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Nucleophilic Ring-Opening of Epoxide and Aziridine Acetates for the Stereodivergent Synthesis of β-Hydroxy and β-Amino γ-Lactams

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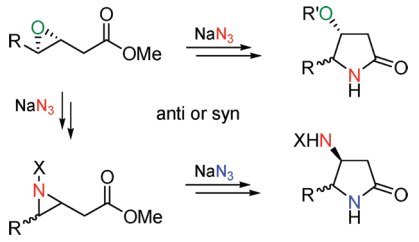

A highly regio- and stereoselective synthesis of novel β,γ-disubstituted γ-lactams with either an *anti* or *syn* relative configuration was developed from readily available epoxide and aziridine acetates. The key steps include the regio- and diastereocontrolled nucleophilic ring-opening of these three-membered heterocycles followed by mild reductive cyclization of the γ-azido ester intermediate. The method was also extended to an asymmetric synthesis of (4*R*,5*S*)-4-hydroxy-5-phenylpyrrolidin-2-one from a chiral epoxide acetate. The main features of this versatile synthesis of functionalized γ-lactams include the involvement of inexpensive reagents and mild conditions together with high chemical efficiency.

Introduction

Multifunctionalized γ-lactams are present as substructural units in biologically active substances and are also important intermediates for the synthesis of a variety of nitrogenated heterocycles that are considered as privileged scaffolds for drug discovery.[1,2] In particular, β-hydroxy and β-amino γ-lactams, as well as their acyclic forms such as γ-amino-β-hydroxy and β,γ-diamino acids, are structurally related to the renin-inhibitor statines and also have unique properties as peptidomimetics or as constituents of biologically active molecules.[3] Furthermore, the reduced form of γ-lactams provides an access to the pyrrolidine family of alkaloids.[4,5] The relative and absolute stereochemistry of the ring substituents, as well as their chemical nature, play critical roles in the biological properties of γ-lactams and analogues. Therefore, the development of efficient methods to synthesize highly functionalized γ-lactams bearing stereochemically tailored functional groups has been pursued by organic and bioorganic chemists.[6]

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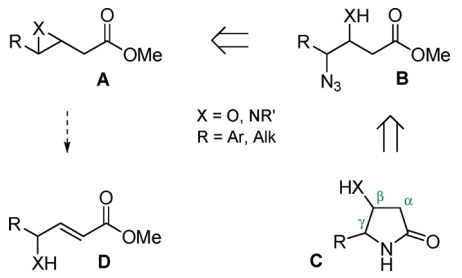
SCHEME 1. **β,γ-Disubstituted γ-Lactams from Epoxide and Aziridine Acetates**



Most of the synthetic approaches to β-hydroxy and β-amino γ-lactams can be divided into two main categories: functionalization of preexisting heterocyclic cores, such as tetramic acids[7] or malimides,[5,8] and annulation from acyclic precursors. In the latter case, the reductive cyclization of γ-nitro[9] and, more frequently, γ-azido esters[2,4,10] has become very appealing as a synthetic strategy due to the facility with which the cyclization occurs under relatively mild conditions. However, many of these methods suffer from drawbacks such as the lack of structural generality, limited availability of substrates (which must be prepared by multistep synthesis), and low selectivity for the assembly of azide or nitro motifs.

The nucleophilic ring-opening of heterocyclic three-membered rings (oxiranes, aziridines) has been widely explored for the construction of two adjacent stereogenic centers.[11] We thus envisioned that the chemo-, regio-, and diastereoselective ring-opening of epoxide and aziridine acetates **A** by the azide anion would lead to *anti*-γ-azido-β-hydroxy and *anti*-β-amino-γ-azido esters **B**, which are able to undergo reductive cyclization to β,γ-disubstituted γ-lactams **C** with *anti* configuration (Scheme 1).

This versatile approach allows the opportunity to explore a diastereodivergent process to obtain the isomeric *syn*-disubstituted γ-lactams based on a double inversion of the configuration, with the use of bromine as the nucleophile in the ring-opening of **A** at the secondary C-γ carbon followed by halide displacement by azide.[12]

While the azidolysis and bromolysis of epoxides and aziridines derived from α,β-unsaturated acids and esters have been well reported in the literature,[13] the behavior of the homologous epoxide and aziridine acetates **A** (Scheme 1) under nucleophilic attack has been much less documented. In fact, only a limited number of papers deal with the synthesis of epoxide[14,15] and aziridine[16] acetates and their reactivity in the presence of nucleophiles.

Therefore, several issues need to be addressed in relation to the synthetic plan depicted in Scheme 1. One of these involves the regioselectivity of the attack (C-β × C-γ) which for vicinal dialkyl substituted epoxides and aziridines is not easy to overcome.[17] Another issue is related to the control of stereoselectivity in the ring-opening of aryloxiranes (R = aryl), as the previous work carried out by Crotti, Macchia, and coworkers[18] has established that the *syn* × *anti* attack cannot be precisely anticipated because of its dependence on multiple factors, such as the substrate structure, the nucleophile, the solvent, the catalyst, and the temperature. Finally, the acidic character of the α-methylene group in epoxide and aziridine acetates **A** may influence the course of the ring-opening and a competitive rearrangement to γ-hydroxy- and γ-amino-α,β-unsaturated esters **D** would be expected in basic medium.[15a,19]

In this context, we describe herein the synthesis of a variety of multifunctionalized γ-lactams from epoxide and aziridine acetates, wherein the nucleophilic ring-opening of these three-membered heterocycles is the key step to the overall efficiency of the process. The synthetic utility of this strategy was then showcased by selective additional transformations, including O- and N-functionalization of γ-azido esters prior to lactamization and the asymmetric preparation of a chiral β-hydroxy γ-lactam, as described below.

Results and Discussion

Preparation and Ring-Opening of Epoxide Acetates. The aryl-substituted epoxide acetate (±)**-1a** and the alkyl analogue

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(20) Both β,γ-unsaturated esters **2a** and **2b** were prepared by esterification ($MeOH/H_2SO_4$) of the corresponding β,γ-unsaturated carboxylic acids (see the Experimental Section).

TABLE 1. Reactivity of Epoxide Acetate (±)-1a: Azidolysis[a]

entry	NaN_3 (equiv)	additive (equiv)	solvent	temp (°C)	time (h)	(±)-3a-*anti*	(±)-3a-*syn*	4a	5
1	2.5		PEG-400	25	0.8	1	0	80	19
2	3.0		$MeOH/H_2O$[b]	80	3	0	0	83	17
3		DABCO (2.0)	DMF	25	3	0	0	50	50[c]
4		DABCO (2.0)	DMF	25	20	0	0	0	100
5	3.0	$Mg(ClO_4)_2$ (2.5)	CH_3CN	80	3	86	14	0	0
6	3.0	NH_4Cl (2.0)	$MeOH/H_2O$[b]	80	3	97[d]	0	3	0
7	3.0	NH_4Cl (2.0)	$EtOH/H_2O$[b]	80	3	97	0	3	0
8	3.0	NH_4Cl (1.5)	$MeOH/H_2O$[b]	μW[e]	0.1[f]	96	0	4	0

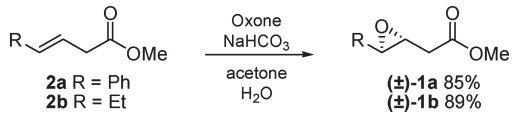
[a]The relative product distribution (%) was determined by ^1H NMR integration (400 MHz, $CDCl_3$). [b]Ratio ROH/H_2O = 8:1. [c]At 50% conversion. [d]Compound (±)-**3a-*anti*** was isolated in 91% yield. [e]Maximum temperature displayed on the microwave reactor was 80 °C. [f]Total reaction time after three pulsed irradiations of 2 min each (does not include the ramp period of 1 min), with intervals of 10−15 min between each pulse (1.5 mmol scale).

(±)-**1b** were chosen as model compounds which were prepared by direct epoxidation of the corresponding β,γ-unsaturated esters[20] **2a** and **2b** (Scheme 2). Although the use of *m*-CPBA has been reported for the epoxidation of related β,γ-unsaturated esters,[14,15c−e] the safety concerns associated with peroxyacids, as well as the difficulty in attaining yields higher than 60%, have led to the application of a much more accessible and reliable method for the epoxidation of **2**. Thus, epoxides (±)-**1** with *anti* configuration were cleanly obtained in high yields when dimethyldioxirane, generated in situ from the combination of Oxone with acetone, was employed as the oxidant in aqueous medium under alkaline pH.[21] This simple methodology allows the preparation of epoxides (±)-**1a** and (±)-**1b** in multigram scale, and, more importantly, was amenable for adaptation to an asymmetric version (vide infra).

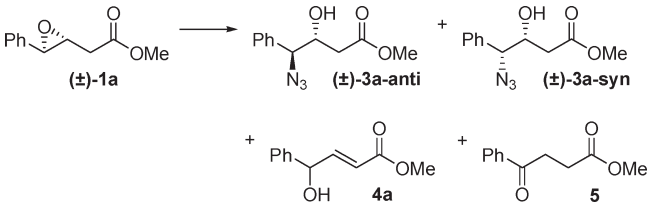
The ring-opening reaction of epoxide (±)-**1a** to produce the desired azido alcohol (±)-**3a-*anti*** was then thoroughly studied and several reaction conditions were screened (Scheme 3). The azidolysis of epoxide (±)-**1a** mediated by molecular sieves in CH_3CN at 25 °C was initially attempted,[22] but only the starting epoxide was recovered even after 24 h. On the other hand, the use of PEG-400 as the reaction medium[23] led to a base-mediated opening of the epoxide (±)-**1a** to give the rearranged allylic alcohol **4a**[24] as the main component in the reaction mixture (Table 1, entry 1), possibly due to the basic character of the azide anion. Interestingly, the observation of small amounts of the isomeric methyl β-benzoylpropionate[25] (**5**) in the crude reaction was also related to the basic character of the medium, a profile that was similarly observed in hydroxylic solvents at high temperature (entry 2). Indeed, treatment of the epoxide (±)-**1a** with an actual base such as DABCO furnished a complete conversion to the rearranged keto derivative **5** through the intermediacy of allylic alcohol **4a** (entries 3 and 4).

A great enhancement in the conversion to (±)-**3a-*anti*** was achieved with the use of an additive with moderate Lewis acidity[14,17d] (Table 1, entry 5). However, the stabilization of a possible coordinated intermediate[18] was so pronounced that it brought about the competitive formation of the epimer (±)-**3a-*syn***. The narrow balance between reactivity and selectivity was finally reached with the use of a classical combination of NaN_3

SCHEME 2. Epoxidation of β,γ-Unsaturated Esters 2



SCHEME 3. Azidolysis of Epoxide Acetate (±)-1a



and NH_4Cl in aqueous methanolic medium[26] (entry 6). In this case, the diastereoselectivity was exclusive in favor of (±)-**3a-*anti*** and only traces of the allylic alcohol **4a** were noted in the crude reaction mixture. The reaction was very clean and pure azido alcohol (±)-**3a-*anti*** was readily obtained in excellent yield after filtration on a pad of silica gel.

Other variations in the reaction conditions, including changes in the relative ratio of the reagents, resulted in no further benefits, but two modifications merit additional comments. First, the NH_4Cl-mediated azidolysis of epoxide (±)-**1a** could also be carried out in an 8:1 mixture of ethanol/H_2O (Table 1, entry 7), thus replacing methanol with a less toxic solvent from renewable resources. Second, the same azidolysis was also adapted to a monomode microwave reactor in order to circumvent the energy requirements of the prolonged reflux. While the reaction gave the expected (±)-**3a-*anti*** with similar selectivity to that obtained with conventional heating in an oil bath, the use of microwave irradiation allowed a much faster transformation (entry 8). However, due to the dimensions of the microwave reactor the scalability was restricted to 1.5 mmol of substrate per batch, which is ca. 10 times less than the multigram scale routinely prepared under conventional heating.

For the azidolysis of the less reactive vicinal dialkyl-substituted epoxide (±)-**1b**, a different set of results was collected. In all cases studied, the *anti*-γ-azido-β-hydroxy ester (±)-**3b-*anti*** was the only isomer detected, and the competitive formation of byproducts **4b** and **6**, originating from elimination reactions,

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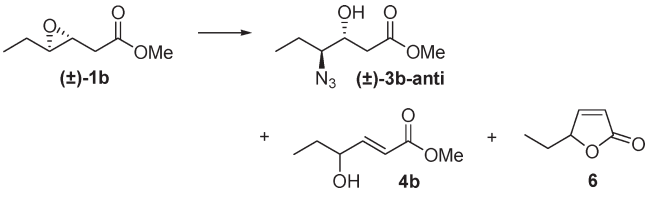
TABLE 2. Reactivity of Epoxide Acetate (±)-1b: Azidolysis[a]

entry	NaN_3 (equiv)	additive (equiv)	solvent	temp (°C)	time (h)	(±)-**3b-*anti***	**4b**	**6**
1	3.0	NH_4Cl (2.0)	$MeOH/H_2O$[b]	80	8	84	12	4
2	3.0		$MeOH/H_2O$[b]	80	8	13	85	2[c]
3		DABCO (2.0)	DMF	25	22	0	100	0
4	1.5	$Mg(ClO_4)_2$ (5.0)	CH_3CN	80	18	99	0	1
5	3.0	$Mg(ClO_4)_2$ (2.5)	CH_3CN	80	8	100[d]	0	0
6	3.0	$Mg(ClO_4)_2$ (2.5)	CH_3CN	μW[e]	0.1[f]	97	2	1

[a]The relative product distribution (%) was determined by ^1H NMR integration (400 MHz, $CDCl_3$). [b]Ratio $MeOH/H_2O$ = 8:1. [c]Unidentified byproducts were also noted. [d]Compound (±)-**3b-*anti*** was isolated in 73% yield. [e]Maximum temperature displayed on the microwave reactor was 80 °C. [f]Total reaction time after three pulsed irradiations of 2 min each (does not include the ramp period of 1 min), with intervals of 10−15 min between each pulse (0.7 mmol scale).

