2-Iminooxetane Chemistry. 4. Synthesis of β-Substituted Propionamides[1]

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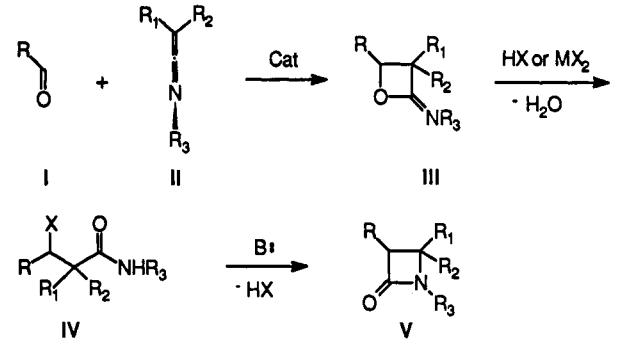
β-substituted propionamides ($RCHXCR_1R_2CONHAr$) were synthesized in high yields by addition of protic and aprotic Lewis acids ($C_6H_5SO_3H$, CF_3COOH, CH_3COOH, HI, $MgBr_2$, ZnI_2, CH_3OH, H_2O, 2,4,6-$(NO_2)_3C_6H_2OH$) to 2-iminooxetanes. Studies on the stereochemistry of the acid addition to unsymmetrically C3,C4-monosubstituted 2-iminooxetanes indicate that product distribution depends on the steric and electronic nature of the substituents of the oxetane moiety as well as on the nucleophilicity of the conjugate base derived from the acid.

Introduction

We have previously reported the synthesis of 2-iminooxetanes via Lewis acid induced cycloaddition of ketene imines to aldehydes.[2a,b] More recently, we have reported the synthesis of 2-iminooxetanes bearing stereogenic centers at C3 and C4 using chiral (*S*)-α-alkoxy aldehydes and unsymmetrically monosubstituted ketene imines as the partners.[3] At the same time, we investigated the reactivity of these versatile heterocycles which can be used for the introduction of C_2, C_3, and C_4 units into organic compounds through medium-controlled ring opening. For instance, in a preliminary study it was found that the 2-(*N*-*p*-tolylimino)-3,3-dimethyl-4-phenyloxetane could be transformed into the corresponding β-keto amide and γ-amino alcohol.[2b] We also reported the synthesis of a variety of β-hydroxy amides[1] by hydrolysis of 2-iminooxetanes. In particular, we observed that the hydriodic acid-induced ring opening of (*N*-*p*-tolylimino)-3,3-dimethyl-4-phenyloxetane afforded the corresponding β-iodo propionamide; this result prompted us to investigate the possibility of formation of β-substituted propionamides (**IV**, Scheme 1) from the reaction of a selected number of 2-iminooxetanes (**III**) with different types of protic and aprotic acids ($MgBr_2$, HI, ZnI_2, $C_6H_5SO_3H$, CF_3COOH, CH_3COOH, CH_3OH, and 2,4,6-$(NO_2)_3C_6H_2OH$).

These studies are of particular interest because β-substituted propionamides constitute an important source for the production of the corresponding β-lactams (**V**) via base-induced N–C3 ring closure.[4] Consequently, a new strategy for the synthesis of β-lactams involves the readily available aldehydes (**I**) and ketene imines (**II**) as starting materials. In the present study we have focused on the stereochemistry of the addition of acids to *trans*- and *cis*-C3,C4-monosubstituted oxetanes which give *erythro* or *threo* β-substituted propionamides. This will provide important information on the mechanism of the ring opening of the oxetane ring. Because it has been demonstrated[5] that the base-induced cyclization of propionamides, as the β-halo derivatives, occurs with inversion of configuration at the C4 of the azetidinone ring, this study will also provide information about the stereochemical relationship between the *cis*/*trans*-iminooxetanes and the corresponding *cis*/*trans*-β-lactams.

Scheme 1



HX = $C_6H_5SO_3H$; CF_3CO_2H; CH_3CO_2H; HI; 2,4,6-$(NO_2)_3C_6H_2OH$; CH_3OH
MX_2 = $MgBr_2$; ZrI_2

Results and Discussion

Addition of Acids to Oxetanes 1–3. The sterically hindered C3-dimethyl-substituted oxetanes, bearing an alkyl or aryl substituent at C4 (**1–3**), were chosen as substrates for the addition of a variety of protic acids (CF_3COOH, CH_3COOH, HI, $C_6H_5SO_3H$, CH_3OH, and 2,4,6-$(NO_2)_3C_6H_2OH$, Scheme 2).

Facile conversion into the corresponding β-substituted propionamides **4–12** was noted upon addition of either strong ($C_6H_5SO_3H$, CF_3COOH, HI) or weak (CH_3COOH, 2,4,6-$(NO_2)_3C_6H_2OH$) acids to these oxetanes, irrespective of the nature of the C4 substituent. Product formation occurred in very high yield (Table 1) and under very mild reaction conditions (25–30 °C) when the C4 substituent was Me, the large Me_2CH, or the aromatic C_6H_5. Only methanol addition at 25 °C to oxetane **1** was unsuccessful; however, this reaction occurred in the presence of catalytic amounts of H_2SO_4 (entry 5) which favored C4–O bond cleavage.

It is worth noting that the addition of hydriodic acid (57% aqueous solution) of oxetanes **1** and **2** gave high

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(1) Part 3: Barbaro, G.; Battaglia, A.; Giorgianni, P. *J. Org. Chem.* **1992**, *57*, 5128.

(2) (a) Barbaro, G.; Battaglia, A.; Giorgianni, P. *J. Org. Chem.* **1988**, *53*, 5501. (b) Barbaro, G.; Battaglia, A.; Giorgianni, P. *Tetrahedron Lett.* **1987**, *26*, 2995.

(3) Barbaro, G.; Battaglia, A.; Giorgianni, P.; Giacomini, D. *Tetrahedron* **1993**, *49*, 4293.

(4) For instance, this type of methodology has been developed by Knunyants in the base-induced cyclization of β-halo propionamides. See: Knunyants, I. L.; Rytslin, E. E.; Sambaryan, N. P. *Izvest. Akad. Nauk S.S.S.R. Odtel Khim Nauk* **1960**, 527.

(5) Isaacs, N. S. *Chem. Soc. Rev.* **1976**, *5*, 181 and references cited therein.

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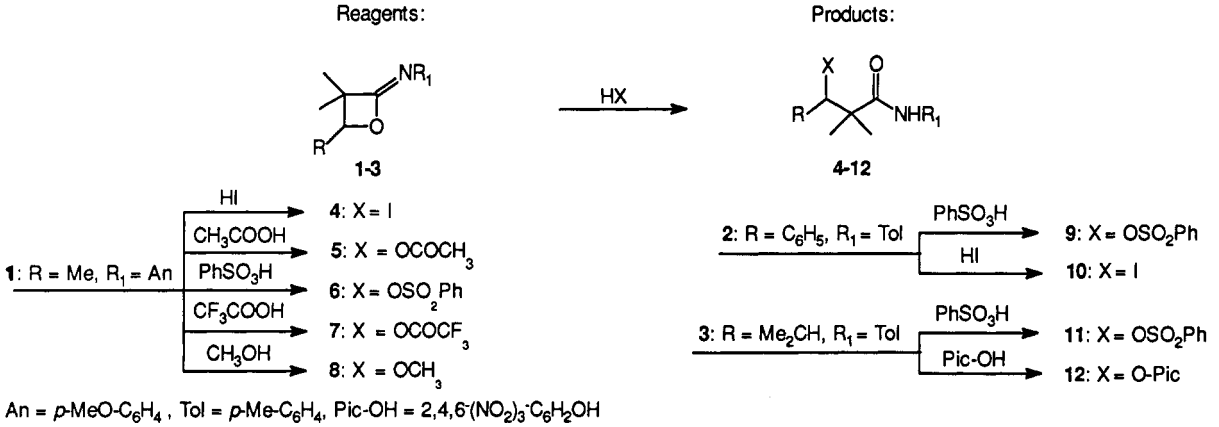
Scheme 2



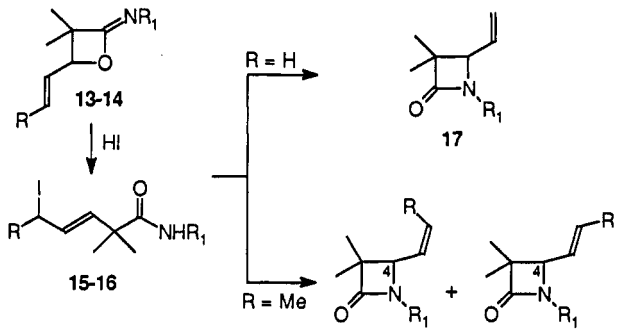
An = *p*-MeO-C_6H_4, Tol = *p*-Me-C_6H_4, Pic-OH = 2,4,6-$(NO_2)_3$-C_6H_2OH

Table 1. Addition of Acids to 2-Iminooxetanes 1–3 at 25 °C in CH_2Cl_2

entry	oxetane	HX	oxetane:HX (mmol:mmol)	product	time (h)	yield (%)
1	1	HI[a]	1:3.2	4	0.5	95
2	1	CH_3COOH	1:1.9	5	72.0	88
3	1	$C_6H_5SO_3H$	1:1.6	6	0.5	93
4	1	CF_3COOH	1:1	7	0.5	93
5	1	CH_3OH	*b*	8	2.0	84
6	2	$C_6H_5SO_3H$	1:1.1	9	0.5	9
7	2	HI[c]	1:1.4	10	0.5	90
8	3	$C_6H_5SO_3H$	1:1	11	15.0	81
9	3	picric[c]	1:1	12	120.0	79

[a] 57% aqueous solution. [b] CH_3OH as the solvent, oxetane/H_2SO_4 = 7.0. [c] Picric = 2,4,6-$(NO_2)_3C_6H_2OH$.

