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An Easy Stereoselective Access to β,γ-Aziridino α-Amino Ester Derivatives via Mannich Reaction of Benzophenone Imines of Glycine Esters with *N*-Sulfonyl α-Chloroaldimines

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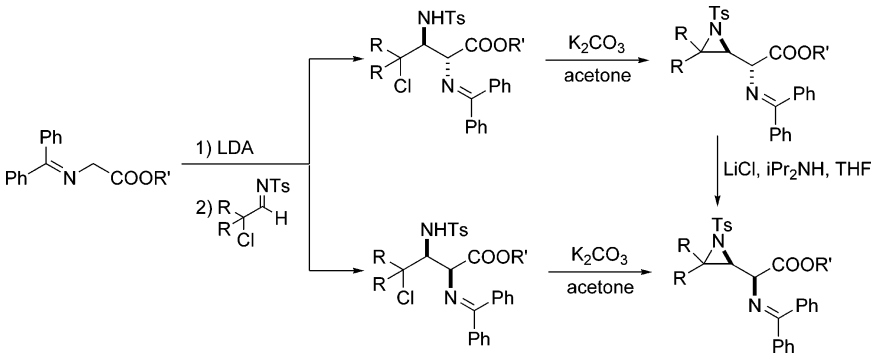

Mannich-type addition of benzophenone imine glycinates across newly synthesized *N*-(*p*-toluenesulfonyl) α-chloroaldimines afforded γ-chloro-α,β-diamino ester derivatives with moderate diastereoselectivity as separable mixtures of *anti* and *syn* diastereomers. The γ-chloro-α,β-diamino esters were efficiently cyclized under basic conditions to the corresponding β,γ-aziridino α-amino ester derivatives, representing a new class of conformationally constrained heterocyclic α,β-diamino acid derivatives. The relative configuration of the aziridines was determined via X-ray diffraction analysis. Mechanisms and intermediate transition states to explain the stereochemical outcome of the Mannich reaction with different substrates or under different conditions are proposed. The synthetic importance of the β,γ-aziridino α-amino ester derivatives is demonstrated by their conversion into the corresponding Boc-protected derivatives and ring opening reactions to α,β-diamino esters and a γ-amino α,β-unsaturated amino ester.

Introduction

The incorporation of conformationally constrained α-amino acids[1] and, more recently, β-amino acids[2] into biologically active peptides has gained great interest in the preparation of peptide-based drug molecules. α,β-Diamino acids **1**, as biological relevant compounds and precursors of 3-amino-β-lactams,[3] have received far less attention.

2-Aziridinylglycines **2** and derivatives thereof, such as esters and amides, can be considered as a virtually new class of conformationally constrained heterocyclic α,β-diamino acid derivatives of which only few representatives have been described. Recently, the synthesis of a *N*-Cbz-protected 2-aziridinylglycinamide **3** was reported in low yield via rearrangement of 3-{[(benzyloxy)carbonyl]amino}-4-(mesyloxymethyl)-1-(4-methoxyphenyl)-2-azetidinone upon treatment with ammonia,[4] analogous to the transformation of 4-(1-haloalkyl)-2-azetidinones with sodium methoxide in methanol to methyl 4-(alkylamino)-pentenoates via intermediate methyl 2-aziridinylacetates.[5] The

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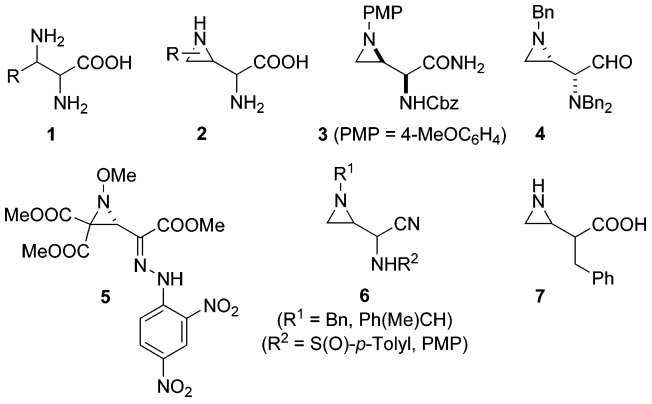
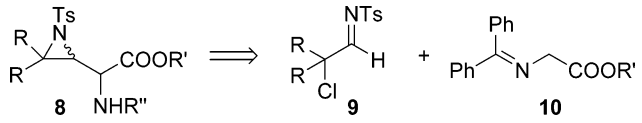
Swern oxidation of a 2-[1-(dibenzyl)amino-2-hydroxyethyl]-aziridine resulted in unstable α-(*N*,*N*-dibenzyl)amino-2-aziridine-acetaldehyde **4**,[6] while hydrazone **5** was prepared from the corresponding *N*-methoxy-2-methoxyoxalyl-3,3-(dimethoxy-carbonyl)aziridine.[7] Strecker reaction of aziridine-2-carbox-aldimines with trimethylsilyl cyanide stereoselectively afforded α-amino 2-aziridinylacetonitriles **6**, which could be used in further ring opening reactions.[8] 2-Aziridinylglycines **2** are potentially very interesting compounds from biological as well as from synthetic point of view. Besides their application as conformationally restricted analogues of physiologically active α,*β*-diamino acids and peptides, they are also related to 2-(aziridin-2-yl)-3-phenylpropionic acid **7** which is a carboxy-peptidase A inhibitor.[9] Aziridines are of great importance as structural components of natural and biologically active prod-ucts.[10] For instance, azinomycines A and B and mitomycin C are potent antitumor and antibiotic agents.[11a] Aziridines are also important heterocyclic compounds in the synthesis of a variety of nitrogen-containing compounds such as amino sugars, alkaloids, and substituted amino acids.[11] Considerable efforts have been made to nucleophilic ring opening of aziridines.[12] 2-Aziridinylglycines **2**, being substituted 2-aziridinylacetates[13] which in their turn are the homologues of aziridine-2-carbox-ylates,[14] could be useful building blocks for the synthesis of functionalized α,*β*- and α,*γ*-diamino acid derivatives.