SCHEME 4. Azidolysis of Epoxide Acetate (±)-1b

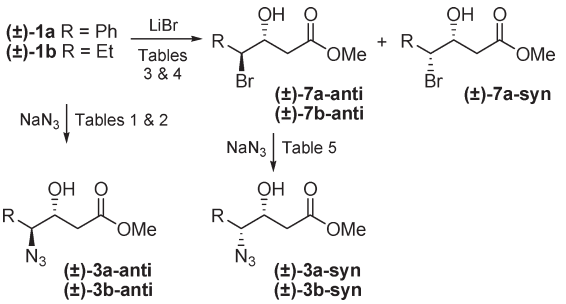


was susceptible to the reaction condition employed (Scheme 4 and Table 2). In contrast to the method described above for the aryl derivative (±)-**1a**, the methanolic solution of NaN_3/NH_4Cl did not provide a good environment for the selective preparation of (±)-**3b-*anti***, which was also accompanied by allylic alcohol **4b**[24] in non-negligible amounts (entry 1), as previously noted by Crotti and co-workers.[14] In our case, however, we also detected the coformation of the γ-butenolide **6**[27] as another contaminant. The effect of the basic character of NaN_3 on the reaction mode was made evident by running a control without the buffering presence of NH_4Cl, which gave the allylic alcohol **4b** as the major product (entry 2). Similarly to the aryl epoxide (±)-**1a**, by forcing the opening of the epoxide (±)-**1b** with DABCO in DMF a complete conversion to the allylic alcohol **4b** was observed (entry 3) but, differently from **4a**, the formation of the corresponding β-acyl propionate from a consecutive allylic rearrangement of **4b** was not observed.

To enhance the reactivity of epoxide acetate (±)-**1b** toward nucleophiles and at the same time reduce its propensity to undergo rearrangement to the allylic alcohol **4b**, Crotti employed $Mg(ClO_4)_2$ as an effective additive to control the reaction outcome.[14] By applying the stated conditions, the near exclusive production of azido alcohol (±)-**3b-*anti*** was indeed achieved (Table 2, entry 4), although the isolated yield never reached the previously reported value of 86%,[14] even after several trials. This was partially solved with the use of half the original quantity of the magnesium salt promoter and twice as much of the azide anion (entry 5). Under these optimized conditions the azidolysis could be run in up to 8 h with good yields and complete selectivity.

Since the reaction is very slow either in the absence of the Mg(II) promoter or without extensive heating (results not shown), we adapted the azidolysis of (±)-**1b** to the microwave reactor under similar conditions employed for the aryl-substituted epoxide (±)-**1a** (Table 2, entry 6). However, the transformation was very susceptible to subtle variations. For instance, the use of sequential pulses (no intervals between each irradiation), or more prolonged periods of irradiation, as well as attempts to scale-up, caused the unavoidable generation of the byproducts **4b**/**6** or the incomplete consumption of the starting epoxide (±)-**1b** (results not shown). This lack of scalability was, to a great extent, due to the restricted solubility of $Mg(ClO_4)_2$ in CH_3CN, which precluded the efficient mixture of reagents inside the microwave vial. Nevertheless, gram-scale azidolysis of (±)-**1b** could be readily performed under conventional reflux by the parameters presented in Table 2, entry 5.

SCHEME 5. Diastereodivergent Strategy for the Synthesis of β-Hydroxy-γ-Azido Esters



The successful diastereoselective preparation of the γ-azido esters (±)-**3a-*anti*** and (±)-**3b-*anti*** from the corresponding epoxide acetates (±)-**1a** and (±)-**1b** stimulated the extension of this strategy to other nucleophiles. In this regard, a double inversion of the configuration at the secondary C-γ carbon in (±)-**1**, obtained through initial ring-opening with bromine and subsequent displacement by azide, would lead to a versatile route to the diastereoisomers (±)-**3a** and (±)-**3b** with *syn* configuration, providing that selectivity is controlled in the whole process[28] (Scheme 5).

Therefore, treatment of aryl-substituted epoxide acetate (±)-**1a** with an excess of LiBr and NH_4Cl in $MeOH/H_2O$ (under similar conditions to the azidolysis reaction) furnished the desired bromohydrin (±)-**7a-*anti***, albeit with the simultaneous generation of a complex mixture of unidentified byproducts. Attempts to carry out the bromolysis of (±)-**1a** with LiBr in combination with HOAc[29a] or SiO_2[29b] led to slow reactions and a mixture of products. More conventional methodologies under strongly acidic conditions[29c] (Table 3,

(27) Liu, H.; Tan, C.-H. *Tetrahedron Lett.* **2007**, *48*, 8220–8222.

(28) (a) Yamaguchi, T.; Harada, N.; Ozaki, K.; Hayashi, M.; Arakawa, H.; Hashiyama, T. *Tetrahedron* **1999**, *55*, 1005–1016. (b) Righi, G.; D'Achille, C.; Pescatore, G.; Bonini, C. *Tetrahedron Lett.* **2003**, *44*, 6999–7002. (c) Ha, J. D.; Kim, S. Y.; Lee, S. J.; Kang, S. K.; Ahn, J. H.; Kim, S. S.; Choi, J.-K. *Tetrahedron Lett.* **2004**, *45*, 5969–5972.

(29) (a) Bajwa, J. S.; Anderson, R. C. *Tetrahedron Lett.* **1991**, *32*, 3021–3024. (b) Kotsuki, H.; Shimanouchi, T. *Tetrahedron Lett.* **1996**, *37*, 1845–1848. (c) Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Tetrahedron* **1992**, *48*, 3805–3812. (d) Palumbo, G.; Ferreri, C.; Caputo, R. *Tetrahedron Lett.* **1983**, *24*, 1307–1310. (e) Lupattelli, P.; Bonini, C.; Caruso, L.; Gambacorta, A. *J. Org. Chem.* **2003**, *68*, 3360–3362. (f) Righi, G.; Chionne, A.; D'Achille, R.; Bonini, C. *Tetrahedron: Asymmetry* **1997**, *8*, 903–907.

TABLE 3. Reactivity of Epoxide Acetate (±)-1a: Bromolysis[a]

entry	source of Br (equiv)	additive (equiv)	solvent	temp (°C)	time (min)	(±)-7a-*anti*	(±)-7a-*syn*
1	HBr[b]		$CHCl_3$	25	10	55	45
2	CBr_4 (2.5)	PPh_3 (5.5)	CH_2Cl_2	25	20	65	35
3	LiBr (4.0)	*p*-TsOH (2.0)	CH_3CN	25	10	75	25
4	LiBr (4.0)	Amberlist 15[c]	CH_3CN	−15	12	90	10
5	LiBr (4.0)	Amberlist 15[c]	THF	−15	60	98	2
6	LiBr (3.0)	$Mg(ClO_4)_2$ (2.5)	CH_3CN	0−25	20	96	4

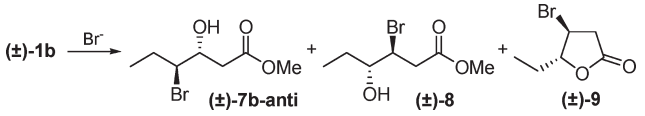
[a]The relative product distribution (%) was determined by ^{1}H NMR integration (400 MHz, $CDCl_3$). [b]48% aq HBr/substrate (±)-**1a** = 1.0 mL/mmol. [c]Amberlist 15/substrate (±)-**1a** = 440 mg/mmol.

TABLE 4. Reactivity of Epoxide Acetate (±)-1b: Bromolysis[a]

entry	source of Br (equiv)	additive (equiv)	solvent	temp (°C)	time (h)	(±)-7b-*anti*	(±)-8	(±)-9
1	LiBr (3.0)	$Mg(ClO_4)_2$ (2.5)	CH_3CN	0−25	1	100	0	0[b]
2	LiBr (4.0)	Amberlist 15[c]	THF	−15	1	70	30	0
3	LiBr (2.0)	98% H_2SO_4 (2.5)	CH_3CN	25	2.5	75	0	25
4	HBr[d]		$CHCl_3$	25	0.5	95	0	5

[a]The relative product distribution (%) was determined by ^{1}H NMR integration (400 MHz, $CDCl_3$). [b]Small amounts of allylic alcohol **4b** and lactone **6** were also noted (ca. 1−2% each). [c]Amberlist 15/substrate (±)-**1b** = 440 mg/mmol. [d]48% aq HBr/substrate (±)-**1b** = 1.0 mL/mmol.

SCHEME 6. Bromolysis of Epoxide Acetate (±)-1b



entry 1) or nearly neutral conditions[29d] (entry 2) gave clean conversions to bromohydrins (±)-**7a-*anti***, although with the concurrent formation of isomer (±)-**7a-*syn***. Interestingly, slightly better figures were observed with *p*-TsOH in acetonitrile (entry 3), while the use of a resin-supported sulfonic acid[29e,f] at subzero temperatures led to a much improved selectivity (entry 4).

Other conditions, including variations in the temperature and in the relative stoichiometry of the bromine salt and additive, did not give better *anti*/*syn* ratios (results not shown). However, the simple replacement of acetonitrile with THF as the solvent resulted in a dramatic improvement in the diastereoselectivity (Table 3, entry 5). Surprisingly, the use of $Mg(ClO_4)_2$ as the additive, which was found to induce the undesirable *syn* attack in the azidolysis of aryl epoxide (±)-**1a** with generation of the (±)-**3a-*syn*** isomer, was able to mediate the near exclusive formation of the bromohydrin (±)-**7a-*anti*** (entry 6).

For the bromolysis of the vicinal dialkyl substituted epoxide acetate (±)-**1b**, $Mg(ClO_4)_2$ showed superior activity in promoting fast ring-opening with excellent regio- as well as diastereoselectivity[30] (Scheme 6 and Table 4, entry 1). In contrast to the total regioselectivity obtained for the aryl epoxide (±)-**1a**, the methodology with Amberlist 15 furnished a 70:30 mixture of the regioisomers (±)-**7b-*anti*** and (±)-**8** (entry 2). It is also worth mentioning that regioselectivity was an issue when strong acids[29c] were present (entries 3 and 4), but in these cases the preformed regioisomer (±)-**8** underwent cyclization under acidic conditions to the known β-bromo γ-lactone (±)-**9**.[31]

(30) To compare the relative nucleophilicity of azide versus bromide ions in the $Mg(ClO_4)_2$-mediated bromolysis of epoxide acetate (±)-**1b**, the reaction was carried out with NaBr (to correlate NaN_3), which was shown to be as good as LiBr. These observations support the fact that bromide ion is much more nucleophilic than azide under the studied conditions, with the former consuming the epoxide (±)-**1b** in 1 h at 0−25 °C (Table 4, entry 1) while the latter takes 8 h at 80 °C (Table 2, entry 5).

(31) Mellegaard, S. R.; Tunge, J. A. *J. Org. Chem.* **2004**, *69*, 8979–8981.

TABLE 5. Reactivity of γ-Bromo-β-hydroxy Ester (±)-7b-*anti*: Displacement by Azide[a,b]

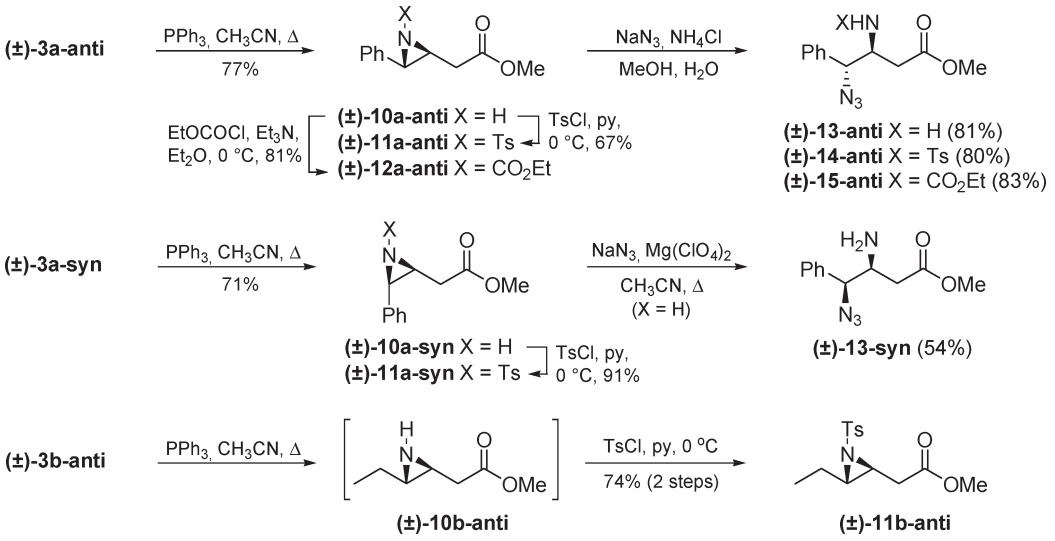
entry	additive (equiv)	solvent	temp (°C)	time (h)	(±)-3b-*syn*	(±)-3b-*anti*
1		DMF	25	120	92	8[c]
2		DMF	60	24	90	10[c]
3	β-CD (0.1)	DMF	60	24	92	8
4	β-CD (0.5)	DMF	25	96	93	7[c]
5	β-CD (0.2)	DMF	40	24	94	6[c]
6	Bu_4NHSO_4 (0.2)	DMF	40	24	94	6
7	β-CD (0.2)	DMSO	40	36	98[d]	2[c]

[a]The relative product distribution (%) was determined by ^{1}H NMR integration (400 MHz, $CDCl_3$). [b]All reactions were carried out with 3.0 equiv of NaN_3. [c]Small amounts of allylic alcohol **4b** and lactone **6** were also noted (ca. 1−2% each). [d]Compound (±)-**3b-*syn*** was isolated as an inseparable mixture with (±)-**3b-*anti*** (98:2) in a combined yield of 72%.

No attempts were made to purify the bromohydrins (±)-**7a-*anti*** and (±)-**7b-*anti*** due to their high overall quality and also to avoid decomposition of these potentially labile compounds. Both the aryl and alkyl bromohydrins (±)-**7a-*anti*** and (±)-**7b-*anti***, respectively, were treated with NaN_3 in DMF at 25 °C in order to prepare the corresponding azido alcohols (±)-**3a-*syn*** and (±)-**3b-*syn*** through an S_N2-type mechanism (Scheme 5). For (±)-**7a-*anti***, this was indeed the case and after 7 h the azido alcohol (±)-**3a-*syn*** was obtained with the same diastereomeric ratio as the initial bromohydrin (±)-**7a-*anti***, thus supporting the fact that no epimerization occurred during the bromide displacement.