Scheme 3



13, 15, 17: R = H; R_1 = *p*-Me-C_6H_4
14, 16, 18: R = Me; R_1 = *p*-Me-C_6H_4

yields of β-iodo amides **4** and **10**, despite the presence of significant amounts of water in the reaction medium. It might be anticipated that HI would catalyze the addition of water[1] leading to competitive formation of the corresponding β-hydroxy amides. However, these side products were detected in the crude reaction mixture only in trace amounts (≤5%).

Each of the β-substituted propionamides exhibited IR, mass, and microanalytical data consistent with the assigned structure. In particular, the IR spectra showed an intense absorption in the 1690-1670 cm^{-1} region (NC=O) and a broad band in the 3600-3200 cm^{-1} region (NH).

The addition of hydriodic acid to C-4-vinyl- and C4-*trans*-propenyl-substituted 2-iminooxetanes **13** and **14** (Scheme 3) was also carried out. These oxetanes gave the corresponding γ-iodoamides **15** and **16** in 75% and 80% yield, respectively. After chromatographic purification, compounds **15** and **16** were obtained. Exposure to light at 25 °C led to decomposition in a few days, but **15** and **16** were indefinitely stable when stored neat in the dark at 0 °C. The stereoconfigurational assignment for **15** and **16** was consistent with spectroscopic data. In particular, the ^1H–^1H vicinal coupling constants of the C3 and C4 protons ($J_{3,4}$ = 15.5 and 15.6 Hz, respectively) were in agreement with an *E* configuration of the ethylene mojety. Finally, the structures of **15** and **16** were independently confirmed by base-induced cyclization experiments. Treatment of the γ-iodo amide **15** with potassium *tert*-butoxide gave the C4-vinyl substituted azetidinone **17** (61% yield). Compound **16** gave a mixture of two isomeric β-lactams, i.e., C4-*trans*-propenyl-18 and C4-*cis*-propenyl-18 with a *trans*/*cis* ratio of 2.8 (68% overall yield).

Stereochemistry of Addition to Oxetanes 19–23. The addition of acids to *cis*- or *trans*-C3,C4-monosubstituted oxetanes produced *erythro* and *threo* diastereomeric pairs of the corresponding β-substituted propionamides **24–33**. For our stereochemical studies we chose five pairs (*cis* and *trans*) of C3-methyl substituted oxetanes (**19–23**, Scheme 4). The R groups at C4 included $MeCH_2$-CH_2 (**19**), Me_2CH (**20**), MeC≡C (**21**), C_6H_5 (**22**), and CO_2-Me (**23**), respectively, for the isomer pairs.

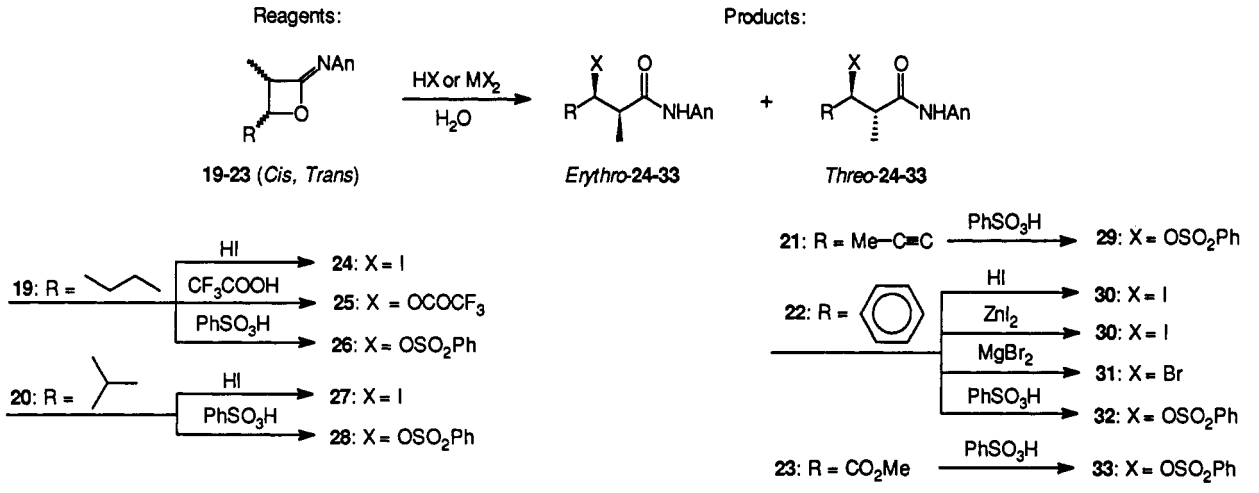
The *erythro*/*threo* stereostructures were assigned on the basis of ^1H NMR data, along with indirect chemical evidence. Base-induced cyclization of a selected number of β-substituted propionamides afforded the corresponding *cis*/*trans*-β-lactams (Scheme 5) and presumably involved an inversion of configuration at the C4 of the azetidinone ring.[5] Table 2 reports the product distribution after the cyclization of *erythro* or *threo* compounds **24** and **26–30**.

The stereoconfigurational assignment of the corresponding β-lactams was straightforward because both *cis*- and *trans*-isomers were available for examination.[6] In some cases, the cyclization was not completely stereoselective, with isomer ratios ranging from 96:4 to 93:7 (entries

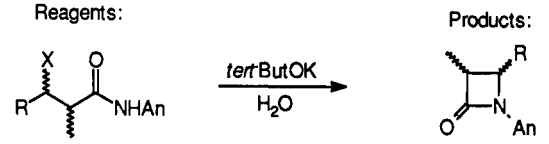
(6) According to the literature data regarding the stereochemical assignment of *trans* and *cis* pairs of small ring heterocycles (β-lactams, azetidines, oxetanes), larger ^1H–^1H coupling constants values of the vicinal hydrogens at C3 and C4 in the *cis* isomers are observed. Additionally, *cis*/*trans* configurational assignments of β-lactams were based on the upfield effect, exerted on the C3-Me of the *cis* isomer by the substituent at C4. Consequently, the hydrogens at C3 and at C4 of the *cis* isomers resonate at a lower field. Finally, the C3 and C4 of the *trans* isomers resonate at a lower field in respect to the *cis* isomers in the ^{13}C NMR spectrum. See, for example: (a) Jackmann, L. M.; Sternhell, S. In *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; Barton, D. H. R., Doering, W., Eds.; International Series of Monographs in Organic Chemistry; Pergamon: Oxford, 1969; Vol. 5, Chapters 3–8, p 234. (b) Aben, R. W. M.; Smit, R.; Schreen, J. W. *J. Org. Chem.* **1987**, *52*, 365. (c) Bouffard, F. A.; Christensen, B. G. *J. Org. Chem.* **1981**, *46*, 2208. (d) See refs 1a and 8c.

(7) α,β-Unsaturated acid amides are obtained as side products.

Scheme 4



Scheme 5



R = *n*-Pr: 24 (X = I), 26 (X = OSO_2Ph), 34
R = Me—C≡C: 29 (X = I), 36

R = *i*-Pr: 27 (X = I), 28 (X = OSO_2Ph), 35
R = C_6H_5: 30 (X = I), 37

Table 2. Potassium *tert*-Butoxide Induced Cyclization of *Erythro* and *Threo* β-Derivatized Propanamides 24 and 26–30[a]

entry	amide	base:amide	time (h)	product (*cis*:*trans*)	yield[b] (%)
1	*threo*-**24**	1.2	1.5	**34** (93:7)	92
2	*erythro*-**24**	1.3	1.5	**34** (5:95)	86
3	*threo*-**26**	1.0	1.5	**34** (*cis*)	93
4	*erythro*-**26**	1.0	1.5	**34** (*trans*)	90
5	*threo*-**27**	1.1	2.0	**35** (*cis*)	81[c]
6	*erythro*-**27**	1.3	2.0	**35** (*trans*)	64[c]
7	*threo*-**28**	1.0	2.0	**35** (*cis*)	91
8	*erythro*-**28**	1.0	2.0	**35** (*trans*)	93
9	*threo*-**29**	1.0	2.0	**36** (*cis*)	92
10	*erythro*-**29**	1.0	2.0	**36** (3:97)	83[c]
11	*threo*-**30**	1.0	2.0	**37** (96:4)	92

[a] At −15 °C, in THF. [b] Isolated yields. [c] See ref 7.

1, 2, 10, and 11). Presumably, the formation of the minor isomers originated from an isomerization of the azetidinones[8] under the basic reaction conditions. This isomerization was demonstrated on compounds *cis*- and *trans*-**34**. These β-lactams were treated with potassium *tert*-butoxide under reaction conditions similar to those used during the cyclization process (see Experimental Section). Inspection of the crude reaction mixture by ^1H NMR revealed that *cis*-**34** and *trans*-**34** equilibrated to a *trans*/*cis* mixture of 87:13.[9] Even though the presence of small amounts of minor isomer was unavoidable, from the data of Table II it appears that an *erythro* configuration can be assigned to the β-substituted amides of entries 2, 4, 6, 8, and 10, since the corresponding β-lactams were formed with high *trans*-diastereoselectivity (≥19:1). Consequently, a *threo* configuration was assigned to the corresponding isomeric amides (entries 1, 3, 5, 7, and 9, respectively) and to the β-iodo amide of entry 11. These compounds afforded the corresponding *cis*-β-lactams as the major stereoisomers.

