 Hz, CH_3).

Preparation of 3-Unsubstituted 2-Azetidinones 33–45. General Procedure.[43] To a suspension of zinc dust (0.9 g, 13.8 mmol) in benzene (20 mL) under nitrogen, trimethylchlorosilane (0.65 mL, 5 mmol) was added, and the resulting mixture was stirred at room temperature for 15 min and then under reflux for 2 min. The suspension was cooled, and the corresponding imine **32** (10 mmol) and ethyl bromoacetate (1.33 mL, 12 mmol) were successively added. The reaction mixture was refluxed under nitrogen for 2.5 h and then was cooled in a ice-water bath and poured over a solution of NH_4Cl (20 mL, saturated solution) and 25% NH_4OH (20 mL). Then, CH_2Cl_2 (20 mL) was added, and the organic layer was separated and washed with 0.1 N HCl (20 mL) and water (20 mL). The organic solution was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give the crude β-lactam, which was purified and characterized.

1,4-Diphenylazetidin-2-one (33) was prepared from *N*-benzylideneaniline (1.81 g, 10 mmol). The crude title product was crystallized from ethanol: yield 1.82 g (82%); mp 154–155 °C (EtOH); IR (KBr) ν 1734 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.50–6.86 (m, 10 H, Ar), 4.93 (dd, 1 H, J = 5.7 Hz, J' = 2.7 Hz, CH), 3.16 (dd, 1 H, J = −15 Hz, J' = 5.7 Hz, HC*H*), 2.90 (dd, J = −15 Hz, J' = 2.7 Hz, *H*CH). Anal. Calcd for $C_{15}H_{13}NO$: C, 80.67; H, 5.88; N, 6.27. Found: C, 80.38; H, 5.88; N, 6.07.

1-(4-Methoxyphenyl)-4-phenylazetidin-2-one (34) was prepared from *N*-benzylidene-*p*-anisidine (2.11 g, 10 mmol). The crude title product was crystallized from ethanol: yield 2.0 g (80%); mp 83–84 °C (EtOH); IR (KBr) ν 1738 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.35–7.20 (m, 7 H, Ar), 6.75 (d, 2 H, J = 9 Hz, Ar), 4.93 (dd, 1 H, J = 5.7 Hz, J' = 2.4 Hz, CH), 3.69 (s, 3 H, OCH_3), 3.50 (dd, 1 H, J = −15 Hz, J' = 5.7 Hz, HC*H*), 2.89 (dd, 1 H, J = −15 Hz, J' = 2.4 Hz, *H*CH). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 79.63; H, 6.28; N, 5.80. Found: C, 79.89; H, 6.20; N, 5.65.

1-(4-Methoxyphenyl)-4-(4-methylphenyl)azetidin-2-one (35) was prepared from *N*-(4-methylbenzylidene)-*p*-anisidine (2.25 g, 10 mmol). The crude title product was crystallized from ethanol: yield 2.13 g (80%); mp 97–99 °C (EtOH); IR (KBr) ν 1729 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.25–7.14 (m, 6 H, Ar), 6.75 (d, 2 H, J = 9 Hz, Ar), 4.90 (dd, 1 H, J = 5.5 Hz, J' = 2.4 Hz, CH), 3.70 (s, 3 H, OCH_3), 3.48 (dd, 1 H, J = −15 Hz, J' = 5.5 Hz, HC*H*), 2.87 (dd, 1 H, J = −15 Hz, J' = 2.4 Hz, *H*CH), 2.32 (s, 3 H, CH_3). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 79.96; H, 6.72; N, 5.48. Found: C, 79.84; H, 6.46; N, 5.17.

1,4-Bis(4-methoxyphenyl)azetidin-2-one (36) was prepared from *N*-(*p*-methoxybenzylidene)-*p*-anisidine (2.41 g, 10 mmol). The crude title product was crystallized from ethanol: yield 2.21 g (78%); mp 157–159 °C (EtOH); IR (KBr) ν 1750 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.46–6.66 (m, 8 H, Ar), 4.86 (dd, 1 H, J = 2.7 Hz, J' = 5.7 Hz, CH), 3.72 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3), 3.47 (dd, 1 H, J = 5.7 Hz, J' = −15 Hz, HC*H*), 2.82 (dd, 1 H, J = 2.7 Hz, J' = −15 Hz, *H*CH). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.06; N, 4.94. Found: C, 72.12; H, 6.09; N, 4.98.