The alkyl-derived bromohydrin (±)-**7b-*anti*** was much less reactive than the corresponding aryl-substituted (±)-**7a-*anti*** and a complete conversion to the azido alcohol (±)-**3b-*syn*** was only achieved by running the reaction with NaN_3 in DMF for 5 days at 25 °C (Table 5, entry 1) or at higher temperatures (entry 2). However, this was also compromised by the fact that small amounts of the undesired diastereoisomer (±)-**3b-*anti*** were observed in the crude reaction. Since it is not common to obtain retention-type products from halide displacement by nucleophiles under conventional S_N2 conditions,[28] the formation of the unwanted (±)-**3b-*anti*** might involve the intramolecular cyclization of bromohydrin (±)-**7b-*anti*** in basic medium to give back the epoxide (±)-**1b** as a reactive intermediate[28a] that can be stereoselectively reopened by azide.[32]

SCHEME 7. Preparation of Aziridine Acetates and Ring-Opening with Azide Anion



To increase the nucleophilicity of the azide anion, a catalytic amount of β-cyclodextrin (β-CD) was added to the reaction mixture. Both the temperature and the relative amount of β-CD exerted limited influence on the reaction rate as well as on the selectivity (Table 5, entries 3−5). After some experimentation we found that acceptable diastereoselectivity for (±)-**3b-*syn***/(±)-**3b-*anti*** (> 15:1 ratio) was achieved with 0.2 equiv of β-CD in DMF at 40 °C (entry 5). Results of similar magnitude were also observed when a phase-transfer catalyst was used (entry 6). Gratifyingly, replacing DMF with the more polar DMSO resulted in much better selectivity in favor of (±)-**3b-*syn*** (47:1) with a small penalty in terms of the reaction time (entry 7).

Preparation and Ring-Opening of Aziridine Acetates. The development of methodologies to access structurally and stereochemically diverse frameworks is an important contribution in diversity-oriented synthesis. We envisioned that, similarly to the epoxide acetates (±)-**1** described above, the aziridine acetates could serve as precursors to β,γ-diamino acid analogues **B** and β-amino γ-lactams **C** (see Scheme 1), which are recognized to be of biological importance.[6a,7a] This sets the stage for considerable interest in the stereocontrolled synthesis of aziridine acetates directly from the azido alcohols (±)-**3**, which were previously obtained from the ring-opening of epoxides (±)-**1** with azide (*anti* isomers) as well as those from the bromine displacement by azide (*syn* isomers).

Accordingly, the Staudinger reaction of vicinal azido alcohol (±)-**3a-*anti*** with triphenylphosphine in anhydrous acetonitrile under reflux furnished the *N*H-aziridine (±)-**10a-*anti*** in a steroselective manner[33,34] (Scheme 7). Azido alcohols (±)-**3a-*syn*** and (±)-**3b-*anti*** were similarly transformed into their corresponding *N*H-aziridines (±)-**10a-*syn*** and (±)-**10b-*anti*** as the sole products.[35] However, purification of vicinal dialkyl substituted *N*H-aziridine (±)-**10b-*anti*** was found to be problematic due to its low molecular weight. In this case (±)-**10b-*anti*** was tosylated in situ, allowing the isolation of *N*-tosyl aziridine (±)-**11b-*anti*** in good overall yield (Scheme 7). Tosylation of diastereomerically pure *N*H-aziridines (±)-**10a-*anti*** and (±)-**10a-*syn*** also proceeded cleanly to furnish *N*-tosylates (±)-**11a-*anti*** and (±)-**11a-*syn*** in moderate to good yields. Additionally, *N*H-aziridine (±)-**10a-*anti*** reacted with ethyl chloroformate in basic medium to give the carbamate (±)-**12a-*anti***.

Next, we explored the nucleophilic ring-opening of selected aziridine acetates with N_3^- in order to obtain β-amino-γ-azido esters as precursors of functionalized γ-lactams. Accordingly, *N*H-aziridine (±)-**10a-*anti***, as well as the activated derivatives (±)-**11a-*anti*** and (±)-**12a-*anti***, reacted with NaN_3/NH_4Cl in aqueous methanol under standard conditions to furnish the expected γ-azido esters (±)-**13-*anti***, (±)-**14-*anti***, and (±)-**15-*anti*** in good yields (Scheme 7).[36] In general, the aryl aziridines with *anti* configuration proved to be more reactive than the corresponding aryl epoxide (±)-**1a**, with the *N*-tosyl derivative (±)-**11a-*anti*** being the most reactive among the aziridines studied.[33a]

On the other hand, the ring-opening of vicinal dialkyl substituted aziridine acetate (±)-**11b-*anti*** and the *N*-tosyl aziridine acetate (±)-**11a-*syn*** with use of the NaN_3/NH_4Cl combination in aqueous methanol led to a mixture of products. Furthermore, $Mg(ClO_4)_2$ also failed to promote the azidolysis of (±)-**11b-*anti***. In the case of the less reactive *N*H-aziridine (±)-**10a-*syn***, a clean conversion to β-amino-γ-azido ester (±)-**13-*syn*** was successfully achieved with NH_4Cl as the additive after 5 h, while the use of $Mg(ClO_4)_2$ gave equally

(32) Attempts to neutralize the basic character of the reaction due to the presence of the azide anion were made by adding acidic species (H_2SO_4, HOAc, or TMSCl) under a variety of solvents (DMF, acetone, water, and aqueous solutions), but the several methodologies tested gave poor results.

(33) (a) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247–258. (b) Pöchlauer, P.; Müller, E. P.; Peringer, P. *Helv. Chim. Acta* **1984**, *67*, 1238–1247.

(34) Interestingly, preferential formation of aziridine acetate was observed even when acetonitrile with high water content was used as the reaction medium. This observation implies that, under the studied conditions, the intermediate iminophosphorane (see refs 10c and 15e) did not suffer hydrolysis, which might lead to the corresponding γ-amino ester and ultimately to the γ-lactam (±)-**16a-*anti*** by spontaneous cyclization (see Scheme 8).

(35) The relative stereochemistry of the ring substituents in the aziridines was determined by ^{1}H NMR on the basis of literature reports. For instance, the coupling constants observed for the methyne protons in the isomeric *anti*-(3.0−4.0 Hz) and *syn*-aziridines (6.5−7.2 Hz) were of similar magnitudes as the model compounds found in the literature: (a) Dalili, S.; Yudin, A. K. *Org. Lett.* **2005**, *7*, 1161–1164. (b) Sayyed, I. A.; Sudalai, A. *Tetrahedron: Asymmetry* **2004**, *15*, 3111–3116.

(36) Treatment of the β-amino-γ-azido ester (±)-**13-*anti*** with tosyl chloride and a base yielded the *N*-tosylamino (±)-**14-*anti***, thus confirming that the two azido esters have the same *anti* configuration (see the Experimental Section).

SCHEME 8. Reductive Cyclization of γ-Azido-β-hydroxy Esters (±)-3

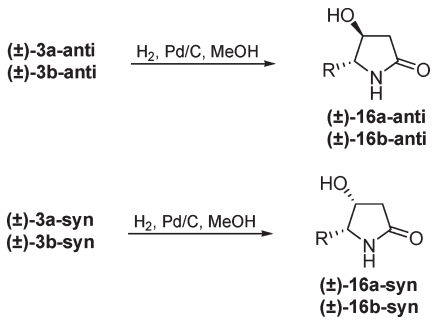
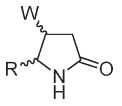


TABLE 6. γ-Lactams Prepared by Reductive Cyclization of γ-Azido Esters



entry	name	R	W	time (h)	yield (%)[a]	$J_{H_\beta-H_\gamma}$ (Hz)[b]
1	(±)-**16a-*anti***	Ph	OH	1	91	3.4
2	(±)-**16a-*syn***	Ph	OH	20	87	5.1
3	(±)-**16b-*anti***	Et	OH	1	94	2.5
4	(±)-**16b-*syn***	Et	OH	1	95	5.0
5	(±)-**19-*anti***	Ph	OEt	1	83	2.5
6	(±)-**19-*syn***	Ph	OEt	22[c]	61	5.7
7	(±)-**23-*anti***	Ph	NH_2	1	86	4.9
8	(±)-**23-*syn***	Ph	NH_2	12	81	6.3
9	(±)-**24-*anti***	Ph	NHTs	1	89	4.8
10	(±)-**25-*anti***	Ph	$NHCO_2Et$	1	92	4.7

[a]Isolated yield. [b]400 MHz, DMSO-d_6. [c]Reaction carried out at 25 °C for 2 h then under reflux for 20 h.

results in a shorter period (1 h). In both cases the nucleophilic ring-opening was completely regio- and diastereoselective, although the purification of the resulting β-amino-γ-azido ester (±)-**13-*syn*** by filtration on a pad of silica gel led to a low recovered mass (probably due to strong interaction of the basic amino group with acidic silica gel).

Reductive Cyclization of β-Substituted-γ-azido Esters. With a variety of aryl- and alkyl-substituted γ-azido esters in hand, the cyclization step for the synthesis of the target γ-lactams was investigated. Considering that catalytic hydrogenation is highly atom-economic and widely employed in academia and industry,[37] the γ-azido esters were submitted to mild chemoselective Pd/C-catalyzed hydrogenation to the amino functionality with subsequent cyclization to *anti*- or *syn*-β,γ-disubstituted γ-lactams. We were delighted to discover that this simple procedure (using a balloon filled with H_2 without any special apparatus) efficiently converted the azido alcohols (±)-**3a-*anti*** and (±)-**3b-*anti*** to the corresponding β-hydroxy γ-lactams (±)-**16a-*anti*** and (±)-**16b-*anti*** as crystalline solids in near quantitative yields (Scheme 8 and Table 6).

Similarly to the results obtained for the *anti* isomers, the reductive cyclization of (±)-**3a-*syn*** and (±)-**3b-*syn*** with H_2 and Pd/C in MeOH gave rise to the expected γ-lactams (±)-**16a-*syn*** and (±)-**16b-*syn*** in high yields under mild conditions (Scheme 8).

Remarkably, the reactions were carried out at ambient temperature under essentially neutral conditions and there was no need for previous protection of the β-hydroxy group. This flexibility compares favorably with known methods based on malimide-derived routes to γ-lactams.[5,8] Another feature of this methodology is related to the simplicity with which the products are obtained in pure form, consisting of a simple filtering off of the catalyst followed by evaporation of the solvent and trituration of the crude γ-lactams with ethyl ether. Besides their full spectroscopic characterization, including the characteristic[1e,38] NMR coupling constants for $H_\beta-H_\gamma$ where $J_{anti} < J_{syn}$ (Table 6), the anticipated relative stereochemistry of each γ-lactam (±)-**16a-*anti***, (±)-**16a-*syn***, (±)-**16b-*anti***, and (±)-**16b-*syn*** was further confirmed by X-ray crystallographic analysis after recrystallization in hot ethyl acetate (see the Supporting Information).

In spite of the excellent results obtained for the reductive cyclization of γ-azido esters (±)-**3**, high conversions to γ-lactam (±)-**16a-*syn*** were only achieved after 20 h (Table 6, entry 2), whereas other azido esters cyclized much faster (entries 1, 3, and 4). In fact, the reduction of the γ-azido ester (±)-**3a-*syn*** was as fast as any other reaction (the starting material was consumed in less than 1 h), but this was not the case for the subsequent cyclization of the preformed γ-amino ester.[39] Although its isolation in pure form was not possible due to the spontaneous cyclization to γ-lactam (±)-**16a-syn** in solution, the formation and buildup of a γ-amino-β-hydroxy ester intermediate was evidenced by monitoring the reaction profile by NMR, suggesting that annulation was the slower step in this case.

Clearly, the stereochemical features influence the relative reactivity of each species involved in the intramolecular reaction. A mechanism tentatively proposed to explain the differences in reactivity observed for the *anti*- and *syn*-γ-azido esters is depicted in Figure 1. For the isomers with relative *anti* configuration, two of the lowest energy rotamers (Anti-A and Anti-B) are favorable to cyclization through a facilitated approximation of the reacting amino and carboxyl groups while the R group is kept away from the hydroxyl (W = OH). Therefore, the *anti* isomers undergo cyclization easily regardless of the size of the R group. On the other hand, in the *syn* isomers the proximity of the amino and carboxyl reactive centers in the rotamers Syn-A and Syn-B brings unfavorable steric interaction when a bulky R group (such as phenyl) and the hydroxyl group are next to one another, resulting in a high-energy transition state for the cyclization to γ-lactam (±)-**16a-*syn*** (Table 6, entry 2).

To evaluate the relative reactivity of *anti*- and *syn*-γ-azido-β-substituted esters by replacement of the OH group with more sterically demanding groups and also to broaden the chemical

(37) (a) Krische, M. J.; Sun, Y. *Acc. Chem. Res.* **2007**, *40*, 1237. (b) Tungler, A.; Sípos, É.; Háda, V. *Arkivoc* **2004**, *vii*, 223–242. (c) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3069.

(38) Lennartz, M.; Sadakane, M.; Steckhan, E. *Tetrahedron* **1999**, *55*, 14407–14420.

(39) Published patents (see ref 10d and Mitsuhashi, S.; Sumi, K.; Moroi, T.; Sotoguchi, T.; Miura, T. *Eur. Pat. Appl.* EP 0947505A2, 1999 (CAS 131:271805) describe the hydrogenation of ethyl γ-azido-β-hydroxybutanoate followed by treatment of the corresponding γ-amino ester intermediate (see the analogous methyl ester in Figure 1, R = H; W = OH) with either strong bases or acids to achieve cyclization to β-hydroxy γ-lactam, an important intermediate for the synthesis of carbapenem antibiotics (Kobayashi, S.; Kobayashi, K.; Hirai, K. *Synlett* **1999**, 909–912). However, in our case, mild palladium-catalyzed hydrogenation of ethyl γ-azido-β-hydroxybutanoate (prepared by reduction of the corresponding ketone with $NaBH_4$ as described in Experimental Section), furnished the β-hydroxy γ-lactam in ~75% yield after 1 h at 25 °C without any additive.