The chemical stereoconfigurational assignment is supported by some important trends deduced from the ^1H and ^{13}C NMR of the *erythro*/*threo* pairs of amides **24–33**. Table 3 reports the relevant ^1H and ^{13}C NMR resonances (C2-Me and CO, respectively) and the ^1H–^1H vicinal coupling constants of the C2–C3 carbon atoms. There was a pronounced chemical shift difference observed in the ^1H NMR C2-Me signals of the diastereomeric pairs of the C3-phenyl substituted amides **30–32** (Δ ppm = 0.5–0.6, entries 13–18). This suggests a shielding difference at C2-Me, caused by the phenyl substituent.[10] The more shielded signal was assigned to the *threo* isomer.

Such assignment is based on the following reasoning. In the absence of an intramolecular hydrogen bond the C2–C3 conformations for each isomer, shown in Figure 1, were considered. For the *erythro* isomer, steric interactions should favor the conformation **I** and for the *threo* isomer conformation **V**. In these two conformers the hydrogens at C2 and at C3 are placed between the two larger

(8) It is well known that isomerization in β-lactams appears to be favored by the presence of aryl substituents at nitrogen, by small substituents at C3, and by substituents that enhance acidity, as the phenyl in C4. (a) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447. (b) Ha, D.-C.; Hart, D. J.; Yang, T. K. *J. Am. Chem. Soc.* **1984**, *106*, 4819. (c) Luche, J. L.; Kagan, H. B.; Parthasarthy, R.; Tsoucaris, G.; DeRango, C.; Zelwer, C. *Tetrahedron* **1968**, *24*, 1275. The formation of the retention products from an isomerization of the corresponding α,β-unsaturated acid amides, through an intramolecular Michel addition, is unlikely but cannot be excluded in principle. In some cases these intermediates were isolated as side products (see ref 7 of Table 2 and Experimental Section).

(9) It is worth noting that the stereoselectivity of the cyclization of amides having the same skeleton of carbon atoms depends on the type of leaving group. For instance, the β-sulfonyl amides *erythro*-**26** and *threo*-**26** gave the β-lactams *trans*-**34** and *cis*-**34** stereoselectively (Table 2), while the corresponding β-iodo amides *erythro*-**24** and *threo*-**24** gave amounts of the retention products.

(10) See, for example, the assignment of stereoconfiguration of *erythro* and *threo* dihydrocinnamates. Barbieux, M.; Martin, R. H. *Tetrahedron Lett.* **1965**, *33*, 2919.

Table 3. Relevant ^1H NMR and ^{13}C NMR Chemical Shifts[a] and ^1H–^1H Vicinal Coupling Constants ($J_{2,3}$)[b] of β-Substituted Propanamides (RCHXCHMeCONHC$_6$H$_4$-*p*-OMe) 22–31

entry	R	X	isomer	^1H NMR C2-Me	^1H NMR J	^{13}C NMR CON
1	*n*-Pr	I	*erythro*-**24**[c]	1.39	6.5	170.9
2	*n*-Pr	I	*threo*-**24**[c]	1.33	7.8	171.4
3	*n*-Pr	$OCOCF_3$	*erythro*-**25**	1.27	6.9	170.7
4	*n*-Pr	$OCOCF_3$	*threo*-**25**	1.27	7.3	170.9
5	*n*-Pr	OSO_2Ph	*erythro*-**26**[c]	1.21	4.9	170.0
6	*n*-Pr	OSO_2Ph	*threo*-**26**[c]	1.21	6.1	170.5
7	Me_2CH	I	*erythro*-**27**[c]	1.45	9.1	171.2
8	Me_2CH	I	*threo*-**27**[c]	1.29	10.6	173.0
9	Me_2CH	OSO_2Ph	*erythro*-**28**[c]	1.22	7.1	170.9
10	Me_2CH	OSO_2Ph	*threo*-**28**[c]	1.20	7.2	171.0
11	MeC≡C	OSO_2Ph	*erythro*-**29**[c]	1.25	7.1	170.5
12	MeC≡C	OSO_2Ph	*threo*-**29**[c]	1.25	8.8	170.6
13	C_6H_5	I	*erythro*-**30**[c]	1.61	10.7	169.7
14	C_6H_5	I	*threo*-**30**[c]	1.00	11.1	172.5
15	C_6H_5	Br	*erythro*-**31**	1.56	9.8	170.2
16	C_6H_5	Br	*threo*-**31**	1.04	11.0	172.0
17	C_6H_5	OSO_2Ph	*erythro*-**32**	1.34	8.7	169.8
18	C_6H_5	OSO_2Ph	*threo*-**32**	0.89	9.8	170.6
19	CO_2Me	OSO_2Ph	*erythro*-**33**	1.29	6.9	168.1
20	CO_2Me	OSO_2Ph	*threo*-**33**	1.18	8.5	168.6

[a] In ppm. [b] In Hz. [c] Assignments of *erythro*/*threo* configuration based on cyclization experiments, see Table 2.

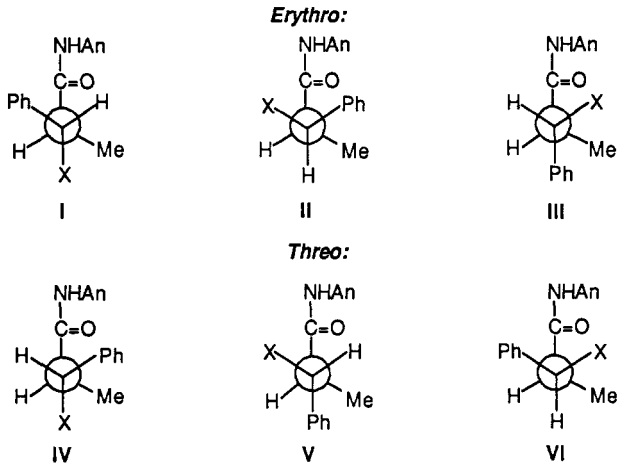


Figure 1. C2–C3 conformations.

substituents of the vicinal carbon atom. On this basis the *threo* configuration is assigned to the conformer where the ^1H NMR signal of the C2-Me resonates at higher field with respect to that of the *erythro*, due to a gauche interaction with the phenyl ring at C3. This upfield shift, caused by the diamagnetic influence of the phenyl ring, has also been observed for the NC=O ^{13}C NMR resonance of the *erythro* isomer. A similar trend was exhibited by the ^1H NMR C2-Me and ^{13}C NMR NC=O resonances of several diastereomeric pairs. As a general rule, the isomer that has the *erythro* configuration displays a C2-Me doublet centered downfield and a NC=O resonance centered upfield with respect to the isomer that has the *threo* configuration assigned.[11,12] Table 3 shows a separation in the C2-Me resonances of the diastereomeric pairs, the maximum separation observed being 0.61 ppm. Similarly, a maximum separation of 2.8 ppm was observed in the NC=O resonances. Although this separation sometimes vanishes, in no case does any crossing over of the *erythro* and *threo* resonances take place. These results are consistent with the body of existing data on diastereomeric pairs of 2-alkyl-3-alkoxycarbonyl derivatives.[13,14]

Therefore, these separations may constitute a reliable method to distiguish between the two isomers of amides **24**, **27**, and **30–33**. This criterion of stereostructure assignment, which parallels the results obtained by the cyclization experiments, is supplemented by the trend observed for the $J_{2,3}$ vicinal coupling constants; *i.e.*, the $J_{2,3}$ of the *threo* isomers are larger than those of *erythro*.[15] It is worth noting that a similar behavior is quite general and also applies to the *erythro*/*threo* pair of amides **25**, **26**, **28**, and **29**.

The stereochemistry of the addition of acids to *cis*- and *trans*-C3-methyl substituted oxetanes **19–23** (Scheme 4, Table 4) provided important information about the mechanism of the ring opening. Each *cis*/*trans* pair of oxetanes was >98% isomerically pure. Yields of product were greater than 75%, with the exception of the addition of benzenesulfonic acid to *trans*-**20** which only gave a moderate yield of the corresponding β-benzensulfonyl amide *erythro*-**28** together with larger amounts of unidentified products. The stereospecificity of the ring opening reaction depends on the nature of the substituents at the C4 of the oxetane moiety and the type of Lewis acid partner. Typically, the addition of acids occurred with high diastereocontrol and with an inversion of configuration. For oxetanes **22** having a phenyl substituent at C4 a different behavior was observed. A substantial loss in stereoselectivity occurred (entries 13–20), the relative amount of retention product depending on the type of Lewis acid and on the stereoconfiguration of the oxetane. For instance, the addition of benzenesulfonic acid to either *cis*-**22** or *trans*-**22** gave a *threo*/*erythro* product distribution of 65:35. However, *cis*-**22** and *trans*-22 gave different *threo*/*erythro* product distributions in reactions with HI, ZnI_2, and $MgBr_2$. Namely, *cis*-**22** gave the product of inversion to a higher degree than *trans*-**22**. In fact, an inversion/retention (*threo*/*eyrthro*) ratio of 5.0 was found for ZnI_2 and a ratio of ≥20 for HI and $MgBr_2$. By contrast, a substantial loss of stereoselectivity was observed in the reaction of *trans*-**22**. In this case, the inversion/retention (*erythro*/*threo*) ratio was 1.1 for ZnI_2, 1.6 for $MgBr_2$, and 2.7 for HI. Therefore, we considered the possibility that the stereochemical outcome of the ring-opening of the initial iminooxetanes could be compromised by a subsequent S_N2 reaction of the acid with the initially formed products. An acid-induced stereochemical scrambling of β-iodopropionamides *erythro*- and *threo*-**30** was observed in the following control experiments. The oxetane *trans*-

(11) No consistent trend in the ^{13}C NMR chemical shifts of the other common carbons of compounds of Table 3, analogous to that observed by us for β-hydroxy amides[3] and by Heathcock for β-hydroxy esters,[12] could be detected for the diastereomers examined. The stereochemical assignment in β-hydroxy amides and β-hydroxy esters is greatly facilitated since these compounds exist as chairlike conformers because of the presence of an intramolecular hydrogen bond between OH and C=O which causes a general upfield shift in the C2, C3, and C2-Me ^{13}C NMR resonances of the *erythro* isomers relative to the corresponding resonances in the *threo* isomers.