4-(4-Chlorophenyl)-1-(4-methoxyphenyl)azetidin-2-one (37) was prepared from *N*-(4-chlorobenzylidene)-*p*-anisidine (2.46 g, 10 mmol). The crude title product was crystallized from ethanol: yield 2.30 g (80%); mp 132–133 °C (EtOH); IR (KBr) ν 1752 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.46–6.63 (m, 8 H, Ar), 4.91 (dd, 1 H, J = 2.5 Hz, J' = 5.7 Hz, CH), 3.69 (s, 3 H, OCH_3), 3.51 (dd, 1 H, J = 5.7 Hz, J' = −15 Hz, HC*H*), 2.83 (dd, 1 H, J = 2.5 Hz, J' = −15 Hz, *H*CH). Anal. Calcd for $C_{16}H_{14}ClNO_2$: C, 66.78; H, 4.91; N, 4.87. Found: C, 66.81; H, 4.97; N, 4.90.

1-(4-Methoxyphenyl)-4-styrylazetidin-2-one (38) was prepared from *N*-cinnamylidene-*p*-anisidine (2.37 g, 10 mmol). The crude title product was purified by column chromatography (silica gel 70–230 mesh, CH_2Cl_2/hexane 1:6 as eluant) and crystallized from ethanol: yield 1.62 g (58%); mp 139–142 °C (EtOH); IR (KBr) ν 1736 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.39–7.25 (m, 7 H, Ar), 6.81 (d, 2 H, J = 9.3 Hz, Ar), 6.77 (d, 1 H, J = 15.9 Hz, =CH), 6.24 (dd, 1 H, J = 15.9 Hz, J' = 8.4 Hz, =CH), 4.50 (m, 1 H, CH), 3.73 (s, 3 H, OCH_3), 3.36 (dd, J = −15 Hz, J' = 5.4 Hz, HC*H*), 2.89 (dd, 1 H, J = −15 Hz, J' = 2.4 Hz, *H*CH). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.28; H, 5.93; N, 5.01.

1-Phenyl-4-styrylazetidin-2-one (39) was prepared from *N*-cinnamylideneaniline. The crude title product was purified by column chromatography (silica gel 70–230 mesh, CH_2Cl_2/hexane 1:6 as eluant) to give the pure β-lactam **39** as an oil: yield 1.17 g (47%); IR (KBr) ν 1750 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.54–7.10 (m, 10 H, Ar), 6.87 (d, 1 H, J = 15.9 Hz, =CH), 6.33 (dd, 1 H, J = 15.9 Hz, J' = 8.1 Hz, =CH), 4.70 (ddd, 1 H, J = 8.1 Hz, J' = 5.7 Hz, J'' = 2.4 Hz, CH), 3.45 (dd, 1 H, J = −15 Hz, J' = 5.7 Hz, HC*H*), 2.98 (dd, 1 H, J = −15 Hz, J' = 2.4 Hz, *H*CH).

1-(4-Methoxybenzyl)-4-styrylazetidin-2-one (40) was prepared from *N*-cinnamylidene-*p*-methoxybenzylamine (2.51 g, 10 mmol). The crude title product was purified by column chromatography (silica gel 70–230 mesh, CH_2Cl_2/hexane 1:6 as eluant) to give the pure β-lactam **40** as an oil: yield 1.44 g (49%); IR (KBr) ν 1743 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.34–7.29 (m, 5 H, Ar), 7.21 (d, 2 H, J = 8.3 Hz, Ar), 6.88 (d, 2 H, J = 8.3 Hz, Ar), 6.56 (d, 1 H, J = 15.9 Hz, =CH), 6.06 (dd, J = 15.9 Hz, J' = 8.9 Hz, =CH), 4.60 (d, 1 H, J = −14.7 Hz, HC*H*), 4.09 (ddd, 1 H, J = 8.0 Hz, J' = 5.1 Hz, J'' = 2.4 Hz, CH), 4.05 (d, 1 H, J = 14.7 Hz, HC*H*), 3.81 (s, 3 H, OCH_3), 3.23 (dd, 1 H, J = −14.7 Hz, J' = 5.1 Hz, HC*H*), 2.81 (dd, 1 H, J = −14.7 Hz, J' = 2.4 Hz, *H*CH).