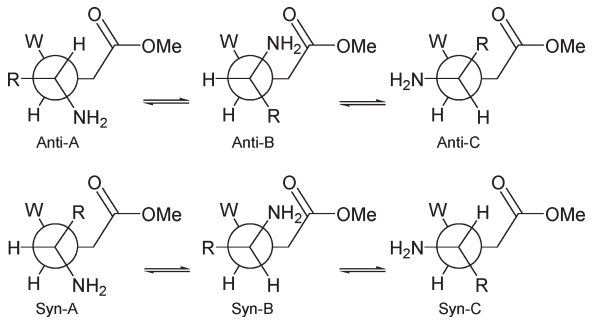
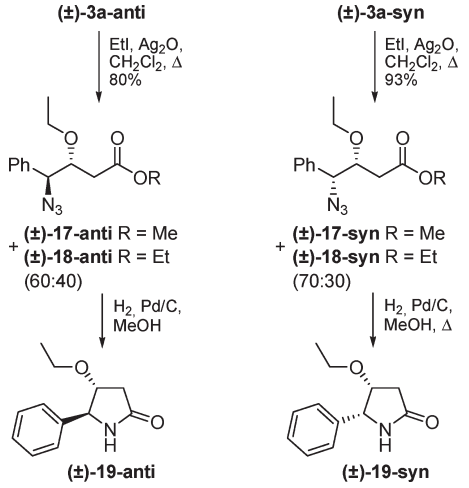


FIGURE 1. Newman projection for the *anti*- and *syn*-γ-amino esters.

SCHEME 9. *O*-Alkylation of γ-Azido-β-hydroxy Esters (±)-3a and Reductive Cyclization

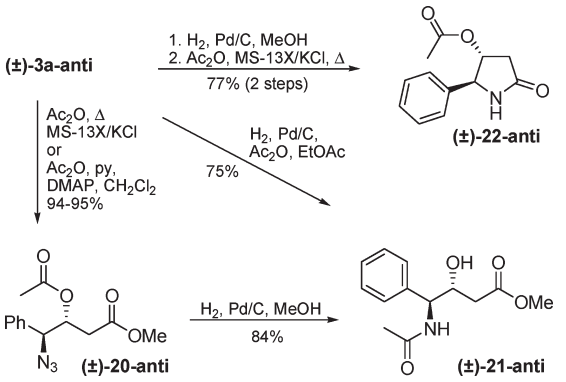


diversity of multifunctionalized γ-lactams, we extended the reductive cyclization reaction to other γ-azido esters and studied their scope and limitations. Accordingly, silver(I) oxide-assisted *O*-alkylation of γ-azido-β-hydroxy esters (±)-**3a-*anti*** and (±)-**3a-*syn*** was undertaken with ethyl iodide as the alkylating agent (Scheme 9). The reactions were slow, but reasonable conversions to the *O*-ethylated derivatives were achieved with a large excess of EtI under reflux for prolonged times. However, the crude reaction consisted of a mixture of the expected methyl ester [(±)-**17-*anti*** or (±)-**17-*syn***] and the corresponding ethyl ester [(±)-**18-*anti*** or (±)-**18-*syn***], which could not be separated after column chromatography. One possible reason for obtaining the transesterification derivatives (±)-**18** relates to the Lewis acid character of Ag(I) salts combined with the excess of EtI necessary to achieve acceptable conversions to the *O*-ethylated products.

Nevertheless, the subsequent reduction of the azido group with H_2-Pd/C followed by cyclization cleanly furnished the β-ethoxy γ-lactams (±)-**19-*anti*** or (±)-**19-*syn*** in high diastereochemical purity and without apparent discrimination between methyl or ethyl esters. The relative configuration of the β-ethoxy γ-lactams (±)-**19-*anti*** and (±)-**19-*syn*** was also in accordance[1e,38] with the expected NMR coupling constants for $H_\beta-H_\gamma$ where $J_{anti} < J_{syn}$ (Table 6, entries 5 and 6).

As expected, the cyclization to β-ethoxy γ-lactam (±)-**19-*syn*** was only accomplished after many hours, but unlike other similar transformations carried out at room temperature it was necessary to maintain the reflux temperature for

SCHEME 10. Preparation of β-Acetyloxy γ-Lactam (±)-22-*anti*



a prolonged period in order to achieve high conversions (Table 6, entry 6). Therefore, the presence of the ethoxy group (Figure 1, W = *O*-ethyl) introduced a much more unfavorable steric interaction when R = phenyl, which prevented the formation of the reactive rotamers Syn-A and Syn-B at room temperature.

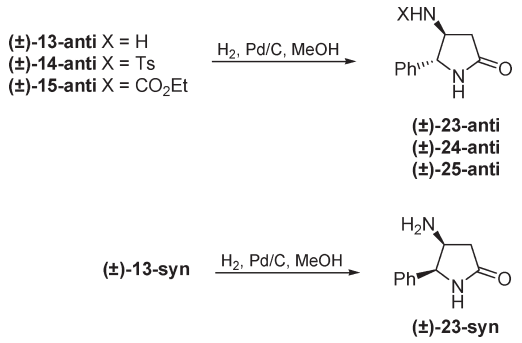
When the hydroxyl group in the γ-azido-β-hydroxy ester (±)-**3a-*anti*** was subjected to acetylation with Ac_2O, either by a sustainable process based on heterogeneous catalysis under solvent-free conditions[40] or the conventional method employing pyridine in a halogenated solvent, the corresponding acetate (±)-**20-*anti*** was obtained in excellent yields (Scheme 10). However, the reduction of the azido group resulted in an O-to-N acetyl migration to give the amide (±)-**21-*anti*** instead of the expected O-acetylated γ-lactam (±)-**22-*anti***. The same amide (±)-**21-*anti*** was also obtained directly from the γ-azido-β-hydroxy ester (±)-**3a-*anti*** in similar overall yield by Pd/C-catalyzed hydrogenation in the presence of Ac_2O. Therefore, acetylated γ-lactam (±)-**22-*anti*** was prepared from acetylation of β-hydroxy γ-lactam (±)-**16a-*anti*** with use of Ac_2O/molecular sieves due to the facile separation and purification of the expected product.[40]

Finally, catalytic hydrogenation reaction of β-amino-γ-azido esters derived from the azidolysis of aziridine acetates also proceeded successfully to give the corresponding β-amino γ-lactams (±)-**23**−**25-*anti*** in high yields (Scheme 11). Similarly to the results observed for the β-hydroxy and β-alkoxy derivatives, the relative configuration of the β-amino γ-lactams (±)-**23**−**25-*anti*** was supported by mechanistic considerations and by NMR analysis, showing the characteristic[1e,38] coupling constants for $H_\beta-H_\gamma$ where $J_{anti} < J_{syn}$ (Table 6, entries 7−10). Remarkably, the reductive cyclization of (±)-**13-*anti***, containing an unprotected amino group, to the γ-lactam (±)-**23-*anti*** was as efficient as in the other cases[41] due to the extremely mild conditions employed. Similar results were obtained for the preparation of the diastereomeric β-amino γ-lactam (±)-**23-*syn*** from the azido ester (±)-**13-*syn*** (Table 6, entry 8), although the cyclization was slower due to the expected unfavorable steric interaction of γ-phenyl and

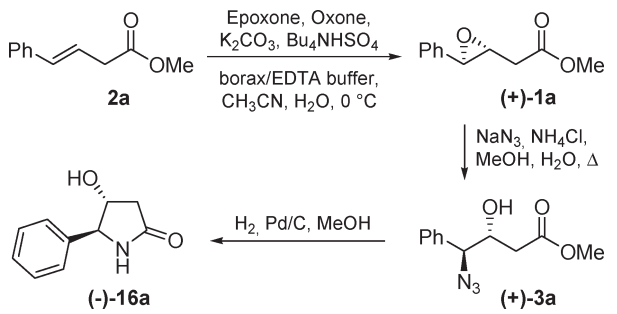
(40) (a) Sá, M. M.; Meier, L.; Fernandes, L.; Pergher, S. B. C. *Catal. Commun.* **2007**, *8*, 1625–1629. (b) Sá, M. M.; Meier, L. *Synlett* **2006**, 3474–3478.

(41) In contrast to the other γ-lactams synthesized here, which are all crystalline solids, (±)-**23-*anti*** is a low-melting point solid that was purified by chromatography and further transformed to β-tosylamino γ-lactam (±)-**24-*anti*** by direct tosylation, thus proving the structural relationship between them (see the Experimental Section).

SCHEME 11. Reductive Cyclization of β-Amino-γ-azido Esters



SCHEME 12. Asymmetric Synthesis of Chiral γ-Lactam (−)-16a



β-amino groups in the *syn* isomer (Figure 1, R = Ph; W = NH_2).

Asymmetric Preparation of Chiral γ-Lactam. To demonstrate the utility of this highly stereocontrolled strategy to convert epoxide and aziridine acetates to β,γ-disubstituted γ-lactams, the asymmetric version was briefly investigated focusing on the preparation of the chiral epoxide (+)**-1a** for further synthetic manipulations (Scheme 12). The key epoxide (+)**-1a** was prepared through an organocatalytic process based on the combination of Shi's epoxone[42] with Oxone to generate a chiral dioxirane, which effected epoxidation of β,γ-unsaturated ester **2a** in aqueous medium under alkaline conditions. The best result that balanced moderate conversion with a high er was observed when 0.5 equiv of epoxone was used as the catalyst in the presence of an excess of both oxidant and base, which were slowly added to the reaction medium at 0 °C to maintain pH control. Conversions up to 76% and er as high as 21:1 were achieved under these conditions when the reaction was performed in gram scale. Determination of the absolute configuration for (+)**-1a** as 3*R*,4*R* was based on model compounds described in the literature.[42a,b]

After the asymmetric synthesis of epoxide (+)**-1a** with a high er was established, the nucleophilic ring-opening with azide and subsequent reductive cyclization of azido alcohol (+)**-3a** were effected, as usual, to give the chiral γ-lactam (−)**-16a** under mild conditions and with excellent diastereoselectivity (Scheme 12).

(42) (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806–9807. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328–2329. (c) Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958–3987.

Conclusions

In summary, we have developed an efficient and unprecedented method for the highly stereoselective synthesis of original β,γ-disubstituted γ-lactams with either an *anti* or *syn* relative configuration, starting from readily available epoxide and aziridine acetates. The key step involves the regio- and diastereocontrolled ring-opening of these three-membered heterocycles with azide or bromine ion, which allows diastereodivergent access to both *anti*- and *syn*-γ-azido-β-substituted esters from the same epoxide acetate. Reductive cyclization of the γ-azido esters gave, also in a straightforward manner, pure γ-lactams under mild conditions, even for the more sterically congested γ-phenyl derivatives with *syn* configuration. The feasibility for asymmetric synthesis was demonstrated by preparing the chiral epoxide acetate from styrylacetic ester using a mild oxidant (Oxone) and inexpensive organocatalyst (epoxone) under aqueous conditions. Due to its flexibility, simplicity, and high regio- and diastereoselectivity, the synthetic protocol outlined here should be applicable to a wide variety of stereochemically defined multifunctionalized γ-lactams.

Experimental Section

General Experimental Methods. (*E*)-4-Phenyl-3-butenoic acid,[43] ethyl 4-azido-3-oxobutanoate,[44] and Shi's epoxone[45] were prepared according to literature procedures. Their IR and ^{1}H NMR spectra were in accordance with reported data. The 10% Pd/C catalyst was purchased from Sigma-Aldrich Co. CH_3CN was freshly distilled from CaH_2. Where appropriate, reagents were purified prior to use following the guidelines of Perrin and Armarego.[46] Column chromatography was performed with silica gel (70−230 mesh) and hexane/ethyl acetate as the eluent. TLC analysis was performed in silica gel plates, using UV, I_2, *p*-anisaldehyde, or phosphomolybdic acid solutions for visualization. ^{1}H NMR spectra were recorded at 400 MHz and splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublet (dd), doublet of triplet (dt), doublet of quartet (dq), doublet of doublet of doublet (ddd), doublet of doublet of triplet (ddt), doublet of doublet of quartet (ddq), apparent quartet (appq), apparent doublet of triplet (appdt), multiplet (m), or broad singlet (br s). ^{13}C NMR spectra were recorded at 100 MHz. Chemical shifts were recorded in parts per million (ppm, δ) relative to TMS at 0.00 ppm or solvent ($CDCl_3$ at 7.26 ppm or DMSO-d_6 at 2.50 ppm for ^{1}H NMR, and $CDCl_3$ at 77.16 ppm or DMSO-d_6 at 39.52 ppm for ^{13}C NMR) as the internal standard. IR spectra were recorded with use of KBr for solids and film for liquid samples. Elemental analysis was conducted in a CHNS analyzer instrument. HRMS data were recorded by using the ESI-TOF technique. Enantiomeric ratios (er) were determined by GC (Restek RT-BetaDEX-sm column). Optical rotations were obtained by using a microcell with 0.90 dm path length. Specific rotations ($[\alpha]^{20}_D$, in units of deg cm^2/g) are based on the equation $[\alpha]^{20}_D = (100\cdot\alpha)/(l\cdot c)$ and are reported as unitless numbers where the concentration c is in g/100 mL and the path length l is in decimeters. Melting points were determined by using a hot plate apparatus and are uncorrected. Microwave-assisted reactions were performed in 10 mL sealed tubes in a

(43) (a) Hoye, T. R.; Richardson, W. S. *J. Org. Chem.* **1989**, *54*, 688–693. (b) Linstead, R. P.; Williams, L. T. D. *J. Chem. Soc.* **1926**, 2735–2747.

(44) Yasohara, Y.; Kizaki, N.; Hasegawa, J.; Wada, M.; Kataoka, M.; Shimizu, S. *Tetrahedron: Asymmetry* **2001**, *12*, 1713–1718.

(45) (a) Kang, J.; Lim, G. J.; Yoon, S. K.; Kim, M. Y. *J. Org. Chem.* **1995**, *60*, 564–577. (b) Mio, S.; Kumagawa, Y.; Sugai, S. *Tetrahedron* **1991**, *47*, 2133–2144.