(12) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294.

(13) Gouzoules, F. H.; Whitney, R. A. *J. Org. Chem.* **1986**, *51*, 2024.

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(15) A similar trend has been observed for several acyclic pairs of *erythro*/*threo* β-amino esters. See: (a) Guanti, G. Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1987**, *37*, 4331. (b) Gennari, C.; Venturini, I.; Gislon, G.; Schimperna, G. *Tetrahedron Lett.* **1987**, *28*, 227.

Table 4. *Threo/Erythro* Product Distribution after the Addition of HI, ZnI_2, $MgBr_2$, CF_3COOH, and of $C_6H_5SO_3H$ to the *Trans/Cis* Pairs of Oxetanes 19–23

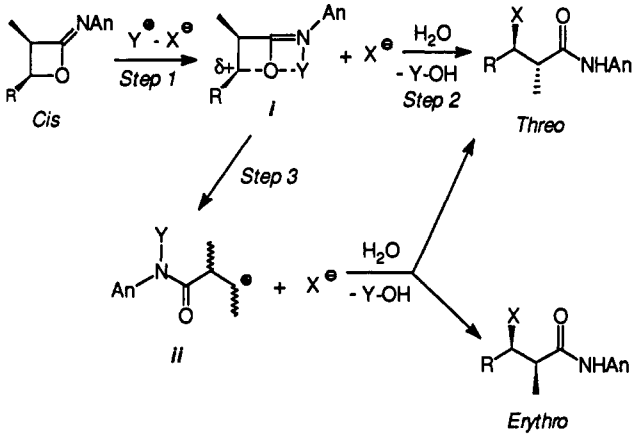
entry	reagent/HX (mmol:mmol)	product (*threo:erythro*)	*T* (°C)	time (h)	yield (%)	solvent
1	*cis*-**19**/HI[a] (1:3.3)	**24** (*threo*)	−25	30	83	CH_2Cl_2
2	*trans*-**19**/HI[a] (1:4.9)	**24** (*erythro*)	−25	30	79	CH_2Cl_2
3	*cis*-**19**/CF_3COOH (1:1)	**25** (95:5)	−50	60	79	CH_2Cl_2
4	*trans*-**19**/CF_3COOH (1:1)	**25** (*erythro*)	−50	60	86	CH_2Cl_2
5	*cis*-**19**/$C_6H_5SO_3H$ (1:1)	**26** (95:5)	−50	60	84	CH_2Cl_2
6	*trans*-**19**/$C_6H_5SO_3H$ (1:1)	**26** (*erythro*)	−50	60	88	CH_2Cl_2
7	*cis*-**20**/HI[a] (1:3.8)	**27** (*threo*)	−25	30	84	CH_2Cl_2
8	*trans*-**20**/HI[a] (1:3.4)	**27** (*erythro*)	−25	30	82	CH_2Cl_2
9	*cis*-**20**/$C_6H_5SO_3H$ (1:1)	**28** (*threo*)	25	30	91	CH_2Cl_2
10	*trans*-**20**/$C_6H_5SO_3H$ (1:1)	**28** (*erythro*)	25	360	37	CH_2Cl_2
11	*cis*-**21**/$C_6H_5SO_3H$ (1:1)	**29** (*threo*)	−50	60	90	CH_2Cl_2
12	*trans*-**21**/$C_6H_5SO_3H$ (1:1)	**29** (*erythro*)	−50	60	76	CH_2Cl_2
13	*cis*-**22**/HI[a] (1:3.2)	**30** (97:3)	25	10	78	CH_2Cl_2
14	*trans*-**22**/HI[a] (1:3.1)	**30** (27:73)	25	10	81	CH_2Cl_2
15	*cis*-**22**/ZnI_2 (1:1.1)	**30** (83:17)	25	120	91	THF
16	*trans*-**22**/ZnI_2 (1:1.1)	**30** (47:53)	25	120	78	THF
17	*cis*-**22**/$MgBr_2$ (1:1)	**31** (95:5)	25	120	83	Et_2O
18	*trans*-**22**/$MgBr_2$ (1:1)	**31** (38:62)	25	120	89	Et_2O
19	*cis*-**22**/$C_6H_5SO_3H$ (1:1)	**32** (65:35)	−50	60	81	CH_2Cl_2
20	*trans*-**22**/$C_6H_5SO_3H$ (1:1)	**32** (64:36)	−50	60	89	CH_2Cl_2
21	*cis*-**23**/$C_6H_5SO_3H$ (1:1)	**33** (*threo*)	−50	60	84	CH_2Cl_2
22	*trans*-**23**/$C_6H_5SO_3H$ (1:1)	**33** (*erythro*)	−50	60	88	CH_2Cl_2

[a] 57% aqueous solution.

22 was reacted with an excess of HI. Aliquots of the reaction mixture were quenched at different times, and the product distribution was determined. It appears that the initial inversion/retention (*erythro/threo*) product distribution of 74:26, obtained at 95% conversion of the reagents after 2 min, decreased very slowly (73:27 after 10 min, 46:34 after 1 h, 57:43 after 24 h, 39:61 after 60 h). This result clearly demonstrates that the extent of the HI-induced *erythro* to *threo* isomerization during the reaction of HI with *trans*-**22** is very small. Instead, the problem of a possible contribution of acid-induced *erythro* to *threo* isomerization on the stereochemical outcome of the reactions of *cis*- and *trans*-**22** with ZnI_2 and $MgBr_2$ is more intriguing due to much longer reaction times and because we were unable to isolate the pure *erythro* isomers of **30** and **31** from their mixtures (see Table 4). We did, however, find a ZnI_2-induced *threo* to *erythro* isomerization of compound **30**. In fact, *threo*-**30** was converted into a *threo*: *erythro* = 91:9 mixture after 3 h at 25 °C in the presence of an equimolar amount of ZnI_2. This result clearly implicates product isomerization as part of the stereochemical outcome of the reaction of *cis*-**22** with ZnI_2 in which a 83:17 *threo/erythro* mixture was obtained after 2 h.

Thus, a stereoselective process (steps 1 and 2, Scheme 6) could yield the product of inversion. Such inversion logically involves breaking the C4–O bond of a complex (*i*) of the oxetane and electrophile. Backside nucleophilic attack at C3 of the complex, via a Pritchard and Long-type mechanism,[16] then affords the inverted product. This process is favored when alkyl or electron-poor substituents are present at C4 of the oxetane ring. A carbocation process, which is responsible for the amount of retention products not derived from the acid-induced *threo/erythro* isomerization, affords, according to an A_1 Ingold-type mechanism,[17] a partial stereochemical scrambling where C4 is substituted by the phenyl group (step 3). The greater nucleophilic character of the halide ions I^- and Br^- with respect to $C_6H_5SO_3^-$ favors a competition between steps

Scheme 6



2 and 3 in the reactions with *cis*-**22** and *trans*-**22**. The higher diastereoselectivity found in the addition of HI, ZnI_2 and $MgBr_2$ to *cis*-**22** with respect to *trans*-**22** may be explained by a more crowded transition state involved in the attack of the halide ions to the coordinated complex of *trans*-**22** than that of *cis*-**22**, due to the presence of one substituent on both sides of the oxetane ring.

Conclusions

The addition of acids to 2-iminooxetanes offers an interesting approach to the synthesis of β-substituted propionamides. These intermediates are obtained in high yield even when the conjugated base of the acid is very weak (e.g., $C_6H_5SO_3^-$).

High diastereocontrol and inversion of configuration are typical features of the addition of acids to C3,C4-monosubstituted 2-iminooxetanes, irrespective of their *cis/trans* stereochemistry. Loss of stereospecificity is found only with substituents that favor the formation of a carbocation at C4 of the oxetane. However, even in this case the loss of stereoselectivity can be reduced by the choice of a proper nucleophilic partner (e.g., I^-) or the right diastereomer of the oxetane (*cis* rather than *trans*).

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Experimental Section

General. The ^1H and ^{13}C NMR data were obtained as $CDCl_3$ solutions, and the internal reference was tetramethylsilane. IR spectra were obtained as CCl_4 solutions. Mass spectra were recorded on a Varian MAT 112 S at an ionizing voltage of 70 eV. All the solvents were dried and purified according to standard procedures.