1-(4-Methylphenyl)-4-(α-methylstyryl)azetidin-2-one (41) was prepared from *N*-α-methylcinnamylidene-*p*-toluidine (2.35

(43) **Caution**: When this procedure is performed in a preparative scale (≥50 mmol), special care must be taken because of the strong exothermic nature of the reaction in the initial stages.

g, 10 mmol). The crude title product was crystallized from ethanol: yield 2.63 g (95%); mp 81–83 °C (EtOH); IR (KBr) ν 1743 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.37–7.25 (m, 7 H, Ar), 7.10 (d, 2 H, J = 8.4 Hz, Ar), 6.70 (s_{br}, 1 H, CH), 4.60 (dd, 1 H, J = 5.7 Hz, J' = 2.7 Hz, CH), 3.33 (dd, 1 H, J = –15.3 Hz, J' = 5.7 Hz, HC*H*), 2.94 (dd, 1 H, J = –15.3 Hz, J' = 2.7 Hz, *H*CH), 2.29 (s, 3 H, CH_3), 1.85 (d, 3 H, J = 1.2 Hz, CH_3). Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 81.95; H, 6.75; N, 5.37.

4-(α-Methylstyryl)-1-phenylazetidin-2-one (42) was prepared from *N*-α-methylcinnamylideneaniline (2.21 g, 10 mmol). The crude title product was crystallized from ethanol: yield 1.97 g (75%); mp 113–116 °C (EtOH); IR (KBr) ν 1733 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.54–7.11 (m, 10 H, Ar), 6.77 (br s, 1 H, CH), 4.67 (dd, 1 H, J = 5.7 Hz, J' = 2.7 Hz, CH), 3.40 (dd, 1 H, J = –15.3 Hz, J' = 5.7 Hz, HC*H*), 3.02 (dd, 1 H, J = –15.3 Hz, J' = 2.7 Hz, *H*CH), 1.92 (d, 3 H, J = 1.5 Hz, CH_3). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.91; H, 6.57; N, 5.72.

1-(4-Methoxybenzyl)-4-(α-methylstyryl)-2-azetidinone (43) was prepared from *N*-α-methylcinnamylidene-*p*-methoxybenzylamine (2.65 g, 10 mmol). The crude title product was purified by column chromatography (silica gel 70–230 mesh, CH_2Cl_2/hexane 1:3 as eluant) to give the pure β-lactam **43** as an oil: yield 2.18 g (71%); IR (KBr) ν 1746 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.33–7.15 (m, 7 H, Ar), 6.82 (d, 2 H, J = 7.5 Hz, Ar), 6.41 (br s, 1 H, CH), 4.53 (d, 1 H, J = –14.7 Hz, NHC*H*Ph), 3.98 (br d, 1 H, J = 4.5 Hz, CH), 3.94 (d, 1 H, J = –14.7 Hz, N*H*CHPh), 3.71 (s, 3 H, OCH_3), 3.02 (dd, 1 H, J = –14.7 Hz, J' = 4.5 Hz, HC*H*), 2.76 (br d, 1 H, J = –14.7 Hz, *H*CH), 1.67 (s, 3 H, CH_3).