(46) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, UK, 1988.

monomode microwave CEM Explorer reactor instrument with infrared temperature monitoring and a noninvasive pressure transducer. The crystallographic analyses for all compounds were carried out with graphite-monochromated Mo Kα radiation, at room temperature. Cell parameters were determined from 25 carefully centered reflections. All data were corrected for Lorentz and polarization effects. The structures were solved by direct methods and refined by full-matrix least-squares methods.

Methyl (*E*)-4-Phenyl-3-butenoate (2a). To a stirred solution of (*E*)-4-phenyl-3-butenoic acid[43] (25.3 g, 156 mmol) in MeOH (403 mL) was added concd H_2SO_4 (4.3 mL) then the reaction was stirred at 25 °C for 22 h. Next, the excess of MeOH was removed under reduced pressure and the residue was diluted with CH_2Cl_2, washed with H_2O, 10% $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a yellow oil. Filtration on a pad of silica gel (hexane/EtOAc 9:1) gave pure **2a** (23.4 g, 86%) as a pale yellow oil. IR and NMR (^{1}H and ^{13}C) spectra are in accordance with reported data.[43a,47]

Methyl (*E*)-3-Hexenoate (2b). 2b was prepared from commercially available (*E*)-3-hexenoic acid (5.00 g, 43.8 mmol) and purified as described above for the analogous **2a**: 75% yield, colorless oil. IR and NMR (^{1}H and ^{13}C) spectra are in accordance with reported data.[48]

Methyl *anti*-3-Phenyloxirane-2-acetate [(±)-1a]. To a stirred mixture of **2a** (3.10 g, 17.6 mmol) and $NaHCO_3$ (7.00 g, 85.7 mmol) in acetone (54 mL) at 0 °C (ice bath) was added dropwise a solution of Oxone (14.1 g, 22.9 mmol) in H_2O (54 mL) during a period of 1 h. Next, the ice bath was removed and the reaction was allowed to stir at 25 °C for 2 h. The insoluble solid was separated by filtration under reduced pressure and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure and the residue was diluted with CH_2Cl_2, washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a pale yellow oil. Filtration on a pad of silica gel (hexane/EtOAc 17:3) gave pure (±)-**1a** (2.9 g, 85%) as a colorless oil. Analytical data: IR (neat) 3002, 2954, 1739, 1438, 1174, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.29 (m, 5H), 3.75 (s, 3H), 3.73 (d, J = 1.9 Hz, 1H), 3.35 (ddd, J = 6.3, 5.3, 1.9 Hz, 1H), 2.76 (dd, J = 16.2, 5.3 Hz, 1H), 2.73 (dd, J = 16.2, 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6 (C), 136.7 (C), 128.5 (2 × CH), 128.4 (CH), 125.7 (2 × CH), 58.2 (CH), 57.9 (CH), 52.0 (CH_3), 37.7 (CH_2); HRMS (ESI TOF-MS) calcd for $C_{11}H_{12}O_3$ 192.0786, found 192.0768.

Methyl *anti*-3-Ethyloxirane-2-acetate [(±)-1b]. (±)-**1b** was prepared by epoxidation of **2b** (1.50 g, 11.7 mmol) and purified as described above for the analogous (±)-**1a**: 89% yield, colorless oil. IR and NMR (^{1}H and ^{13}C) spectra are in accordance with reported data.[48]

Methyl *anti*-4-Azido-3-hydroxy-4-phenylbutanoate [(±)-3a-*anti*]. Method A: To a stirred solution of NaN_3 (50.8 mg, 0.781 mmol) and NH_4Cl (27.8 mg, 0.521 mmol) in H_2O (0.25 mL) at 25 °C was added a solution of (±)-**1a** (50.0 mg, 0.260 mmol) in MeOH (2.0 mL) then the reaction was stirred at 80 °C for 3 h. [**Caution!** *Organic azides are potentially explosive*[12a,49] *and should be handled with care, although we experienced no problems in handling solutions of sodium azide or organic azides, which can be stored indefinitely at 0 °C.*] After the solution had cooled to room temperature, the excess of MeOH was removed under reduced pressure and the residue was diluted with EtOAc, washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a brown oil. Filtration on a pad of silica gel (hexane/EtOAc 4:1) gave pure (±)-**3a-*anti*** (55.7 mg, 91%) as a yellow oil. Analytical data: IR (neat) 3462 (broad), 3030, 2952, 2105, 1730, 1255, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42−7.34 (m, 5H), 4.67 (d, J = 5.7 Hz, 1H), 4.28−4.23 (m, 1H), 3.69 (s, 3H), 2.54−2.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8 (C), 135.9 (C), 128.8 (2 × CH), 128.6 (CH), 127.6 (2 × CH), 71.2 (CH), 69.1 (CH), 52.0 (CH_3), 36.5 (CH_2); HRMS (ESI TOF-MS) calcd for $C_{11}H_{13}N_3O_3$ 235.0957, found 235.0957. **Method B:** To a 10 mL glass tube containing a solution of NaN_3 (304 mg, 4.68 mmol) and NH_4Cl (125 mg, 2.34 mmol) in H_2O (0.45 mL) was added a solution of (±)-**1a** (300 mg, 1.56 mmol) in MeOH (3.6 mL). The vessel was sealed with a septum, placed into the microwave cavity, and irradiated by three pulses (maximum potency = 100 W, t = 1 min ramp, 2 min hold, T_{max} = 80 °C, stirring mode "on"). After the solution had cooled to room temperature, the excess of MeOH was removed under reduced pressure and the residue was diluted with EtOAc, washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude (±)-**3a-*anti*** (312 mg, 85%) as a yellow oil that was not purified further. Analytical data were in accordance with those reported in Method A.

Methyl *anti*-4-Azido-3-hydroxyhexanoate [(±)-3b-*anti*]. Method A: To a stirred solution of (±)-**1b** (500 mg, 3.47 mmol) in anhydrous CH_3CN (7.5 mL) at 25 °C was added NaN_3 (676 mg, 10.4 mmol) and $Mg(ClO_4)_2$ (1.94 g, 8.67 mmol) then the reaction was stirred at 80 °C for 8 h. After cooling to room temperature, the mixture was diluted with CH_2Cl_2 and washed with 1 M HCl, then the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a yellow oil. Filtration on a pad of silica gel (hexane/EtOAc 4:1) gave pure (±)-**3b-*anti***[14] (473 mg, 73%) as a yellow oil. Analytical data: IR (neat) 3469 (broad), 2969, 2103, 1731, 1271, 1172 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.02 (dt, J = 7.7, 5.1 Hz, 1H), 3.73 (s, 3H), 3.36 (ddd, J = 9.2, 5.1, 4.0 Hz, 1H), 2.57−2.55 (m, 2H), 1.65 (ddq, J = 14.3, 7.3, 4.0 Hz, 1H), 1.51 (ddq, J = 14.3, 9.2, 7.3 Hz, 1H), 1.04 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4 (C), 70.2 (CH), 67.9 (CH), 52.1 (CH_3), 36.9 (CH_2), 23.7 (CH_2), 10.8 (CH_3). **Method B:** To a 10 mL glass tube containing a solution of (±)-**1b** (100 mg, 0.693 mmol) and NaN_3 (135 mg, 2.08 mmol) in anhydrous CH_3CN (1.4 mL) was added $Mg(ClO_4)_2$ (387 mg, 1.73 mmol). The vessel was sealed with a septum, placed into the microwave cavity, and irradiated by three pulses (maximum potency =100 W, t = 1 min ramp, 2 min hold, T_{max} = 80 °C, stirring mode "on"). After cooling to room temperature, the mixture was diluted with CH_2Cl_2 and washed with 1 M HCl, then the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a yellow oil. Purification by column chromatography on silica gel (hexane/EtOAc 4:1) gave pure (±)-**3b-*anti***[14] (91 mg, 70%) as a pale yellow oil. Analytical data were in accordance with those reported in Method A.

Methyl (*E*)-4-Hydroxy-2-hexenoate (4b). To a stirred solution of (±)-**1b** (50 mg, 0.35 mmol) in DMF (1.0 mL) was added DABCO (78 mg, 0.69 mmol) then the reaction was stirred at 25 °C for 22 h. Next, the mixture was diluted with EtOAc, washed with 1 M HCl and H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude **4b** (37 mg, 73%) as a colorless oil that was not purified further. IR and ^{1}H NMR spectra are in accordance with reported data.[24]

Methyl 3-Benzoylpropionate (5). 5 was prepared by basic treatment of (±)-**1a** (50 mg, 0.26 mmol) for 20 h as described above for **4b**: 98% yield, colorless oil. IR and ^{1}H NMR spectra are in accordance with reported data.[25]

Methyl *anti*-4-Bromo-3-hydroxy-4-phenylbutanoate [(±)-7a-*anti*]. To a stirred solution of (±)-**1a** (1.0 g, 5.2 mmol) in THF (105 mL) at −15 °C (ice/NaCl/EtOH bath) was added LiBr (1.81 g,

(47) Eissler, S.; Nahrwold, M.; Neumann, B.; Stammler, H.-G.; Sewald, N. *Org. Lett.* **2007**, *9*, 817–819.
(48) Curtis, N. R.; Holmes, A. B.; Looney, M. G. *Tetrahedron* **1991**, *47*, 7171–7178.
(49) Badgujar, D. M.; Talawar, M. B.; Asthana, S. N.; Mahulikar, P. P. *J. Hazard. Mater.* **2008**, *151*, 289–305.

20.8 mmol) and Amberlist 15 (2.29 g, 440 mg/mmol) then the reaction was stirred at −15 °C for 1 h. Next, the insoluble solid was separated by filtration on a filter paper and washed with CH_2Cl_2. The filtrate was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude mixture (98:2) of (±)-**7a-*anti***:(±)-**7a-*syn*** (1.2 g, 85%) as a colorless oil that was used in the next step without further purification. Analytical data: IR (neat) 3472 (broad), 3029, 2951, 1734, 1170, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (data for the major isomer (±)-**7a-*anti***) δ 7.47−7.32 (m, 5H), 4.98 (d, J = 6.8 Hz, 1H), 4.52 (ddd, J = 8.7, 6.8, 3.1 Hz, 1H), 3.71 (s, 3H), 2.89 (dd, J = 16.5, 3.1 Hz, 1H), 2.63 (dd, J = 16.5, 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) (data for the major isomer (±)-**7a-*anti***) δ 172.3 (C), 138.0 (C), 128.9 (CH), 128.8 (CH), 128.6 (CH), 71.9 (CH), 57.3 (CH), 52.1 (CH_3), 38.6 (CH_2).

Methyl *anti*-4-Bromo-3-hydroxyhexanoate [(±)-7b-*anti*]. To a stirred solution of (±)-**1b** (500 mg, 3.47 mmol) in anhydrous CH_3CN (7.0 mL) at 0 °C (ice bath) was added LiBr (904 mg, 10.4 mmol) and $Mg(ClO_4)_2$ (1.94 g, 8.68 mmol). [**Caution!** *The reactions conducted on a gram scale showed to be sensitive to the temperature. In this case the addition of $Mg(ClO_4)_2$ must be slow and under vigorous stirring to avoid highly exothermic transformation that causes formation of byproducts.*] The ice bath was removed and the reaction was allowed to stir at 25 °C for 1 h. Next, the mixture was diluted with CH_2Cl_2 and washed with 1 M HCl, then the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude (±)-**7b-*anti*** (742 mg, 95%) as a colorless oil that was used in the next step without further purification. Analytical data: IR (neat) 3470 (broad), 2971, 1736, 1438, 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.11 (ddd, J = 8.8, 5.8, 3.1 Hz, 1H), 4.02 (ddd, J = 9.4, 5.8, 3.4 Hz, 1H), 3.73 (s, 3H), 2.77 (dd, J = 16.6, 3.1 Hz, 1H), 2.66 (dd, J = 16.6, 8.8 Hz, 1H), 1.99 (ddq, J = 14.6, 7.3, 3.4 Hz, 1H), 1.79 (ddq, J = 14.6, 9.4, 7.3 Hz, 1H), 1.08 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9 (C), 70.8 (CH), 62.6 (CH), 52.0 (CH_3), 38.4 (CH_2), 27.5 (CH_2), 12.2 (CH_3).

Methyl *syn*-4-Azido-3-hydroxy-4-phenylbutanoate [(±)-3a-*syn*]. To a stirred solution of the 98:2 mixture of (±)-**7a-*anti***:(±)-**7a-*syn*** (1.0 g, 3.7 mmol) in DMF (25 mL) was added NaN_3 (0.72 g, 11.1 mmol) then the reaction was stirred at 25 °C for 7 h. Next, the mixture was diluted with EtOAc, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a pale yellow oil. Filtration on a pad of silica gel (hexane/EtOAc 4:1) gave a 98:2 mixture of (±)-**3a-*syn***:(±)-**3a-*anti*** (0.74 g, 86%) as colorless oil. Analytical data: IR (neat) 3491 (broad), 3030, 2947, 2103, 1734, 1252, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (data for the major isomer (±)-**3a-*syn***) δ 7.40−7.33 (m, 5H), 4.51 (d, J=7.4 Hz, 1H), 4.23 (ddd, J = 8.2, 7.4, 4.1 Hz, 1H), 3.66 (s, 3H), 2.39 (dd, J = 16.3, 8.2 Hz, 1H), 2.33 (dd, J = 16.3, 4.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) (data for the major isomer (±)-**3a-*syn***) δ 172.0 (C), 136.0 (C), 128.9 (2 × CH), 128.8 (CH), 127.6 (2 × CH), 71.3 (CH), 70.1 (CH), 51.8 (CH_3), 37.8 (CH_2).