Starting Materials. The 2-iminooxetanes[1] were prepared from the corresponding aldehydes and ketene imines according to the literature. In particular, **2-[(4-methoxyphenyl)imino]-3,3,4-trimethyloxetane** (1) and **2-[(4-methylphenyl)imino]-3,3-dimethyl-4-*trans*-propenyloxetane** (14) were prepared for the first time. Oxetane 1 was purified for analytical purposes by flash chromatography (*n*-pentane/ethyl acetate (12:3)). Instead, oxetane 14 totally decomposed on a column when its purification was attempted. For this reason compound 14 was used directly as the crude reaction mixture. For the MS, IR, ^1H NMR, and ^{13}C NMR spectral data of 1 and 14 and the microanalytical data of 1 see the supplementary material (Table 5).

General Procedure for the Synthesis of β-Substituted Propionamides. The 2-iminooxetanes were added, with stirring at the selected temperature, to a solution of the indicated acid in the proper solvent. The reaction mixture was neutralized with a 10% solution of $NaHCO_3$ or with an aqueous solution (5%) of sodium hydrogen sulfite when HI (57% aqueous solution) was used. The organic layer was dried over magnesium sulfate, and the solvent was removed under vacuum (10^{-2} Torr). The *threo*/*erythro* isomer distribution of compounds **24–33** was evaluated directly on the crude product material by ^1H NMR spectroscopy (Table 4). The products were purified or separated by flash chromatography (SiO_2). In particular, the following eluants were used: CH_2Cl_2/ethyl acetate (14:1) (**4**, **5**, **6**, **7**, **9**, **10**, and **30**), *n*-pentane/ethyl acetate (2:1) (**8**, **24**, **25**, **27**, **28**, **29**, **31**, **32**, and **33**), benzene/ethyl ether (13:2) (**11**, **12**, and **26**), and *n*-pentane/ethyl acetate (13:2) (**15** and **16**). Reaction conditions and yields of propionamides **4–12** are given in Table 1. Reaction conditions and yields of propionamides **24–33** are given in Table 4. For the microanalytical MS, IR, ^1H NMR, and ^{13}C NMR spectroscopic data of β-substituted propionamides **5–9**, **11**, and **25–27** see the supplementary material (Table 6).

Reaction of 2-[(4-Methoxy-phenyl)imino]-3,3,4-trimethyloxetane (1) with Hydriodic Acid. Reaction of oxetane 1 (0.52 g, 2.37 mmol) with HI (1.0 mL, 7.57 mmol) gave 0.78 g (2.25 mmol, 95% yield) of **3-iodo-*N*-(4-methoxyphenyl)-2,2-dimethylbutyramide** (4): mp 80–81 °C (benzene/*n*-hexane); ^1H NMR ($CDCl_3$) δ 1.37 (s, 3 H), 1.41 (s, 3 H), 1.89 (d, 3 H), 3.77 (s, 3 H), 4.72 (q, 1 H), 6.8–7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 22.4, 24.2, 25.1, 39.0, 48.5, 55.5, 114.1, 122.7, 130.4, 156.8, 172.3; IR (CCl_4) 3500–3200 (NH), 1680 (CON); mass spectrum *m*/*z* 347 (M^+), 219, 192, 149, 122. Anal. Calcd for $C_{13}H_{18}INO_2$: C, 44.97; H, 5.23; N, 4.03. Found: C, 45.06; H, 5.20; N, 4.00.

Reaction of 2-[(4-methylphenyl)imino]-3,3-dimethyl-4-phenyloxetane (2) with Hydriodic Acid. Reaction of oxetane 2 (0.42 g, 1.58 mmol) with HI (0.3 mL, 2.27 mmol) gave 0.56 g (1.42 mmol, 90% yield) of **3-iodo-*N*-(4-methylphenyl)-2,2-dimethyl-3-phenylpropionamide** (10): mp 110–112 °C (ethyl ether); ^1H NMR ($CDCl_3$) δ 1.23 (s, 3 H), 1.55 (s, 3 H), 2.31 (s, 3 H), 5.6 (s, 1 H), 7.1–7.5 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 20.9, 23.5, 24.4, 43.9, 49.8, 120.9, 128.0, 128.1, 129.4, 130.2, 134.5, 134.6, 139.6, 172.4; IR (CCl_4) 3600–3200 (NH), 1670–1695 (CON); mass spectrum *m*/*z* 393 (M^+), 266. Anal. Calcd for $C_{18}H_{20}INO$: C, 54.97; H, 5.13; N, 3.56. Found: C, 55.02; H, 5.05; N, 3.50.

Reaction of 2-[(4-Methylphenyl)imino]-3,3-dimethyl-4-isopropyloxetane (3) with 2,4,6-Trinitrophenol. Reaction of oxetane 3 (0.25 g, 1.08 mmol) with 2,4,6-trinitrophenol (0.248 g, 1.08 mmol) gave 0.395 g (0.85 mmol, 79% yield) of **2,2,4-trimethyl-3-(2,4,6-trinitrophenoxy)pentanoic acid (4-methylphenyl)amide** (12): mp 131–133 °C (CH_2Cl_2/ethyl ether); ^1H NMR ($CDCl_3$) δ 1.06 (d, 3 H), 1.15 (d, 3 H), 1.28 (s, 3 H), 1.56 (s, 3 H), 2.09–2.22 (m, 1 H), 2.23 (s, 3 H), 4.85 (d, 1 H), 6.9–7.3 (m, 4 H), 7.3–7.4 (b, 1 H), 8.42 (s, 2 H); $J_{3,4}$ = 7.2 Hz; ^{13}C NMR ($CDCl_3$) δ 18.1, 18.9, 20.6, 22.6, 24.1, 29.1, 48.9, 95.3, 119.2, 123.1, 129.4, 134.8, 135.2, 138.6, 142.9, 149.6, 172.7; IR ($CDCl_3$) 3600–3200 (NH), 1680–1700 (CON); mass spectrum *m*/*z* 460 (M^+), 231. Anal. Calcd for $C_{21}H_{24}N_4O_8$: C, 54.78; H, 5.25; N, 12.17. Found: C, 54.70; H, 5.16; N, 12.29.

Reaction of 2-[(4-Methylphenyl)imino]-3,3-dimethyl-4-vinyloxetane (13) with Hydriodic Acid. Reaction of oxetane 13 (0.80 g, 3.72 mmol) with HI (0.74 mL, 5.6 mmol) gave 0.96 g (2.80 mmol, 75% yield) of **5-iodo-2,2-dimethylpent-3-enoic acid (4-methylphenyl)amide** (15): oil; ^1H NMR ($CDCl_3$) δ 1.36 (s, 6 H), 2.30 (s, 3 H), 3.98 (m, 2 H), 5.93 (m, 1 H), 6.07 (m, 1 H), 7.1–7.45 (m, 5 H); $J_{4,5}$ = 7.2 Hz, $J_{3,4}$ = 15.5 Hz; ^{13}C NMR ($CDCl_3$) δ 5.3, 20.8, 25.0, 45.3, 119.6, 129.1, 129.5, 133.9, 135.4, 138.5, 173.9; IR (CCl_4) 3600–3200 (NH), 1695 (CON); mass spectrum *m*/*z* 343 (M^+), 216. Anal. Calcd for $C_{14}H_{18}INO$: C, 48.99; H, 5.29; N, 4.08. Found: C, 49.14; H, 5.22; N, 4.14.

Reaction of 2-[(4-Methylphenyl)imino]-3,3-dimethyl-4-*trans*-propenyloxetane (14) with Hydriodic Acid. Reaction of oxetane 14 (0.50 g, 2.18 mmol) with HI (0.60 mL, 4.54 mmol) gave 0.625 g (1.75 mmol, 80% yield) of **5-iodo-2,2-dimethyl-*trans*-hex-3-enoic acid (4-methylphenyl)amide** (16): oil; ^1H NMR ($CDCl_3$) δ 1.35 (s, 3H), 1.36 (s, 3 H), 2.01 (d, 3 H), 2.30 (s, 3 H), 5.04 (m, 1 H), 5.85 (m, 1 H), 6.16 (m, 1 H), 7.1–7.5 (m, 5 H); $J_{H5,Me}$ = 6.8 Hz, $J_{4,5}$ = 8.8 Hz, $J_{3,5}$ = 0.5 Hz, $J_{3,4}$ = 15.6 Hz; ^{13}C NMR ($CDCl_3$) δ 20.8, 24.9, 25.2, 26.8, 27.8, 44.9, 119.6, 129.4, 133.8, 133.9, 135.5, 136.6, 174.1; IR (CCl_4) 3600–3200 (NH), (CON); mass spectrum *m*/*z* 357 (M^+), 230. Anal. Calcd for $C_{15}H_{20}INO$: C, 50.43; H, 5.64; N, 3.92. Found: C, 50.59; H, 5.71; N, 3.84.