1-(4-Methoxyphenyl)-4-(1-methyl-1-butenyl)azetidin-2-one (44) was prepared from *N*-α-methyl-α-pentenylidene-*p*-anisidine (2.03 g, 10 mmol). The crude title product was purified by column chromatography (silica gel 70–230 mesh, CH_2Cl_2/hexane 1:2 as eluant) and crystallized from ethanol: yield 1.49 g (61%); mp 85–87 °C (EtOH); IR (BrK) ν 1735 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.34 (d, 2 H, J = 9 Hz, Ar), 6.83 (d, 2 H, J = 9 Hz, Ar), 5.64 (t, 1 H, J = 6.9 Hz, C=CH), 4.40 (dd, 1 H, J = 5.4 Hz, J' = 2.4 Hz, CH), 3.77 (s, 3 H, OCH_3), 3.20 (dd, 1 H, J = –15 Hz, J' = 5.4 Hz, *H*CH), 2.83 (dd, 1 H, J = –15 Hz, J' = 2.4 Hz, HC*H*), 2.14–2.04 (m, 2 H, CH_2), 1.57 (s, 3 H, CH_3), 0.99 (t, 3 H, J = 7.6 Hz, CH_3). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.13; H, 7.68; N, 5.69.

1-(4-Methoxyphenyl)-4-(α-methylstyryl)azetidin-2-one (45) was prepared from *N*-α-methylcinnamylidene-*p*-anisidine (2.51 g, 10 mmol). The crude title product was purified by column chromatography (silica gel 70–230 mesh, CH_2Cl_2/hexane 1:2 as eluant) and crystallized from ethanol: yield 2.77 g (95%); mp 138–139 °C (EtOH); IR (KBr) ν 1735 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.44 (d, 2 H, J = 9 Hz, Ar), 7.39–7.26 (m, 5 H, Ar), 6.87 (d, 2 H, J = 9 Hz, Ar), 6.71 (br s, 1 H, CH), 4.57 (dd, 1 H, J = 5.4 Hz, J' = 2.7 Hz, CH), 3.76 (s, 3 H, OCH_3), 3.31 (dd, 1 H, J = –15 Hz, J' = 5.4 Hz, HC*H*), 2.97 (dd, 1 H, J = –15 Hz, J' = 2.7 Hz, *H*CH), 1.37 (d, 3 H, J = 1.8 Hz, CH_3). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.77; H, 6.65; N, 4.68.

Formation of the Lithium Derivative of 45 and Its Reaction with Electrophiles.[35c] General Procedure. To a solution of lithium diisopropylamide (LDA), prepared from diisopropylamine (0.49 mL, 3.5 mmol) and *n*-butyllithium (2.19 mL, 3.15 mmol) in tetrahydrofuran (25 mL) under nitrogen atmosphere, was added a solution of 1-(4-methoxyphenyl)-4-(α-methylstyryl)azetidin-2-one (**45**, 0.73 g, 2.5 mmol) in tetrahydrofuran (10 mL) at –78 °C. After this stirred at the same temperature for 30 min, 4 equiv of the appropriate electrophile was added, and the solution was kept at –78 °C for 30 min. The resulting mixture was allowed to stand at room temperature for an additional 30 min. To this mixture a solution of ammonium chloride (1.5 g) in water (25 mL) was added and extracted with methylene chloride (25 mL). The extract was washed with 0.1 N HCl (25 mL), $NaHCO_3$ (25 mL, saturated solution), and then water (25 mL). The organic phase was separated and dried with Na_2SO_4. Concentration in a rotary evaporator yielded an oil which was purified by crystallization or column chromatography.

***trans*-3-Ethyl-4-(α-methylstyryl)-1-(4-methoxyphenyl)azetidin-2-one (21)** was prepared following the above procedure using ethyl iodide (0.8 mL, 10 mmol). The crude title compound was purified by column chromatography (silica gel 70–230 mesh, CH_2Cl_2 1:2 as eluant) to give the title compound, yield 2.95 g (92%).

***trans*-3-Isopropyl-4-(α-methylstyryl)-1-(4-methoxyphenyl)azetidin-2-one (22)** was prepared following the above procedure using isopropyl iodide (2.5 mL, 25 mmol) and hexametylphosphoric triamide (3.5 mL) as cosolvent. The crude product was purified by column chromatography and crystallized from hexane, yield 0.59 g (70%).