Methyl *syn*-4-Azido-3-hydroxyhexanoate: [(±)-3b-*syn*]. To a stirred solution of (±)-**7b-*anti*** (700 mg, 3.11 mmol) in DMSO (14.0 mL) at 25 °C was added NaN_3 (606 mg, 9.33 mmol) then the reaction was stirred at 40 °C for 30 h. Next, the mixture was diluted with EtOAc, washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a yellow oil. Filtration on a pad of silica gel (hexane/EtOAc 4:1) gave a 98:2 mixture of (±)-**3b-*syn***:(±)-**3b-*anti*** (420 mg, 72%) as colorless oil. Analytical data: IR (neat) 3477 (broad), 2970, 2104, 1734, 1173 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (data for major isomer (±)-**3b-*syn***)[14] δ 4.10−4.05 (m, 1H), 3.72 (s, 3H), 3.11 (ddd, J=8.1, 5.8, 3.9 Hz, 1H), 3.01 (d, J=4.9 Hz, exchanges with D_2O, 1H), 2.64 (dd, J=16.4, 9.2 Hz, 1H), 2.51 (dd, J=16.4, 3.5 Hz, 1H), 1.76−1.67 (m, 2H), 1.04 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (data for major isomer (±)-**3b-*syn***)[14] δ 172.8 (C), 69.6 (CH), 67.0 (CH), 52.0 (CH_3), 38.5 (CH_2), 23.4 (CH_2), 10.7 (CH_3).

Methyl *anti*-3-Phenylaziridine-2-acetate [(±)-10a-*anti*]. In a three-necked round-bottomed flask, a stirred solution of (±)-**3a-*anti*** (2.00 g, 8.50 mmol) in anhydrous CH_3CN (47 mL) was heated to reflux under N_2 atmosphere. Next, PPh_3 (2.20 g, 8.50 mmol) was immediately added at once and the reaction was stirred under reflux for 3 h. After cooling to room temperature, the mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (hexane/EtOAc 7:3) to give pure (±)-**10a-*anti*** (1.25 g, 77%) as a greenish oil. Analytical data: IR (neat) 3285 (broad), 3026, 2952, 1735, 1200, 1170, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.31−7.18 (m, 5H), 3.70 (s, 3H), 2.77 (br s, 1H), 2.66−2.62 (m, 1H), 2.54−2.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8 (C), 139.4 (C), 128.6 (2 × CH), 127.4 (CH), 125.7 (2 × CH), 52.0 (CH_3), 39.4 (CH), 38.7 (CH_2), 36.3 (CH); HRMS (ESI TOF-MS) calcd for $C_{11}H_{13}NO_2$ 191.0946, found 191.0939.

Methyl *syn*-3-Phenylaziridine-2-acetate [(±)-10a-*syn*]. (±)-**10a-*syn*** was prepared from the 98:2 mixture of (±)-**3a-*syn***:(±)-**3a-*anti*** as described above for (±)-**10a-*anti***. Purification by column chromatography on silica gel (hexane/EtOAc 3:2) gave the sole isomer (±)-**10a-*syn*** (71%) as a white solid, mp 67−68 °C. Analytical data: IR (KBr) 3204 (broad), 3028, 2995, 1732, 1160, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.24 (m, 5H), 3.63 (s, 3H), 3.39 (d, J=6.3 Hz, 1H), 2.75 (appq, J=6.5 Hz, 1H), 2.19 (dd, J=17.2, 7.1 Hz, 1H), 2.11 (dd, J=17.2, 5.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.6 (C), 136.8 (C), 128.2 (2 × CH), 127.8 (2 × CH), 127.1 (CH), 51.7 (CH_3), 36.3 (CH), 33.8 (CH_2), 32.9 (CH). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.91; H, 7.20; N, 7.29

Methyl *anti*-3-Phenyl-1-(4-toluenesulfonyl)aziridine-2-acetate [(±)-11a-*anti*]. To a stirred mixture of (±)-**10a-*anti*** (191 mg, 1.00 mmol) and pyridine (0.77 mL, 10 mmol) at 0 °C (ice bath) was added TsCl (210 mg, 1.10 mmol) then the reaction was stirred at 0 °C for 45 min. Next, the mixture was diluted with CH_2Cl_2, washed with 0.5 M HCl and H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a yellow oil. Addition of EtOH, followed by grinding the insoluble residue with a spatula, induced precipitation of a solid that was separated by filtration (this procedure was repeated until no more solid was precipitated from the filtrate) to give pure (±)-**11a-*anti*** (230 mg, 67%) as a white solid, mp 89−90 °C. Analytical data: IR (KBr) 3037, 2954, 1735, 1320, 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.83 (d, J=8.2 Hz, 2H), 7.30−7.25 (m, 5H), 7.20−7.18 (m, 2H), 3.88 (d, J=3.9 Hz, 1H), 3.73 (s, 3H), 3.31 (dt, J=8.2, 3.9 Hz, 1H), 3.20 (dd, J=16.5, 8.2 Hz, 1H), 3.18 (dd, J=16.5, 8.2 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9 (C), 144.5 (C), 137.2 (C), 134.8 (C), 129.8 (CH), 128.7 (CH), 128.4 (CH), 127.6 (CH), 126.8 (CH), 52.3 (CH_3), 48.2 (CH), 47.4 (CH), 33.4 (CH_2), 21.8 (CH_3). Anal. Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06; S, 9.28. Found: C, 62.85; H, 5.47; N, 4.10; S, 8.89.

Methyl *syn*-3-Phenyl-1-(4-toluenesulfonyl)aziridine-2-acetate [(±)-11a-*syn*]. (±)-**11a-*syn*** was prepared from (±)-**10a-*syn*** as described above for (±)-**11a-*anti***. Purification by column chromatography on silica gel (hexane/EtOAc 4:1) gave pure (±)-**11a-*syn*** (91%) as a white solid, mp 79−80 °C. Analytical data: IR (KBr) 3001, 2949, 1738, 1319, 1155 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.6 Hz, 2H), 7.28−7.22 (m, 5H), 4.02 (d, J = 7.2 Hz, 1H), 3.50 (s, 3H), 3.41 (appq, J = 6.5 Hz, 1H), 2.42 (s, 3H), 2.33 (dd, J = 17.0, 6.6 Hz, 1H), 2.17 (dd, J = 17.0, 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1 (C), 144.6 (C), 134.5 (C), 131.9 (C), 129.6 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.3 (CH), 51.7 (CH_3), 44.4 (CH), 41.7 (CH), 31.9 (CH_2), 21.5 (CH_3). Anal. Calcd for

$C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06; S, 9.28. Found: C, 62.49; H, 5.62; N, 4.08; S, 9.66.

Methyl *anti*-3-Ethyl-1-(4-toluenesulfonyl)aziridine-2-acetate [(±)-11b-*anti*]. In a three-necked round-bottomed flask, a stirred solution of (±)-**3b-*anti*** (468 mg, 2.50 mmol) in anhydrous CH_3CN (18.0 mL) was heated to reflux under N_2 atmosphere. Next, PPh_3 (655 mg, 2.50 mmol) was immediately added at once and the reaction was stirred under reflux for 2 h. After the solution had cooled to room temperature, CH_3CN was removed under reduced pressure. The residue was diluted with pyridine (2.0 mL, 25 mmol), TsCl (524 mg, 2.75 mmol) was added at 0 °C (ice bath), then the reaction was stirred at 0 °C for 30 min. The final mixture was diluted with CH_2Cl_2, washed with 0.5 M HCl and H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a yellow oil. Filtration on a pad of silica gel (hexane/EtOAc 1:1) gave pure (±)-**11b-*anti*** (550 mg, 74% in two steps) as a colorless oil. Analytical data: IR (neat) 3003, 2953, 1741, 1254, 1173 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.83 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 3.65 (s, 3H), 2.98 (ddd, J = 7.2, 5.5, 4.3 Hz, 1H), 2.93 (dd, J = 16.5, 5.5 Hz, 1H), 2.80 (dd, J = 16.5, 7.2 Hz, 1H), 2.72 (dt, J = 6.4, 4.3 Hz, 1H), 2.43 (s, 3H), 1.82−1.64 (m, 2H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8 (C), 144.1 (C), 137.5 (C), 129.5 (2 × CH), 127.5 (2 × CH), 52.0 (CH_3), 50.0 (CH), 44.3 (CH), 34.4 (CH_2), 23.4 (CH_2), 21.6 (CH_3), 11.5 (CH_3).

Methyl *anti*-1-Ethoxycarbonyl-3-phenylaziridine-2-acetate [(±)-12a-*anti*]. To a stirred solution of (±)-**10a-*anti*** (191 mg, 1.00 mmol) in Et_2O (12 mL) at 0 °C (ice bath) was added triethylamine (0.21 mL, 1.5 mmol) and ethyl chloroformate (0.14 mL, 1.5 mmol) then the reaction was stirred at 0 °C for 20 min. Next, the mixture was diluted with Et_2O, washed with sat. $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give pure (±)-**12a-*anti*** (213 mg, 81%) as a pale yellow oil. Analytical data: IR (neat) 2983, 1739, 1720, 1192, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33−7.28 (m, 5H), 4.20−4.05 (m, 2H), 3.74 (s, 3H), 3.39 (d, J = 3.1 Hz, 1H), 3.00 (ddd, J = 6.8, 6.0, 3.1 Hz, 1H), 2.83 (dd, J = 16.6, 6.0 Hz, 1H), 2.54 (dd, J = 16.6, 6.8 Hz, 1H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7 (C), 161.0 (C), 135.9 (C), 128.6 (2 × CH), 128.1 (CH), 126.7 (2 × CH), 62.7 (CH_2), 52.2 (CH_3), 45.1 (CH), 41.8 (CH), 36.0 (CH_2), 14.3 (CH_3).

Methyl *anti*-3-Amino-4-azido-4-phenylbutanoate [(±)-13-*anti*]. To a stirred solution of NaN_3 (975 mg, 15.0 mmol) and NH_4Cl (160 mg, 3.00 mmol) in H_2O (1.5 mL) at 25 °C was added a solution of (±)-**10a-*anti*** (287 mg, 1.50 mmol) in MeOH (12 mL) then the reaction was stirred at 80 °C for 20 min. After the solution had cooled to room temperature, the excess of MeOH was removed under reduced pressure and the reaction was diluted with CH_2Cl_2, washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a brown oil. Filtration on a pad of silica gel (hexane/EtOAc 1:1) gave pure (±)-**13-*anti*** (284 mg, 81%) as a pale yellow oil. Analytical data: IR (neat) 3379, 3322, 3027, 2949, 2103, 1733, 1251, 707 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.45−7.33 (m, 5H), 4.47 (d, J = 7.3 Hz, 1H), 3.69 (s, 3H), 3.43 (ddd, J = 9.0, 7.3, 3.5 Hz, 1H), 2.67 (dd, J = 16.2, 3.5 Hz, 1H), 2.37 (dd, J = 16.2, 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.7 (C), 136.6 (C), 129.1 (2 × CH), 128.9 (CH), 127.8 (2 × CH), 70.6 (CH), 52.7 (CH), 51.9 (CH_3), 37.9 (CH_2).

Methyl *syn*-3-Amino-4-azido-4-phenylbutanoate [(±)-13-*syn*]. To a stirred solution of (±)-**10a-*syn*** (250 mg, 1.31 mmol) in anhydrous CH_3CN (4.2 mL) at 25 °C was added NaN_3 (255 mg, 3.92 mmol) and $Mg(ClO_4)_2$ (730 mg, 3.27 mmol) then the reaction was stirred at 80 °C for 1 h. After cooling to room temperature, the mixture was diluted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a brown oil. Purification by column chromatography on silica gel (hexane/EtOAc 1:1) gave pure (±)-**13-*syn*** (165 mg, 54%) as a yellow oil. Analytical data: IR (neat) 3384, 3322, 3030, 2951, 2103, 1732, 1251, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44−7.30 (m, 5H), 4.49 (d, J = 7.2 Hz, 1H), 3.66 (s, 3H), 3.40 (ddd, J = 8.6, 7.2, 4.2 Hz, 1H), 2.38 (dd, J = 16.2, 4.2 Hz, 1H), 2.24 (dd, J = 16.2, 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.3 (C), 137.0 (C), 129.1 (2 × CH), 128.9 (CH), 127.6 (2 × CH), 71.4 (CH), 53.2 (CH), 51.9 (CH_3), 38.6 (CH_2).

Methyl *anti*-4-Azido-4-phenyl-3-[(4-toluenesulfonyl)amino]-butanoate [(±)-14-*anti*]. Method A: To a stirred solution of NaN_3 (325 mg, 5.00 mmol) and NH_4Cl (53 mg, 1.0 mmol) in H_2O (1.0 mL) at 0 °C (ice bath) was added a solution of (±)-**11a-*anti*** (173 mg, 0.50 mmol) in MeOH (8.0 mL) then the reaction was stirred at 0 °C for 30 min. Next, the excess of MeOH was removed under reduced pressure and the reaction was diluted with CH_2Cl_2, washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a colorless oil. Addition of Et_2O, followed by grinding the insoluble residue with a spatula, induced precipitation of a solid that was separated by filtration (this procedure was repeated until no more solid was precipitated from the filtrate) to give pure (±)-**14-*anti*** (155 mg, 80%) as a white solid, mp 99−100 °C. Analytical data: IR (KBr) 3413, 3314, 3032, 2958, 2110, 1727, 1324, 1151 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.63 (d, J = 8.3 Hz, 2H), 7.32−7.31 (m, 3H), 7.24−7.20 (m, 4H), 5.46 (d, J = 9.0 Hz, exchanges with D_2O, 1H), 4.87 (d, J = 5.6 Hz, 1H), 3.84−3.77 (m, 1H), 3.53 (s, 3H), 2.55 (dd, J = 16.2, 6.5 Hz, 1H), 2.41 (s, 3H), 2.37 (dd, J = 16.2, 4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5 (C), 143.7 (C), 137.4 (C), 136.0 (C), 129.8 (CH), 129.0 (CH), 128.8 (CH), 127.2 (CH), 127.1 (CH), 68.3 (CH), 55.4 (CH), 52.0 (CH_3), 33.9 (CH_2), 21.7 (CH_3). Anal. Calcd for $C_{18}H_{20}N_4O_4S$: C, 55.66; H, 5.19; N, 14.42; S, 8.25. Found: C, 55.87; H, 5.29; N, 14.37; S, 7.89. **Method B:** To a stirred mixture of (±)-**13-*anti*** (130 mg, 0.550 mmol) and pyridine (0.45 mL, 5.5 mmol) at 0 °C (ice bath) was added TsCl (116 mg, 0.610 mmol) then the reaction was stirred at 0 °C for 50 min. Next, the mixture was diluted with CH_2Cl_2, washed with 0.5 M HCl and H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a yellow oil. Addition of Et_2O, followed by grinding the insoluble residue with a spatula, induced precipitation of a solid that was separated by filtration (this procedure was repeated until no more solid was precipitated from the filtrate) to give pure (±)-**14-*anti*** (134 mg, 62%) as a white solid. Analytical data were in accordance with those reported in Method A.