Reaction of *trans*- and *cis*-2[(4-Methoxyphenyl)imino]-3-methyl-4-propyloxetane (*trans*-19 and *cis*-19) with Hydriodic Acid. A. Reaction of oxetane *trans*-19 (0.18 g, 0.77 mmol) with HI (0.5 mL, 3.8 mmol) gave 0.22 g (0.61 mmol, 79.0% yield) of ***erythro*-3-iodo-2-methylhexanoic acid (4-methoxyphenyl)amide** (*erythro*-24): mp 135–136 °C (benzene/*n*-hexane); ^1H NMR ($CDCl_3$) δ 0.92 (t, 3 H), 1.39 (d, 3 H), 1.5–2.0 (m, 4 H), 2.53 (m, 1 H), 3.79 (s, 3 H), 4.43 (m, 1 H), 6.8–7.5 (m, 5 H); $J_{2,3}$ = 6.5 Hz; ^{13}C NMR ($CDCl_3$) δ 13.1, 18.0, 23.2, 40.3, 41.5, 49.8, 55.5, 114.2, 122.3, 130.4, 156.8, 170.9; IR (CCl_4) 3500–3200 (NH), 1686 (CON); mass spectrum *m*/*z* 361 (M^+), 233, 149, 122. Anal. Calcd for $C_{14}H_{20}INO_2$: C, 46.55; H, 5.58; N, 3.88. Found: C, 46.58; H, 5.67; N, 3.83. **B.** Reaction of oxetane *cis*-19 (0.16 g, 0.69 mmol) with HI (0.3 ml, 2.27 mmol) gave 0.206 g (0.57 mmol, 83% yield) of ***threo*-3-iodo-2-methylhexanoic acid (4-methoxyphenyl)amide** (*threo*-24): mp 126–127 °C (benzene/*n*-hexane); ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H), 1.33 (d, 3 H), 1.40–1.80 (m, 4 H), 2.78 (m, 1 H), 3.79 (s, 3 H), 4.43 (m, 1 H), 6.8–7.5 (m, 5 H); $J_{2,3}$ = 7.8 Hz; ^{13}C NMR ($CDCl_3$) δ 13.1, 16.6, 22.8, 38.4, 39.7, 51.1, 55.5, 114.2, 122.2, 130.5, 156.4, 171.4; IR (CCl_4) 3500–3200 (NH), 1686; mass spectrum *m*/*z* 361 (M^+), 233, 149, 122. Anal. Calcd for $C_{14}H_{20}INO_2$: C, 46.55; H, 5.58; N, 3.88. Found: C, 46.46; H, 5.66; N, 3.87.

Reaction of *trans*- and *cis*-2-[(4-Methoxyphenyl)imino]-3-methyl-4-isopropyloxetane (*trans*-20 and *cis*-20) with Benzenesulfonic Acid. A. Reaction of oxetane *cis*-20 (0.16 g, 0.69 mmol) with benzenesulfonic acid (0.109 g, 0.69 mmol) gave 0.246 g (0.63 mmol, 91.0% yield) of ***threo*-Benzenesulfonic Acid 1-isopropyl-2-[(4-methoxyphenyl)carbamoyl)]propyl ester (threo-28)**: mp 88–89 °C (ethyl ether); ^1H NMR ($CDCl_3$) δ 0.84 (d, 3 H), 1.01 (d, 3 H), 1.20 (d, 3 H), 1.9–2.1 (m, 1 H), 2.76 (m, 1 H), 3.78 (s, 3 H), 4.88 (m, 1 H), 6.7–7.9 (m, 10 H); $J_{2,3}$ = 7.2 Hz, $J_{3,4}$ = 3.6 Hz; ^{13}C NMR ($CDCl_3$) δ 14.7, 16.7, 19.5, 29.3, 45.3, 55.5, 90.3, 113.9, 121.5, 127.5, 128.8, 131.0, 133.3, 137.4, 156.3, 171.0; IR (CCl_4) 3500–3200 (NH), 1685 (CON); mass spectrum *m*/*z* 391 (M^+), 233, 149. Anal. Calcd for $C_{20}H_{25}NO_5S$: C, 61.36; H, 6.44; N, 3.58. Found: C, 61.49; H, 6.42; N, 3.68. **B.** Reaction of oxetane *trans*-20 (0.12 g, 0.52 mmol) with benzenesulfonic acid (0.081 g, 0.52 mmol) gave 0.074 g (0.19 mmol, 37.0% yield) of ***erythro*-benzenesulfonic Acid 1-isopropyl-2-[(4-methoxyphenyl)carbamoyl]propyl ester (*erythro*-28)**: mp 120–122 °C (ethyl ehter); ^1H NMR ($CDCl_3$) δ 0.83 (d, 3 H), 0.85 (d, 3 H), 1.22 (d, 3 H), 1.9–2.1 (m, 1 H), 2.80 (m, 1 H), 3.77 (s, 3 H), 4.87 (m, 1 H), 6.7–7.9 (m, 10 H); $J_{2,3}$ = 7.1 Hz, $J_{3,4}$ = 3.7 Hz; ^{13}C NMR ($CDCl_3$) δ 14.7, 16.7, 19.9, 30.7, 44.6, 55.5, 89.7, 114.1, 121.9, 127.6, 129.1, 130.7, 133.7, 137.3, 156.6, 170.9; IR (CCl_4) 3500–3200 (NH), 1685 (CON); mass spectrum *m*/*z* 391 (M^+), 233, 149. Anal. Calcd for $C_{20}H_{25}NO_5S$: C, 61.36; H, 6.44; N, 3.58. Found: C, 61.22; H, 6.54; N, 3.55.

Reaction of *trans*- and *cis*-2-[(4-Methoxyphenyl)imino]-3-methyl-4-prop-1-ynyloxetane (21) with Benzenesulfonic

Acid. A. Reaction of oxetane *trans*-**21** (0.105 g, 0.46 mmol) with benzenesulfonic acid (0.072 g, 0.46 mmol) gave 0.135 g (0.35 mmol, 76% yield) of ***erythro*-benzenesulfonic Acid 1-[1-[(4-methoxyphenyl)carbamoyl]ethyl]but-2-ynyl ester (*erythro*-29)**: mp 94–95 °C (ethyl ether); ^{1}H NMR ($CDCl_3$) δ 1.25 (d, 3 H), 1.53 (d, 3 H), 2.90 (m, 1 H), 3.74 (s, 3 H), 5.26 (m, 1 H), 6.8–7.3 (m, 4 H), 7.4–7.9 (m, 5 H), 8.30–8.50 (b, 1 H); $J_{2,3}$ = 7.1 Hz; ^{13}C NMR ($CDCl_3$) δ 3.4, 13.5, 47.1, 55.4, 72.7, 73.6, 87.1, 114.0, 122.6, 126.4, 128.1, 128.6, 129.0, 130.3, 131.8, 133.7, 136.7, 156.7, 170.5; IR (CCl_4) 3500–3200 (NH), 1694 (CON); mass spectrum *m/z* 387 (M^+), 229, 150, 149. Anal. Calcd for $C_{20}H_{21}NO_5S$: C, 62.00; H, 5.46; N, 3.62. Found: C, 62.11; H, 5.35; N, 3.65. **B.** Reaction of oxetane *cis*-**21** (0.069 g, 0.30 mmol) with benzenesulfonic acid (0.048 g, 0.30 mmol) gave 0.105 g (0.27 mmol, 90% yield) of ***threo*-Benzenesulfonic acid 1-[1-[(4-methoxyphenyl)carbamoyl]ethyl]but-2-ynyl ester (*threo*-29)**: mp 95–97 °C (ethyl ether); ^{1}H NMR ($CDCl_3$) δ 1.25 (d, 3 H), 1.65 (d, 3 H), 2.86 (m, 1 H), 3.75 (s, 3 H), 5.31 (m, 1 H), 6.7–7.3 (m, 4 H), 7.4–7.9 (m, 5 H), 8.15–8.25 (b, 1 H); $J_{2,3}$ = 8.8 Hz; ^{13}C NMR ($CDCl_3$) δ 3.5, 14.0, 47.0, 55.4, 73.0, 73.9, 87.3, 114.0, 122.5, 126.4, 128.0, 128.6, 128.9, 130.3, 131.6, 133.6, 136.6, 156.6, 170.6; IR (CCl_4) 3500–3200 (NH), 1694 (CON); mass spectrum *m/z* 387 (M^+), 229, 150, 149. Anal. Calcd for $C_{14}H_{21}NO_5S$: C, 62.00; H, 5.46; N, 3.62. Found: C, 59.91; H, 5.38; N, 3.57.

Reaction of *trans*- and *cis*-2-[(4-Methoxyphenyl)imino]-3-methyl-4-phenyloxetanes (*trans*-22 and *cis*-22) with Hydriodic Acid. A. Reaction of oxetane *trans*-**22** (0.198 g, 0.74 mmol) with HI (0.30 mL, 2.29 mmol) gave 0.24 g (0.60 mmol, 81.0% yield) of a mixture of *erythro*-**30**/*threo*-**30** = 73/27. Anal. Calcd for $C_{17}H_{18}INO_2$: C, 51.66; H, 4.59; N, 3.54. Found: C, 51.49; H, 4.52; N, 3.60. *Erythro*-**3-Iodo-*N*-(4-methoxyphenyl)-3-phenylpropionamide (*erythro*-30)**: ^{1}H NMR ($CDCl_3$) δ 1.61 (d, 3 H), 3.11 (m, 1 H), 3.69 (s, 3 H), 5.28 (d, 1 H), 6.8–7.6 (m, 10 H); $J_{2,3}$ = 10.7 Hz, ^{13}C NMR ($CDCl_3$) δ 20.9, 37.4, 52.0, 55.4, 114.0, 122.8, 127.6, 128.2, 128.7, 129.9, 142.8, 156.8, 169.7; IR (CCl_4) 3500–3200 (NH), 1696 (CON); mass spectrum *m/z* 395 (M^+), 267, 149. **B.** Reaction of oxetane *cis*-**22** (0.16 g, 0.60 mmol) with HI (0.25 ml, 1.90 mmol) gave a *threo*/*erythro* = 97/3 mixture of compounds **30**. Chromatography afforded 0.185 g (0.47 mmol, 78.0% yield) of ***threo*-3-iodo-3-phenyl-*N*-(4-methoxyphenyl)-propionamide (*threo*-30)**: mp 139–140 °C (benzene/*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 1.00 (d, 3 H), 3.34 (m, 1 H), 3.77 (s, 3 H), 5.30 (d, 1 H), 6.8–7.6 (m, 10 H); $J_{2,3}$ = 11.1 Hz; ^{13}C NMR ($CDCl_3$) δ 17.1, 33.8, 52.4, 55.5, 114.2, 122.4, 127.8, 128.2, 128.9, 130.5, 141.6, 156.8, 172.5; IR (CCl_4) 3500–3200 (NH), 1696 (CON); mass spectrum *m/z* 395 (M^+), 267, 149. Anal. Calcd for $C_{17}H_{18}INO_2$: C, 51.66; H, 4.59; N, 3.54. Found: C, 51.54; H, 4.66; N, 3.55.