***trans*-3-(1-Hydroxyethyl)-4-(α-methylstyryl)-1-(4-methoxyphenyl)azetidin-2-one (46)** was prepared in a 20 mmol scale following the above procedure using acetaldehyde (2.54 mL, 80 mmol). The crude mixture of epimers was purified by column chromatography (silica gel 70–230 mesh, diethyl ether/methylene chloride 1:1 as eluant) to give the title compound in 98% yield as a yellow oil: IR ($CHCl_3$) ν 3400 (OH), 1733 and 1732 cm^{-1} (C=O) both diastereoisomers; ^1H NMR ($CDCl_3$) δ (1′*R*)-**46** 7.41–6.80 (m, 9 H, Ar), 6.72 (s, 1 H, CH=), 4.65 (d, 1 H, J = 2.1 Hz, CH), 4.33 (dq, 1 H, J = 6.6 Hz, J' = 5.4 Hz, HCO), 3.74 (s, 3 H, OCH_3), 3.12 (dd, 1 H, J = 5.4 Hz, J' = 2.1 Hz, CH), 3.00 (s_{br}, 1 H, OH), 1.86 (s, 3 H, CH_3), 1.35 (d, 3 H, J = 6.6 Hz, CH_3); (1′*S*)-**46** 7.41–6.80 (m, 9 H, Ar), 6.69 (s, 1 H, CH=), 4.45 (d, 1 H, J = 2.4 Hz, CH), 4.21 (dq, 1 H, J = 6.3 Hz, J' = 6.3 Hz, HCO), 3.74 (s, 3 H, OCH_3), 3.14 (dd, 1 H, J = 6.3 Hz, J' = 2.4 Hz, CH), 3.00 (s_{br}, 1 H, OH), 1.86 (s, 3 H, CH_3), 1.40 (d, 3 H, J = 6.3 Hz, CH_3).

***trans*-3-Acetyl-4-(α-methylstyryl)-1-(4-methoxyphenyl)-azetidin-2-one (50)** was prepared in a 20 mmol scale following the above procedure using methyl acetate (6.4 mL, 80 mmol). The crude product was purified by column chromatography (silica gel 70–230 mesh, CH_2Cl_2/hexane 1:2 as eluant) to give the title compound in 95% yield as a yellow oil: IR ($CHCl_3$) ν 1743 (C=O), 1714 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.40–6.78 (m, 9 H, Ar), 6.73 (s_{br}, 1 H, CH=), 5.00 (dd, 1 H, J = 2.4 Hz, J' = 0.6 Hz, CH), 4.13 (d, 1 H, J = 2.4 Hz, CH), 3.73 (s, 3 H, OCH_3), 2.38 (s, 3 H, $COCH_3$), 1.84 (d, 3 H, J = 1.5 Hz, CH_3).

K-Selectride Reduction of 50. A 1 M solution of K-Selectride (9.6 mL, 9.6 mmol) in tetrahydrofuran was added to a solution of *trans*-3-acetyl β-lactam **50** (1.34 g, 4 mmol) and KI (0.75 g, 4.5 mmol) in diethyl ether (40 mL) at room temperature under nitrogen atmosphere. The resulting solution was stirred for 4 h and further K-Selectride (9.6 mL, 9.6 mmol) was added and stirred for 14 h at the same temperature. The reaction was quenched by the addition of glacial acetic acid, and the solid residue was filtered through a pad of Celite and washed with diethyl ether. The resulting colorless solution was washed with 0.1 N HCl (20 mL) and aqueous $NaHCO_3$ (20 mL, saturated solution). The organic layer was separated and dried (Na_2SO_4). Evaporation of the solvent at reduced pressure gave the crude carbinol **51** together with the starting product which were separated by column chromatography (silica gel 70–230 mesh, CH_2Cl_2/hexane 1:1 as eluant) to give **51**; yield 0.83 g (58%) as a 3:1 mixture of diastereoisomers, with the major diastereoisomer being the desired *1R* carbinol.