Methyl *anti*-4-Azido-4-phenyl-3-[(ethoxycarbonyl)amino]-butanoate [(±)-15-*anti*]. To a stirred solution of NaN_3 (650 mg, 10.0 mmol) and NH_4Cl (107 mg, 2.00 mmol) in H_2O (2.0 mL) at 25 °C was added a solution of (±)-**12a-*anti*** (263 mg, 1.00 mmol) in MeOH (16 mL) then the reaction was stirred at 25 °C for 3 h. Next, the excess of MeOH was removed under reduced pressure and the reaction was diluted with CH_2Cl_2, washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a yellow oil. Filtration on a pad of silica gel (hexane/EtOAc 3:2) gave pure (±)-**15-*anti*** (254 mg, 83%) as a white solid, mp 68−71 °C. Analytical data: IR (KBr) 3329 (broad), 3031, 2982, 2106, 1786, 1716, 1531, 1255, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.42−7.33 (m, 5H), 5.31 (d, J = 8.4 Hz, exchanges with D_2O, 1H), 4.94 (d, J = 5.9 Hz, 1H), 4.25−4.20 (m, 1H), 4.05 (q, J = 7.3 Hz, 2H), 3.67 (s, 3H), 2.63 (dd, J = 16.2, 7.0 Hz, 1H), 2.49 (dd, J = 16.2, 4.4 Hz, 1H), 1.19 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9 (C), 155.9 (C), 136.4 (C), 129.0 (2 × CH), 128.8 (CH), 127.4 (2 × CH), 68.0 (CH), 61.3 (CH_2), 52.7 (CH), 52.1 (CH_3), 34.0 (CH_2), 14.7 (CH_3). Anal. Calcd for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 55.14; H, 6.31; N, 17.91.

Methyl *anti*-4-Azido-3-ethoxy-4-phenylbutanoate [(±)-17-*anti*] + Ethyl *anti*-4-azido-3-ethoxy-4-phenylbutanoate [(±)-18-*anti*]. To a stirred solution of (±)-**3a-*anti*** (300 mg, 1.27 mmol) in

CH_2Cl_2 (3.0 mL) at 25 °C was added EtI (0.61 mL, 7.7 mmol) and Ag_2O (1.77 g, 7.66 mmol) then the reaction was refluxed for 24 h in the absence of light. Next, another portion of EtI (0.61 mL, 7.7 mmol) was added and the reaction was stirred under reflux for an additional period of 18 h. After cooling to room temperature, the solid was separated by filtration through a pad of Celite and the filtrate was concentrated under reduced pressure to give a yellow oil. Filtration on a pad of silica gel (hexane/EtOAc 4:1) gave a 60:40 mixture of (±)-**17-*anti***:(±)-**18-*anti*** (274 mg, 80%) as a pale yellow oil. Analytical data: IR (neat) 3031, 2978, 2104, 1738, 1252, 1172, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.31 (m, 5H major, 5H minor), 4.73 (d, J = 5.1 Hz, 1H major), 4.72 (d, J = 5.1 Hz, 1H minor), 4.10 (q, J = 7.2 Hz, 2H minor), 4.01−3.97 (m, 1H major, 1H minor), 3.63 (s, 3H major), 3.57−3.46 (m, 2H major, 2H minor), 2.61−2.53 (m, 1H major, 1H minor), 2.42 (dd, J = 15.9, 3.8 Hz, 1H major), 2.41 (dd, J = 15.8, 3.9 Hz, 1H minor), 1.23 (t, J = 7.2 Hz, 3H minor), 1.10 (t, J = 7.0 Hz, 3H major, 3H minor); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9 (C), 171.4 (C), 136.5 (C), 136.4 (C), 128.7 (CH), 128.4 (CH), 128.3 (CH), 127.5 (CH), 80.0 (CH), 79.9 (CH), 67.3 (CH_2), 67.2 (CH_2), 66.6 (CH), 66.5 (CH), 60.7 (CH_2), 51.8 (CH_3), 36.3 (CH_2), 36.0 (CH_2), 15.4 (CH_3), 14.2 (CH_3).

Methyl *syn*-4-Azido-3-ethoxy-4-phenylbutanoate [(±)-17-*syn*] + Ethyl *syn*-4-Azido-3-ethoxy-4-phenylbutanoate [(±)-18-*syn*]. To a stirred solution of a 98:2 mixture of (±)-**3a-*syn***:(±)-**3a-*anti*** (330 mg, 1.40 mmol) in CH_2Cl_2 (3.3 mL) at 25 °C was added EtI (0.67 mL, 8.4 mmol) and Ag_2O (1.95 g, 8.42 mmol) then the reaction was refluxed for 23 h in the absence of light. After cooling to room temperature, the solid was separated by filtration through a pad of Celite and the filtrate was concentrated under reduced pressure to give a yellow oil. Filtration on a pad of silica gel (hexane/EtOAc 4:1) gave a 70:30 mixture of (±)-**17-*syn***:(±)-**18-*syn*** (343 mg, 93%) as a pale yellow oil. Analytical data: IR (neat) 3032, 2977, 2104, 1738, 1253, 1169, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.30 (m, 5H major, 5H minor), 4.58 (d, J = 7.2 Hz, 1H major, 1H minor), 4.10−4.04 (m, 2H minor), 3.97−3.92 (m, 1H major, 1H minor), 3.68−3.63 (m, 2H major, 2H minor), 3.61 (s, 3H major), 2.38−2.35 (m, 2H major, 2H minor), 1.22 (t, J = 7.2 Hz, 3H minor), 1.19 (t, J = 7.0 Hz, 3H major), 1.10 (t, J = 7.0 Hz, 3H minor); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5 (C), 136.7 (C), 136.6 (C), 128.9 (CH), 128.7 (CH), 127.8 (CH), 79.7 (CH), 79.6 (CH), 69.1 (CH), 67.5 (CH_2), 60.7 (CH_2), 51.8 (CH_3), 37.5 (CH_2), 37.2 (CH_2), 15.6 (CH_3), 14.3 (CH_3).

General Procedure for Reductive Cyclization of γ-Azido Esters. To a stirred solution of the γ-azido ester (1.00 mmol) in MeOH (20 mL) was added 10 mol % Pd/C (10% w/w) then the system was charged with H_2 (balloon). The mixture was stirred at 25 °C until the reaction was complete (monitored by TLC). The catalyst was separated by filtration on a filter paper and the filtrate was eluted through a pad of Celite and concentrated under reduced pressure. Unless otherwise noted, the purification of each γ-lactam was achieved by addition of Et_2O followed by grinding the insoluble residue with a spatula to induce precipitation of a solid that was separated by filtration under reduced pressure (this procedure was repeated until no more solid was precipitated from the filtrate).

anti*-4-Hydroxy-5-phenylpyrrolidin-2-one [(±)-16a-*anti*].** (±)-**16a-*anti was obtained in 91% yield as a white solid, mp 119−121 °C. Analytical data: IR (KBr) 3232 (broad), 3050, 2915, 1694, 1668, 1352, 703 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.10 (br s, exchanges with D_2O, 1H), 7.39−7.36 (m, 2H), 7.31−7.27 (m, 3H), 5.56 (br s, exchanges with D_2O, 1H), 4.36 (d, J = 3.4 Hz, 1H), 4.01−3.98 (m, 1H), 2.51 (dd, J = 16.5, 6.8 Hz, 1H), 2.03 (dd, J = 16.5, 4.1 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 174.9 (C), 141.4 (C), 128.5 (2 × CH), 127.4 (CH), 125.9 (2 × CH), 74.4 (CH), 66.2 (CH), 39.5 (CH_2). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 68.16; H, 6.34; N, 7.54.

syn*-4-Hydroxy-5-phenylpyrrolidin-2-one [(±)-16a-*syn*].** (±)-**16a-*syn was prepared from the 98:2 mixture of (±)-**3a-*syn***:(±)-**3a-*anti***. Purification by column chromatography on silica gel (EtOAc) gave pure (±)-**16a-*syn*** (87%) as a white solid, mp 138−139 °C. Analytical data: IR (KBr) 3338, 3215, 3086, 1672, 1358, 1108, 700 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.91 (br s, exchanges with D_2O, 1H), 7.25−7.13 (m, 5H), 4.73 (d, J = 5.1 Hz, exchanges with D_2O, 1H), 4.59 (d, J = 5.1 Hz, 1H), 4.29 (ddt, J = 6.2, 5.1, 2.9 Hz, 1H), 2.43 (dd, J = 16.5, 6.2 Hz, 1H), 1.98 (dd, J = 16.5, 2.9 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 175.9 (C), 138.2 (C), 127.8 (2 × CH), 127.7 (2 × CH), 127.1 (CH), 68.8 (CH), 62.7 (CH), 40.4 (CH_2). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 68.15; H, 6.37; N, 7.72.

anti*-5-Ethyl-4-hydroxypyrrolidin-2-one [(±)-16b-*anti*].** (±)-**16b-*anti was obtained in 94% yield as a white solid, mp 132−134 °C. Analytical data: IR (KBr) 3351, 3212, 3076, 2927, 1674, 1070 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.75 (br s, exchanges with D_2O, 1H), 5.16 (br s, exchanges with D_2O, 1H), 3.90 (appdt, J = 6.5, 3.0 Hz, 1H), 3.11 (dt, J = 6.7, 2.5 Hz, 1H), 2.44 (dd, J = 16.8, 6.5 Hz, 1H), 1.91 (dd, J = 16.8, 3.5 Hz, 1H), 1.50−1.25 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 174.6 (C), 70.6 (CH), 64.1 (CH), 39.7 (CH_2), 26.8 (CH_2), 10.1 (CH_3). Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.57; H, 8.96; N, 10.52.

syn*-5-Ethyl-4-hydroxypyrrolidin-2-one [(±)-16b-*syn*].** (±)-**16b-*syn was prepared from the 98:2 mixture of (±)-**3b-*syn***:(±)-**3b-*anti*** in 95% yield as a white solid, mp 179−181 °C. Analytical data: IR (KBr) 3310 (broad), 3205 (broad), 2967, 1668, 1185, 1078 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.65 (br s, exchanges with D_2O, 1H), 5.01 (d, J = 5.0 Hz, exchanges with D_2O, 1H), 4.18 (ddt, J = 6.0, 5.0, 2.5 Hz, 1H), 3.30 (dt, J = 7.0, 5.0 Hz, 1H), 2.38 (dd, J = 16.8, 6.0 Hz, 1H), 1.94 (dd, J = 16.8, 2.5 Hz, 1H), 1.60−1.30 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 175.2 (C), 67.0 (CH), 60.4 (CH), 40.8 (CH_2), 21.9 (CH_2), 10.5 (CH_3). Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.71; H, 8.72; N, 10.81.

anti*-4-Ethoxy-5-phenylpyrrolidin-2-one [(±)-19-*anti*].** (±)-**19-*anti was prepared from the 60:40 mixture of (±)-**17-*anti***:(±)-**18-*anti*** in 83% yield as a white solid, mp 84−85 °C. Analytical data: IR (KBr) 3191 (broad), 3097, 2918, 2866, 1712, 1085, 698 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.19 (br s, exchanges with D_2O, 1H), 7.41−7.28 (m, 5H), 4.55 (d, J = 2.5 Hz, 1H), 3.85 (appdt, J = 6.5, 3.2 Hz, 1H), 3.55 (dq, J = 9.3, 7.0 Hz, 1H), 3.43 (dq, J = 9.3, 7.0 Hz, 1H), 2.61 (dd, J = 17.0, 6.7 Hz, 1H), 2.11 (dd, J = 17.0, 3.5 Hz, 1H), 1.11 (t, J = 7.0 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 174.9 (C), 141.2 (C), 128.8 (2 × CH), 127.6 (CH), 126.1 (2 × CH), 81.9 (CH_2), 64.0 (CH), 63.3 (CH), 36.7 (CH_2), 15.3 (CH_3). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.90; H, 7.09; N, 6.72.

syn*-4-Ethoxy-5-phenylpyrrolidin-2-one [(±)-19-*syn*].** (±)-**19-*syn was prepared from the 70:30 mixture of (±)-**17-*syn***:(±)-**18-*syn***. The reaction was carried out at 25 °C for 2 h then the balloon with H_2 was removed and the mixture was refluxed for 20 h. Purification by column chromatography on silica gel (hexane/EtOAc 1:1) gave pure (±)-**19-*syn*** (61%) as a white solid, mp 80−82 °C. Analytical data: IR (KBr) 3191 (broad), 3086, 2923, 1691, 1121,1089, 699 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.12 (br s, exchanges with D_2O, 1H), 7.36−7.28 (m, 5H), 4.84 (d, J = 5.7 Hz, 1H), 4.25−4.22 (m, 1H), 3.20 (dq, J = 9.4, 7.0 Hz, 1H), 2.89 (dq, J = 9.4, 7.0 Hz, 1H), 2.55 (dd, J = 16.7, 6.7 Hz, 1H), 2.20 (dd, J = 16.7, 4.2 Hz, 1H), 0.75 (t, J = 7.0 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 175.2 (C), 138.1 (C), 127.9 (2 × CH), 127.8 (2 × CH), 127.4 (CH), 76.7 (CH_2), 64.4 (CH), 61.4 (CH), 37.8 (CH_2), 14.9 (CH_3). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.84; H, 7.75; N, 6.60.