Reaction of *trans*- and *cis*-2-[(4-Methoxyphenyl)imino]-3-methyl-4-phenyloxetane (*trans*-22 and *cis*-22) with Zinc Iodide. A. Reaction of oxetane *trans*-**22** (0.20 g, 0.75 mmol) with ZnI_2 (0.263 g, 0.82 mmol) gave 0.215 g (0.59 mmol, 78% yield) of a mixture of *threo*-**30**/*erythro*-**30** = 47/53. **B.** Reaction of oxetane *cis*-**22** (0.18 g, 0.67 mmol) with ZnI_2 (0.125 g, 0.74 mmol) gave 0.214 g (0.61 mmol, 91% yield) of a mixture of *threo*-**30**/*erythro*-**30** = 83/17.

Reaction of *trans*- and *cis*-2-[(4-Methoxyphenyl)imino]-3-methyl-4-phenyloxetane (*trans*-22 and *cis*-22) with Magnesium Bromide. A. Reaction of oxetane *trans*-**22** (0.10 g, 0.37 mmol) with $MgBr_2{\cdot}Et_2O$ (0.10 g, 0.38 mmol) gave 0.115 g (0.33 mmol, 89% yield) of a mixture of *threo*-**31**/**erythro-31** = 38/62; IR (CCl_4) 3500–3200 (NH), 1695 (CON); mass spectrum *m/z* 348 (M^+), 267, 149, 122. Anal. Calcd for $C_{17}H_{18}BrNO_2$: C, 58.63; H, 5.21; N, 4.02. Found: C, 58.50; H, 5.11; N, 3.95. ***erythro*-3-Bromo-*N*-(4-methoxyphenyl)-2-methylpropionamide (*erythro*-31)**: ^{1}H NMR ($CDCl_3$) δ 1.56 (d, 3 H), 2.97 (m, 1 H), 3.75 (s, 3 H), 5.14 (d, 1 H), 6.6–7.4 (m, 10 H); $J_{2,3}$ = 9.8 Hz; ^{13}C NMR ($CDCl_3$) δ 17.8, 51.8, 55.4, 58.0, 114.0, 122.6, 127.6, 128.6, 128.7, 129.8, 140.2, 156.8, 170.2. **B.** Reaction of oxetane *cis*-**22** (0.13 g, 0.49 mmol) with $MgBr_2{\cdot}Et_2O$ (0.125 g, 0.49 mmol) gave a *threo*/*erythro* = 95/5 mixture of compounds **31**. Chromatography afforded 0.142 g (0.41 mmol, 83% yield) of ***threo*-3-bromo-*N*-(4-methoxyphenyl)-2-methylpropionamide (*threo*-31)**: mp 136–137 °C (benzene/*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 1.04 (d, 3 H), 3.20 (m, 1 H), 3.77 (s, 3 H), 5.19 (d, 1 H), 6.8–7.6 (m, 9 H), 7.7–7.8 (b, 1 H); $J_{2,3}$ = 11.0 Hz; ^{13}C NMR ($CDCl_3$) δ 17.1, 51.3, 55.5, 55.7, 114.2, 122.3, 127.9, 128.7, 128.9, 130.7, 139.5, 156.8, 172.0; IR (CCl_4) 3500–3200 (NH), 1695 (CON); mass spectrum *m/z* 348 (M^+), 267, 149, 122. Anal. Calcd for $C_{17}H_{18}BrNO_2$: C, 58.63; H, 5.21; N, 4.02. Found: C, 58.77; H, 5.27; N, 3.96.

Reaction of *trans*- and *cis*-2-[(4-Methoxyphenyl)imino]-3-methyl-4-phenyloxetane (*trans*-22 and *cis*-22) with Benzenesulfonic Acid. A. Reaction of oxetane *cis*-**22** (0.082 g, 0.31 mmol) with benzenesulfonic acid (0.049 g, 0.31 mmol) gave 0.107 g (0.252 mmol, 81% yield) of a mixture of *threo*-**32**/*erythro*-**32** = 65/35. Anal. Calcd for $C_{23}H_{23}NO_5S$: C, 64.92; H, 5.45; N, 3.29. Found: C, 64.83; H, 5.56; N, 3.23. **B.** Reaction of oxetane *trans*-**22** (0.010 g, 0.37 mmol) with benzenesulfonic acid (0.059 g, 0.38 mmol) gave 0.140 g (0.33 mmol, 89% yield) of a mixture of *threo*-**32**/*erythro*-**32** = 64/36: IR ($CDCl_3$) 3500–3200 (NH), 1650–1690 (CON); mass spectrum *m/z* 285 ($M^+ - C_6H_5SO_2$), 268 ($M^+ - C_6H_5SO_3$), 267, 150, 149. Anal. Calcd. for $C_{23}H_{23}NO_5S$: C, 64.92; H, 5.45; N, 3.29. Found: C, 65.05; H, 5.42; N, 3.36. ***Threo*-Benzenesulfonic acid 2-[(4-methoxyphenyl)carbamoyl]-1-phenylpropyl ester (*threo*-32)**: ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 3 H), 2.84 (m, 1 H), 3.77 (s, 3 H), 5.58 (d, 1 H), 6.8–8.1 (m, 10 H); $J_{2,3}$ = 9.8 Hz; ^{13}C NMR ($CDCl_3$) relevant resonances at δ 14.5, 48.1, 86.2, 170.6. ***Erythro*-Benzenesulfonic acid 2-[(4-methoxyphenyl)carbamoyl]-1-phenylpropyl ester (*erythro*-32)**: ^{1}H NMR ($CDCl_3$) δ 1.34 (d, 3 H), 2.85 (m, 1 H), 3.72 (s, 3 H), 5.57 (d, 1 H), 6.8–8.10 (m, 10 H); $J_{2,3}$ = 8.7 Hz; ^{13}C NMR ($CDCl_3$) relevant resonances at δ 14.2, 49.3, 85.6, 169.8.

Reaction of *trans*- and *cis*-2[(4-Methoxyphenyl)imino]-3-methyloxetane-2-carboxylic Acid Methyl ester (*trans*-23 and *cis*-23) with Benzenesulfonic Acid. A. Reaction of oxetane *trans*-**23** (0.055 g, 0.22 mmol) with benzenesulfonic acid (0.035 g, 0.22 mmol) gave 0.078 g (0.19 mmol, 88% yield) of ***erythro*-2-[(Benzenesulfonyl)oxy]-*N*-(4-methoxyphenyl)-3-methylsuccinamic acid Methyl ester (*erythro*-33)**: mp 90–92 °C (ethyl ether); ^{1}H NMR ($CDCl_3$) δ 1.29 (d, 3 H), 3.0 (m, 1 H), 3.61 (s, 3 H), 3.77 (s, 3 H), 5.2 (m, 1 H), 6.7–7.3 (m, 4 H), 7.4–7.9 (m, 5 H), 7.9–8.1 (b, 1 H); $J_{2,3}$ = 6.9 Hz; ^{13}C NMR ($CDCl_3$) δ 13.0, 44.3, 52.8, 55.5, 78.9, 114.0, 122.0, 128.1, 129.2, 130.4, 134.1, 135.8, 156.7, 168.1, 168.2; IR (CCl_4) 3500–3200 (NH), 1763, 1694 (CON); mass spectrum *m/z* 407 (M^+), 250, 249, 150, 149. Anal. Calcd for $C_{19}H_{21}NO_7S$: C, 56.01; H, 5.20; N, 3.44. Found: C, 55.88; H, 5.28; N, 3.46. **B.** Reaction of oxetane *cis*-**10** (0.035 g, 0.14 mmol) with benzenesulfonic acid (0.023 g, 0.14 mmol) gave 0.048 g (0.12 mmol, 84% yield) of ***threo*-2-[(benzenesulfonyl)-oxy]-*N*-(4-methoxyphenyl)-3-methylsuccinamic acid methyl ester (*threo*-33)**: mp 97–99 °C (ethyl ether); ^{1}H NMR ($CDCl_3$) δ 1.18 (d, 3 H), 2.93 (m, 1 H), 3.74 (s, 3 H), 3.80 (s, 3 H), 4.93 (m, 1 H), 6.7–7.3 (m, 4 H), 7.4–7.9 (m, 5 H), 7.8–8.0 (b, 1 H); $J_{2,3}$ = 8.5 Hz; ^{13}C NMR ($CDCl_3$) δ 13.3, 44.1, 52.8, 55.5, 74.0, 114.0, 121.8, 128.1, 129.2, 130.7, 134.2, 135.1, 156.5, 168.6, 168.7; IR (CCl_4) 3500–3200 (NH), 1763, 1694 (CON); mass spectrum *m/z* 407 (M^+), 250, 249, 150, 149. Anal. Calcd for $C_{19}H_{12}NO_7S$: C, 56.01; H, 5.20; N, 3.44. Found: C, 56.20; H, 5.26; N, 3.39.