Dimethylphenylsilane Reduction of 50. To a solution of ketone **50** (0.32 g, 1 mmol) in HMPA (2 mL), dimethylphenylsilane (0.19 mL, 1.2 mmol) and tris(diethylamino)sulfonium difluorotrimethylsiliconate (TASF, 0.2 mmol) were added at room temperature. After 23 h at the same temperature, a solution of hydrochloric acid in methanol (1 M, 6 mL) was slowly added during 30 min. The mixture was filtered off through a pad of silica gel eluting with diethyl ether–hexane (1:1). Evaporation of the solvents gave an oil which was diluted with CH_2Cl_2 (25 mL) and washed with 1 N HCl (3 × 20 mL) and with aqueous $NaHCO_3$ (20 mL, saturated solution). The organic extract was dried ($MgSO_4$), and evaporation of the solvent under reduced pressure gave a residue which was analyzed by ^1H NMR and purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane 1:1 as eluant) to give **51**: yield 0.32 g, 90% as a 1:8 mixture of diastereoisomers, with the major diastereoisomer being the 1*S*-carbinol **51**.

***trans*-3-(1-Acetoxyethyl)-1-(4-methoxyphenyl)-4-(α-methylstyryl)azetidin-2-one (23).** To a solution of both epimers of **46** in a ratio 1:1 3-(1-hydroxyethyl) β-lactam **46** (6.46 g, 20 mmol) and pyridine (2.19 mL, 27 mmol) in methylene chloride (40 mL) was slowly added a solution of acetyl chloride (1.77 mL, 25 mmol)

in methylene chloride (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 25 h and then was washed with water (25 mL), with aqueous 1 N HCl (2 × 25 mL) and with $NaHCO_3$ (25 mL, saturated solution). The organic layer was separated and dried (Na_2SO_4). Evaporation of the solvent at reduced pressure afforded the title compound as a mixture of epimers in 93% yield: ^1H NMR ($CDCl_3$) δ 7.48–6.72 (m, 9 H, Ar), 6.65 (s_{br}, 1 H, CH=), 5.30 (m, 1 H, HCO), 4.48 (d, 1 H, J = 2.5 Hz, CH-4), 4.30 (d, 1 H, J = 2.5 Hz, CH-4), 3.72 (s, 3 H, OCH_3), 3.20 (m, 1 H, CH-3 both diastereoisomers), 2.00 (s, 3 H, CH_3CO), 1.82 (s_{br}, 3 H, CH_3), 1.38 (d, 3 H, J = 6.5 Hz, CH_3).

***trans*-3-(1-Acetoxyethyl)-4-acetyl-1-(4-methoxyphenyl)-azetidin-2-one (47).** Following the same procedure as described for the preparation of **24** starting from 4-(α-methylstyryl) β-lactam **23** (6.82, 18 mmol) the title compound **47** was obtained and purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane 1:2, 1:1 as eluant): yield 3.28 g (60%); ^1H NMR ($CDCl_3$) δ 7.24–6.85 (m, 4 H, Ar), 5.35 (m, 1 H, HCO, both diastereoisomers), 4.45 (d, 1 H, J = 2.7 Hz, CH-4) and 4.31 (d, 1 H, J = 2.7 Hz, CH-4), 3.77 (s, 3 H, OCH_3), 3.41 (dd, 1 H, J = 4.8 Hz, J' = 2.7 Hz, CH-3) and 2.70 (dd, 1 H, J = 7.5 Hz, J' = 2.7 Hz, CH-3), 2.21 (s, 3 H, $COCH_3$, both diastereoisomers), 2.06 (s, 3 H, $OCOCH_3$) and 2.05 (s, 3 H, $OCOCH_3$), 1.45 (d, 3 H, J = 6.3 Hz, CH_3, both diastereoisomers).