4-Hydroxypyrrolidin-2-one. To a stirred solution of ethyl 4-azido-3-oxobutanoate[44] (3.80 g, 22.2 mmol) in absolute EtOH

(46 mL) at 0 °C (ice bath) was added $NaBH_4$ (420 mg, 11.1 mmol). The ice bath was removed then the reaction was stirred at 25 °C for 2 h. Next, the final mixture was quenched with 1 M HCl and the excess of EtOH was removed under reduced pressure. The mixture was extracted with Et_2O and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a yellow oil. Filtration on a pad of silica gel (hexane/EtOAc 7:3) gave pure ethyl 4-azido-3-hydroxybutanoate (2.5 g, 65%) as a pale yellow oil. Analytical data: IR (neat) 3449 (broad), 2983, 2105, 1727, 1291, 1177 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.21−4.16 (m, 3H), 3.38 (dd, J = 12.4, 4.4 Hz, 1H), 3.32 (dd, J = 12.4, 6.3 Hz, 1H), 2.55 (dd, J = 14.3, 5.5 Hz, 1H), 2.52 (dd, J = 14.3, 2.6 Hz, 1H), 1.28 (t, J = 7.2 Hz, 3H). Reductive cyclization of ethyl 4-azido-3-hydroxybutanoate following the general procedure described above furnished 4-hydroxypyrrolidin-2-one as a pale yellow solid in 71% yield, mp 116−118 °C (lit.[50] mp 118−120 °C). IR and NMR (^1H and ^{13}C) spectra are in accordance with reported data.[50]

anti*-4-Amino-5-phenylpyrrolidin-2-one [(±)-23-*anti*].** **(±)-23-*anti was purified by filtration on a pad of silica gel (hexane/EtOAc 3:7) in 86% yield as a colorless oil. Analytical data: IR (neat) 3226, 3025, 2896, 1692, 1281, 699 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.99 (br s, exchanges with D_2O, 1H), 7.38−7.27 (m, 5H), 4.19 (d, J = 4.9 Hz, 1H), 3.20−3.15 (m, 1H), 2.43 (dd, J = 16.5, 7.5 Hz, 1H), 1.98 (dd, J = 16.5, 6.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 175.5 (C), 142.0 (C), 128.5 (2 × CH), 127.4 (CH), 126.1 (2 × CH), 66.7 (CH), 57.5 (CH), 40.1 (CH_2).

syn*-4-Amino-5-phenylpyrrolidin-2-one [(±)-23-*syn*].** **(±)-23-*syn was obtained in 81% yield as a white solid, mp 119−121 °C. Analytical data: IR (KBr) 3379, 3353, 3193 (broad), 3087, 2922, 1681, 1353, 701 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.02 (br s, exchanges with D_2O, 1H), 7.39−7.23 (m, 5H), 4.66 (d, J = 6.3 Hz, 1H), 3.72 (appq, J = 6.4 Hz, 1H), 2.42 (dd, J = 16.4, 7.1 Hz, 1H), 1.93 (dd, J = 16.4, 5.7 Hz, 1H), 0.97 (br s, exchanges with D_2O, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.2 (C), 138.4 (C), 128.2 (2 × CH), 127.4 (CH), 127.3 (2 × CH), 62.1 (CH), 51.3 (CH), 39.5 (CH_2). Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 67.80; H, 7.14; N, 15.53.

anti*-5-Phenyl-4-[(4-toluenesulfonyl)amino]pyrrolidin-2-one [(±)-24-*anti*]. Method A:** **(±)-24-*anti was prepared from **(±)-14-*anti*** following the general procedure for reductive cyclization described above in 89% yield as a white solid, mp 210 °C dec. Analytical data: IR (KBr) 3416 (broad), 3235, 3095, 2924, 1703, 1336, 1153 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.15 (br s, exchanges with D_2O, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.31−7.25 (m, 5H), 7.15 (d, J = 8.4 Hz, 2H), 4.39 (d, J = 4.8 Hz, 1H), 3.53 (ddd, J = 8.1, 5.5, 4.8 Hz, 1H), 2.35 (s, 3H), 2.30 (dd, J = 16.9, 8.1 Hz, 1H), 1.90 (dd, J = 16.9, 5.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.9 (C), 142.9 (C), 140.4 (C), 138.0 (C), 129.7 (2 × CH), 128.6 (2 × CH), 127.8 (CH), 126.5 (2 × CH), 126.2 (2 × CH), 63.5 (CH), 57.5 (CH), 36.7 (CH_2), 21.0 (CH_3). Anal. Calcd for $C_{17}H_{18}N_2O_3S$: C, 61.80; H, 5.49; N, 8.48; S, 9.70. Found: C, 61.50; H, 5.49; N, 8.26; S, 9.41. **Method B:** To a stirred mixture of **(±)-23-*anti*** (114 mg, 0.650 mmol) and pyridine (0.52 mL, 6.5 mmol) at 0 °C (ice bath) was added TsCl (136 mg, 0.710 mmol) then the reaction was stirred at 0 °C for 30 min. Next, the mixture was diluted with CH_2Cl_2, washed with 0.5 M HCl and H_2O, and concentrated under reduced pressure to give **(±)-24-*anti*** (111 mg, 52%) as a pale yellow solid that was not purified further. Analytical data were in accordance with those reported in Method A.

anti*-5-Phenyl-4-[(ethoxycarbonyl)amino]pyrrolidin-2-one [(±)-25-*anti*].** **(±)-25-*anti was obtained in 92% yield as a white solid, mp 206 °C dec. Analytical data: IR (KBr) 3327, 3215 (broad), 3092, 2984, 1711, 1686, 1538, 1275, 696 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.17 (br s, exchanges with D_2O, 1H), 7.72 (d, J = 7.2 Hz, exchanges with D_2O, 1H), 7.39−7.27 (m, 5H), 4.45 (d, J = 4.7 Hz, 1H), 4.00−3.85 (m, 3H), 2.52 (dd, J = 16.8, 8.2 Hz, 1H), 2.15 (dd, J = 16.8, 5.9 Hz, 1H), 1.14 (t, J = 7.0 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 174.5 (C), 155.9 (C), 141.2 (C), 128.6 (2 × CH), 127.7 (CH), 126.1 (2 × CH), 63.4 (CH), 59.9 (CH_2), 55.6 (CH), 36.2 (CH_2), 14.6 (CH_3). Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.08; H, 6.82; N, 11.03.

anti*-4-Acetyloxy-5-phenylpyrrolidin-2-one [(±)-22-*anti*].** To a stirred mixture of **(±)-16a-*anti (50 mg, 0.28 mmol) and potassium-exchanged molecular sieves (13X/KCl)[40] (168 mg, 600 mg/mmol) at 25 °C was added acetic anhydride (0.37 mL, 3.9 mmol) then the reaction was allowed to stir at 100 °C for 30 min. After the mixture had cooled to room temperature, the catalyst was separated by filtration on a pad of Celite and washed with CH_2Cl_2, then the filtrate was concentrated under reduced pressure until removal of all the volatiles. Addition of Et_2O, followed by grinding the insoluble residue with a spatula, induced precipitation of a solid that was separated by filtration under reduced pressure (this procedure was repeated until no more solid was precipitated from the filtrate) to give pure **(±)-22-*anti*** (53 mg, 85%) as a white solid, mp 157 °C dec. Analytical data: IR (KBr) 3207 (broad), 3093, 2951, 1738, 1701, 1242, 702 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.42 (br s, exchanges with D_2O, 1H), 7.42−7.30 (m, 5H), 4.97 (appdt, J = 6.7, 1.4 Hz, 1H), 4.63 (br s, 1H), 2.76 (dd, J = 17.7, 6.7 Hz, 1H), 2.14 (dd, J = 17.7, 2.1 Hz, 1H), 2.08 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 174.2 (C), 170.1 (C), 139.9 (C), 128.7 (2 × CH), 127.8 (CH), 125.9 (2 × CH), 76.2 (CH), 63.1 (CH), 35.3 (CH_2), 20.9 (CH_3). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.37; H, 6.33; N, 6.10.

Methyl *anti*-3-Acetyloxy-4-azido-4-phenylbutanoate [(±)-20-*anti*]. Method A: To a stirred solution of **(±)-3a-*anti*** (100 mg, 0.425 mmol) in CH_2Cl_2 (6.0 mL) was added acetic anhydride (0.20 mL, 2.1 mmol) followed by pyridine (0.20 mL, 2.5 mmol) and DMAP (5.3 mg, 0.043 mmol) then the reaction was stirred at 25 °C for 4 h. Next, the mixture was diluted with CH_2Cl_2, washed with 1 M HCl, sat. $NaHCO_3$, and H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a yellow oil. Filtration on a pad of silica gel (hexane/EtOAc 9:1) gave pure **(±)-20-*anti*** (112 mg, 95%) as a pale yellow oil. Analytical data: IR (neat) 3030, 2954, 2107, 1745, 1228, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39−7.33 (m, 5H), 5.47 (ddd, J = 9.0, 4.7, 3.8 Hz, 1H), 4.93 (d, J = 4.7 Hz, 1H), 3.61 (s, 3H), 2.71 (dd, J = 16.4, 9.0 Hz, 1H), 2.48 (dd, J = 16.4, 3.8 Hz, 1H), 2.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.5 (C), 170.0 (C), 135.2 (C), 128.9 (2 × CH), 128.7 (CH), 127.2 (2 × CH), 72.9 (CH), 66.8 (CH), 51.9 (CH_3), 33.9 (CH_2), 20.9 (CH_3). **Method B:** To a stirred mixture of **(±)-3a-*anti*** (100 mg, 0.425 mmol) and potassium-exchanged molecular sieves (13X/KCl)[40] (255 mg, 600 mg/mmol) at 25 °C was added acetic anhydride (0.50 mL, 5.3 mmol) then the reaction was stirred at 100 °C for 3.5 h. After the mixture had cooled to room temperature, the catalyst was separated by filtration and washed with CH_2Cl_2. The filtrate was eluted through a pad of Celite and concentrated under reduced pressure. The residue was diluted with EtOAc then washed with sat. $NaHCO_3$ and H_2O and the combined aqueous phases were back-extracted with CH_2Cl_2. The combined organic phases (EtOAc and CH_2Cl_2) were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give pure **(±)-20-*anti*** (111 mg, 94%) as a pale yellow oil. Analytical data were in accordance with those reported in Method A.

Methyl *anti*-4-(*N*-Acetylamino)-3-hydroxy-4-phenylbutanoate [(±)-21-*anti*]. Method A: **(±)-21-*anti*** was prepared by hydrogenation of **(±)-20-*anti*** following the general procedure for reductive cyclization described above. After the reaction, crude **(±)-21-*anti*** (84%) was obtained as a yellow oil that was not purified further. Analytical data: IR (neat) 3303 (broad), 3064,

(50) Baker, J. T.; Sifniades, S. *J. Org. Chem.* **1979**, *44*, 2798–2800.

3031, 2952, 1736, 1654, 1543, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.23 (m, 5H), 6.79 (d, J = 8.4 Hz, exchanges with D_2O, 1H), 4.94 (dd, J = 8.4, 4.3 Hz, 1H), 4.37 (appdt, J = 9.6, 3.7 Hz, 1H), 3.62 (s, 3H), 2.46 (dd, J = 16.6, 3.0 Hz, 1H), 2.20 (dd, J = 16.6, 9.6 Hz, 1H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9 (C), 170.1 (C), 137.8 (C), 128.5 (2 × CH), 128.2 (2 × CH), 127.9 (CH), 69.9 (CH), 57.1 (CH), 51.9 (CH_3), 38.3 (CH_2), 23.2 (CH_3). **Method B:** To a stirred solution of (±)-**3a-*anti*** (100 mg, 0.425 mmol) in EtOAc (5.0 mL) was added acetic anhydride (0.50 mL, 5.3 mmol) and 10% Pd/C (10 mg, 10% w/w), then the system was charged with H_2 (balloon). The reaction was stirred at 25 °C for 1 h, then the catalyst was separated by filtration on a filter paper followed by elution through a pad of Celite. The filtrate was concentrated under reduced pressure to give crude (±)-**21-*anti*** (81.0 mg, 75%) as a colorless oil that was not purified further. Analytical data were in accordance with those reported in Method A.

(3*R*,4*R*)-Methyl 3-phenyloxirane-2-acetate [(+)-1a]. In a three-necked round-bottomed flask containing a stirred solution of **2a** (1.00 g, 5.68 mmol) in CH_3CN (85 mL) was added buffer (50 mM $Na_2B_4O_7 \cdot 10H_2O$ in 0.4 mM Na_2EDTA; 56.5 mL), Bu_4NHSO_4 (77 mg, 0.23 mmol), and Shi's epoxone[42,45] (733 mg, 2.84 mmol). Next, the mixture was cooled to 0 °C (ice bath) and a solution of Oxone (6.98 g, 11.36 mmol) in 0.4 mM Na_2EDTA (72.3 mL) and a solution of K_2CO_3 (6.58 g, 47.7 mmol) in water (72.3 mL), each in separate addition funnels, were added dropwise over a period of 2.5 h (pH of the reaction mixture was maintained around 10.5). Then the mixture was quenched with water and extracted with cyclopentane. Combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a colorless oil. Purification by column chromatography on silica gel (hexane/EtOAc 19:1) gave pure (+)-**1a** (744 mg, 68%, or 91% based on recovered starting material; 95.5:4.5 er) as a colorless oil. $[\alpha]^{23}_D$ +24.2 (*c* 1.0, $CHCl_3$). Analytical data were in accordance with those reported above for the racemic epoxide (±)-**1a**.

(3*R*,4*S*)-Methyl 4-Azido-3-hydroxy-4-phenylbutanoate [(+)-3a]. (+)-**3a** was prepared from (+)-**1a** as described above for racemic (±)-**3a-*anti*** in 89% yield as a pale yellow oil. $[\alpha]^{23}_D$ +127.0 (*c* 0.83, $CHCl_3$). Analytical data were in accordance with those reported above for the racemic azido alcohol (±)-**3a-*anti***.

(4*R*,5*S*)-4-Hydroxy-5-phenylpyrrolidin-2-one [(−)-16a]. (−)-**16a** was prepared from (+)-**3a** following the general procedure for reductive cyclization described above in 87% yield as a pale yellow solid, mp 159−161 °C dec. $[\alpha]^{23}_D$ −15.7 (*c* 1.0, MeOH). Analytical data were in accordance with those reported above for the racemic γ-lactam (±)-**16a-*anti***.

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Supporting Information Available: X-ray crystallographic data (for compounds (±)-**16a-*anti***, (±)-**16a-*syn***, (±)-**16b-*anti***, and (±)-**16b-*syn***) and copies of IR, ^1H and ^{13}C NMR spectra, and GC chromatograms for er determination. This material is available free of charge via the Internet at http://pubs.acs.org.