Hydriodic Acid-Induced *Erythro* to *Threo* Isomerization of a Erythro/Threo = 74/26 Mixture of β-Iodoamides 30 Obtained after Addition of HI to *trans*-22. Oxetane *trans*-**22** (0.198 g, 0.74 mmol) and HI (0.30 mL, 2.29 mmol) were reacted in CH_2Cl_2 (30 mL) at 25 °C. Aliquots (4 mL) of the reaction mixture were quenched at different times (2 min, 10 min, 1 h, 24 h, and 60 h) with an aqueous solution (5%) of sodium hyrogen sulfite, and the product distribution was determined by ^{1}H NMR spectroscopy.

ZnI_2-Induced *Threo* to *Erythro* Isomerization of threo-30. A mixture of *threo*-**30** (0.16 g, 0.40 mmol) and ZnI_2 (0.14 g, 0.44 mmol) was reacted at 25 °C in THF (20 mL). The reaction mixture was quenched after 3 h with an aqueous solution (5%) of sodium hydrogen sulfite, and the product distribution was determined by ^{1}H NMR spectroscopy.

General Procedure for the Synthesis of β-Lactams. β-Substituted Propionamides and potassium *tert*-butoxide were reacted with THF at −15 °C for the time required (Table 2). The reaction mixture was washed with 5% ammonium chloride solution and dried over magnesium sulfate. The solvent was removed under vacuum (10^{-2} Torr), and the *trans*/*cis* product distribution was evaluated directly on the crude by ^{1}H NMR spectroscopy. All the β-lactams were purified or separated by flash chromatography (SiO_2). In particular, the β-lactams **17** and **18** were purified by flash chromatography using *n*-pentane/

ethyl ether (12:3), while the *trans*/*cis* pairs of β-lactams **34–37** were separated using the following eluants: *n*-pentane/ethyl acetate (2:1) (*trans*-*cis*-**34**, *trans*/*cis*-**36**, and *trans*/*cis*-**37**), and *n*-pentane/ethyl acetate/Et_3N (10.0:1.5:2.5) (*trans*/*cis*-**35**). Reaction conditions, yields, and *trans*/*cis* product distribution of azetidinones **34–37** are given in Table 2. For the microanalytical, MS, IR, ^1H NMR, and ^{13}C NMR spectroscopic data of compounds **34–37** see the supplementary Material (Table 7).

Reaction of 15 with Potassium *tert*-Butoxide. **15** (0.27 g, 0.79 mmol) and potassium *tert*-butoxide (0.11 g, 0.98 mmol) were reacted for 90 min. Flash chromatography gave 0.102 g (0.48 mmol, 61%) of **3,3-Dimethyl-1-*p*-tolyl-4-vinylazetidin-2-one** (**17**): oil; ^1H NMR ($CDCl_3$) δ 1.10 (s, 3 H), 1.33 (s, 3 H), 2.29 (s, 3 H), 4.16 (d, 1 H), 5.35–5.46 (m, 2 H), 5.77–5.96 (m, 1 H), 7.0–7.4 (m, 9 H); $J_{4,5}$ = 7.7 Hz; $J_{trans\text{-}5,6}$ = 17.3, $J_{cis\text{-}5,6}$ = 10.1 Hz; ^{13}C NMR ($CDCl_3$) δ 17.7, 20.8, 22.4, 54.4, 65.4, 117.0, 120.1, 129.4, 133.1, 134.1, 136.0, 166.3; IR (CCl_4) 1744 (C=O); mass spectrum *m*/*z* 215 (M^+), 133. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.95; H, 8.04; N, 6.48.

Reaction of 16 with Potassium *tert*-Butoxide. **16** (0.24 g, 0.67 mmol) and potassium *tert*-butoxide (0.091 g, 0.81 mmol) were reacted for 90 min. Flash chromatography gave 0.126 g (0.55 mmol, 68%) of a mixture of azetidinones **18** (*trans*-4-propenyl/*cis*-4-propenyl = 2.8): IR (CCl_4) 1752 (C=O), 1515; mass spectrum *m*/*z* 229 (M^+), 133. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.60; H, 8.31; N, 6.20. ***trans*-4-Propenyl-3,3-dimethyl-1-*p*-tolylazetidin-2-one** (***trans*-18**): oil; ^1H NMR ($CDCl_3$) δ 1.18 (s, 3 H), 1.37 (s, 3 H), 1.78 (dd, 3 H), 2.29 (s, 3 H), 4.12 (d, 1 H), 5.48 (m, 1 H), 5.89 (m, 1 H), 7.05–7.35 (m, 4 H); $J_{4,5}$ = 8.3 Hz, $J_{5,6}$ = 15.3 Hz, $J_{4,6}$ = 0.7 Hz, $J_{5,Me}$ = 1.7 Hz, $J_{6,Me}$ = 6.5 Hz; ^{13}C NMR ($CDCl_3$) δ 17.8, 18.0, 20.9, 22.4, 54.3, 65.2, 117.0, 126.9, 129.3, 131.7, 133.0, 136.1, 171.3. ***cis*-4-Propenyl-3,3-dimethyl-1-*p*-tolylazetidin-2-one** (**cis-18**): oil; ^1H NMR ($CDCl_3$) δ 1.18 (s, 3 H), 1.42 (s, 3 H), 1.81 (dd, 3 H), 2.29 (s, 3 H, Me), 4.5 (m, 1 H), 5.45 (m, 1 H), 5.88 (m, 1 H), 7.0–7.4 (m, 4 H arom); $J_{4,5}$ = 8.8 Hz, $J_{5,6}$ = 11.2 Hz, $J_{4,6}$ = 1.2 Hz, $J_{5,Me}$ = 1.8 Hz, $J_{6,Me}$ = 7.0 Hz; ^{13}C NMR ($CDCl_3$) δ 13.7, 17.9, 20.9, 22.6, 54.3, 59.9, 116.7, 126.7, 129.5, 130.3, 133.5, 135.8, 171.2.

Reaction of a *threo*/*erythro*-30 Mixture (1.8:1.0) with Potassium *tert*-Butoxide. The *threo*/*erythro* = 1.8 mixture of amides **30** (0.140 g, 0.33 mmol) and potassium *tert*-butoxide (0.039 g, 0.35 mmol) were reacted for 2 h. The ^1H NMR analysis of the crude reaction mixture revealed the presence of a mixture of *trans*-**37**/*cis*-**37** = 0.78. Flash chromatography gave *cis*-**37** (0.049 g, 0.18 mmol, 52%) and *trans*-**37** (0.035 g, 0.13 mmol, 39%).

Cis to *Trans* Isomerization of *cis*-1-(4-Methoxyphenyl)-3-methyl-4-propylazetidin-2-one (*cis*-34) with Potassium *tert*-Butoxide. *cis*-**34** (0.05 g, 0.215 mmol) and potassium *tert*-butoxide (0.031 g, 0.28 mmol) were reacted at 0 °C for 3 h. An ^1H NMR analysis of the crude reaction mixture revealed the presence of both *trans*-**34** and ***cis*-34** in a *cis*/*trans* = 13/87 ratio. Flash chromatography gave 0.042 g (0.18 mmol, 84% yield) of *trans*-**34** and 0.006 g (0.026 mmol, 12% yield) of *cis*-**34**.

***Trans* to *Cis* Isomerization of *trans*-1-(4-Methoxyphenyl)-3-methyl-4-propylazetidin-2-one (*trans*-34) with Potassium *tert*-Butoxide.** *trans*-**34** (0.05 g, 0.215 mmol) and potassium *tert*-butoxide (0.031 g, 0.28 mmol) were reacted at 0 °C for 3 h. An ^1H NMR analysis of the crude reaction mixture revealed the presence of both *trans*-**34** and ***cis*-34** in a *cis*/*trans* = 13/87 ratio. Flash chromatography gave 0.040 g (0.17 mmol, 80% yield) of *trans*-**34** and 0.006 g (0.026 mmol, 12% yield) of *cis*-**34**.

Supplementary Material Available: Table 5 (MS, IR, ^1H NMR, and ^{13}C NMR spectroscopic data of 2-iminooxetanes **1** and **14** and microanalytical data of **1**), Table 6 (microanalytical, MS, IR, ^1H NMR, and ^{13}C NMR spectroscopical data of β-substituted propionamides **5–9**, **11**, and **25–27**), Table 7 (microanalytical, MS, IR, ^1H NMR, and ^{13}C NMR spectroscopical data of β-lactams **34–37**), and Table 8 (complete peak assignments of ^1H NMR and ^{13}C NMR spectroscopic data of β-substituted propionamides **4**, **10**, **12**, **15**, **16**, **24**, and **28–33** and of β-lactams **17** and **18**) (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.