***trans*-4-Acetoxy-3-(1-acetoxyethyl)-1-(4-methoxyphenyl)azetidin-2-one (48).** Following the same procedure as described for the preparation of **26** starting from 4-acetyl β-lactam **47** (3.28 g, 10 mmol) the title compound **48** was obtained in 57% yield (1.83 g): ^1H NMR ($CDCl_3$) δ 7.42–6.85 (m, 4 H, Ar), 6.47 (d, 1 H, J = 1.0 Hz, CH-4) and 6.24 (d, 1 H, J = 1.2 Hz, CH-4), 5.40–5.29 (m, 1 H, CHO, both diastereoisomers), 3.79 (s, 3 H, OCH_3), 3.41 (dd, 1 H, J = 4 Hz, J' = 1.2 Hz, CH-3), and 3.34 (dd, 1 H, J = 7.1 Hz, J' = 1.0 Hz, CH-3), 2.13 (s, 6 H, $OCOCH_3$) and 2.05 (s, 3 H, $OCOCH_3$) and 2.02 (s, 3 H, $OCOCH_3$), 1.45 (d, 3 H, J = 6.6 Hz, CH_3) and 1.43 (d, 3 H, J = 6.3 Hz, CH_3).

***trans*-4-Acetoxy-3-(1-acetoxyethyl)azetidin-2-one (49).** Ammonium cerium(IV) nitrate (18.1 g, 33 mmol) dissolved in water (56 mL) was added to a cooled (0–5 °C) solution of β-lactam **48** (1.76 g, 5.5 mmol) in acetonitrile (200 mL) and water (10 mL). The reaction mixture was stirred at 0–5 °C for 30 min and then poured into water (150 mL). Following the same workup as in the preparation of **28** a syrup was obtained which was purified by column chromatography (silica gel 70–230 mesh, AcOEt/hexane 1:2 as eluant): yield 0.80 g (68%, colorless oil); IR (neat) ν 3294 cm^{-1} (NH); ^1H NMR ($CDCl_3$) δ 6.93 (s_{br}, 1 H, NH) and 6.91 (s_{br}, 1 H, NH), 5.70 (d, 1 H, J = 1.2 Hz, CH-4) and 5.61 (d, 1 H, J = 1.3 Hz, CH-4), 5.26 (m, 1 H, HCO, both diastereoisomers), 3.39 (dd, 1 H, J = 3.9 Hz, J' = 1.4 Hz, CH-3) and 3.32 (dd, 1 H, J = 6.5 Hz, J' = 1.3 Hz, CH-3, 2.12 and 2.11 (s, 3 H, $OCOCH_3$), 2.07 and 2.05 (s, 3 H, $OCOCH_3$), 1.41 (d, 3 H, J = 6.5 Hz, CH_3) and 1.37 (d, 3 H, J = 6.4 Hz, CH_3).

Preparation of (±)-α-Methyl-*N*-(α-methylcinnamylidene)benzylamine (54). α-Methylcinnamaldehyde (27.8 mL, 200 mmol) and (±)-1-phenylethylamine (25.8 mL, 200 mmol) were mixed at room temperature, and the mixture was heated until water was formed and then was kept to stand at room temperature for 1 h. The resulting viscous oil was dissolved in methylene chloride, dried (Na_2SO_4), and filtered off. Evaporation of the solvent under reduced pressure gave the imine **54** as an oil: yield 47.2 g (94%); ^1H NMR ($CDCl_3$) δ 8.10 (s, 1 H, CH), 7.50–7.10 (m, 10 H, Ar), 6.75 (s, 1 H, CH), 4.45 (q, 1 H, J = 6 Hz, CH), 2.2 (s, 3 H, CH_3), 1.55 (d, 3 H, J = 6 Hz, CH_3).

Preparation of (*S*)-(−)-α-Methyl-*N*-(α-methylcinnamylidene)benzylamine (54). Following the above procedure the title imine was obtained: yield 9.73 g (78%); mp 49–50 °C (EtOH); IR (KBr) ν 1624 cm^{-1} (C=N). Anal. Calcd for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62. Found: C, 86.54; H, 7.61; N, 5.53. $[\alpha]_D^{20}$ = −51.7 (*c* 1.5, CCl_4).

Reformatsky Reaction between 17 and (±)-Imine 54. A mixture of the (±)-imine **54** (1.25 g, 5 mmol), zinc dust (0.45 g, 6.9 mmol), *dl*-methyl 2-bromobutyrate **17** (1.09 g, 0.7 mL, 6 mmol), and iodine (0.15 g, 0.6 mmol) in toluene (10 mL) was refluxed under nitrogen for 2.5 h. Then the resulting mixture was cooled at room temperature and poured into an aqueous solution of NH_4Cl (10 mL, saturated solution) and 25% NH_4OH (10 mL) and extracted with methylene chloride (10 mL). The organic layer was successively washed with 0.1 N HCl (10 mL) and water (10 mL) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave an oil which was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane 1:2, 1:1, as eluant) to give a mixture of β-lactams **55a–58a**: yield 0.67 g (42%); IR (film) ν 1740 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.38–7.22 (m, 10 H, Ar), 6.38 (s_{br}, 1 H, =CH), 4.91, 4.29, 4.46, 4.79 (q, 1 H, J = 7.2, 6.9, 6.9, and 7.2 Hz, respectively, NC*H*Me), 3.73–3.59 (m, 1 H, CH), 2.86–2.94 (m, 1 H, CH), 1.84–1.74 (m, 6 H, CH, CH_2, CH_3), 1.62–1.49 (m, 3 H, NCH*Me*), 1.00–0.88 (m, 3 H, *Me*CH_2).

Reformatsky Reaction between 18 and (±)-Imine 54. Following the above procedure starting from *dl*-methyl 2-bromoisovalerate (1.17 g, 0.86 mL, 6 mmol), an oil mixture of the β-lactams **55b–57b** was obtained after purification by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane 1:2, 1:1): yield 0.83 g (50%); IR (film) ν 1740 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.35–7.22 (m, 10 H, Ar), 6.38 (s_{br}, 1 H, =CH), 4.91, 4.30, 4.46 (q, 1 H, J = 7.2, 6.3, and 7.2 Hz, respectively, NC*H*Me), 3.67–3.62 (m, 1 H, CH), 2.78–2.70 (m, 1 H, CH), 2.08–1.73 (m, 1 H, C*H*Me_2), 1.83 (s_{br}, 3 H, CH_3), 1.57–1.51 (m, 3 H, NCH*Me*), 1.08–0.87 (m, 6 H, CH*Me*$_2$).

Reformatsky Reaction between 31 and (*S*)-Imine 54. Following the same procedure as those used for the preparation of 3-unsubstituted 2-azetidinones starting from the (*S*)-imine **54** (2.5 g, 10 mmol) and ethyl bromoacetate **31** (1.33 mL, 12 mmol) a mixture of the β-lactams **59** and **60** was obtained in a ratio 3:1, respectively, after purification by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane 1:3 and 1:1 as eluant): yield 1.2 g (50%); IR (film) ν 1743 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.36–7.24 (m, 10 H, Ar), 6.39 (s_{br}, 1 H, =CH), 4.95 (q, 1 H, J = 7.2 Hz, C*H*, compound **59**), 4.57 (q, 1 H, J = 7.2 Hz, C*H*Me, compound **60**), 4.09 (dd, 1 H, J = 2.4, J' = 5.2 Hz, CH, compound **60**), 4.00 (dd, 1 H, J = 2.4, J' = 5.3 Hz, CH, compound **59**), 3.05 (dd, 1 H, J = 5.2, J' = −14.8 Hz, HC*H*, compound **60**), 2.99 (dd, 1 H, J = 5.3, J' = −14.8 Hz, HC*H*, compound **59**), 2.78 (dd, 1 H, J = 2.4, J' = −14.8 Hz, *H*CH, compound **59**), 2.77 (dd, 1 H, J = 2.4, J' = −14.8 Hz, *H*CH, compound **60**), 1.81 (s_{br}, 3 H, CH_3), 1.76 (d, 3 H, J = 7.2 Hz, NCH*Me*, compound **60**), 1.57 (d, 3 H, J = 7.2 Hz, NCH*Me*, compound **59**).

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