Our present aim was to develop a method for the synthesis of conformationally constrained aziridino amino ester diaster-eomers **8** bearing the nitrogen moieties in α,*β*,*γ*-positions of the ester, filling up part of the gap of the chemistry of α-amino 2-aziridinylacetate derivatives.

SCHEME 1. Retrosynthetic Analysis of the *β*,*γ*-Aziridino α-Amino Esters 8



Results and Discussion

According to the retrosynthetic analysis of the target com-pounds **8**, the readily available benzophenone imine glycine esters **10** and *N*-(*p*-toluenesulfonyl) α-chloroimine derivatives **9** seemed to be suitable starting materials for this goal (Scheme 1).

A convenient method for the stereoselective synthesis of α,*β*-diamino acid derivatives involves Mannich reaction of α-amino ester derivatives across imines.[15] This methodology has also been applied in the synthesis of 3-amino-*β*-lactams via cyclization of intermediate α,*β*-diamino esters.[16] Despite the numerous approaches to *β*-amino esters,[17] *β*-trifluoromethyl-*β*-amino esters,[18] α-oxy-*β*-amino esters,[19] *γ*-alkoxy-*β*-amino esters,[20] α,α-difluoro-*β*-amino esters,[21] α-cyano-*β*-amino esters,[22] *β*-amino diesters,[23] aspartic acid derivatives,[24] *β*′-keto-*β*-amino esters,[25] aziridine-2-carboxylic esters,[26] C-glycosyl *β*-amino esters,[27] and α,*β*-diamino acid derivatives of biological importance by Mannich condensation of ester enolates or equivalents with imines recently reported, only two isolated examples have been published in which a chloro substituent is present at the α-position of the C═N double bond of the reacting imine in broad sense, that is, hydrazones and in situ formed imines included.[28,29] More specifically, it concerned here chloroacet-

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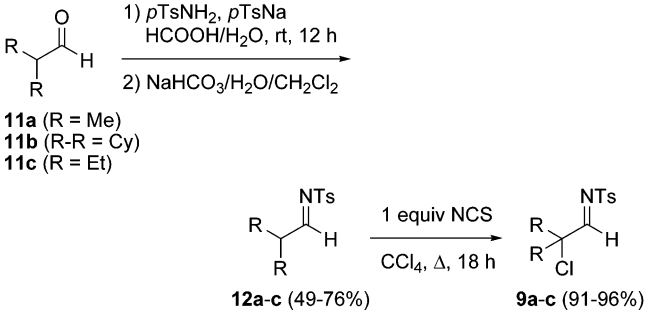
aldehyde derivatives which are not general in view of their lability. The condensation of ester enolates with α-chloroimines would lead to β-amino-γ-chloro esters as suitable intermediates for further cyclization to 2-aziridinylacetates. An acylhydrazone derived from chloroacetaldehyde reacted via a zirconium-catalyzed asymmetric Mannich-type reaction with the silyl enol ether derived from methyl isobutyrate to afford the corresponding β-*N*′-acylhydrazino-γ-chlorocarboxylic ester adduct.[28] Similarly, HBF_4-catalyzed three-component coupling reaction of chloroacetaldehyde, aniline, and the silyl enol ether derived from methyl isobutyrate took place smoothly in water in the presence of a surfactant.[29] However, in neither of the latter two reports the β-amino-γ-chloro esters were further investigated.

SCHEME 2. Synthesis of α-Chloroaldimines 9



The aliphatic aldehydes **11a**−**c** were first transformed to their corresponding *N*-(*p*-toluenesulfonyl) aldimines **12a**−**c** according to a known literature procedure involving the reaction of aldehydes **11** with *p*-toluenesulfonamide and sodium *p*-toluenesulfinate in aqueous formic acid and subsequent treatment with sodium bicarbonate.[30] The aliphatic aldimines **12** were then submitted to α-chlorination with *N*-chlorosuccinimide (NCS), furnishing the desired new α-chloroimines **9a**−**c** in 91−96% yield (Scheme 2). These new non-enolizable activated α-chloroaldimines **9** were obtained exclusively as the *E*-isomers in acceptable purity after removal of the formed succinimide by simple filtration or extractive workup. All attempts to obtain analytically pure samples of the α-chloroaldimines **9** via recrystallization failed, however, due to their instability upon storage in solution, even at low temperature, and it proved necessary to immediately use the aldimines **9** as such in the next step.

The nucleophilic attack of the benzophenone imine glycine esters **10** across the *N*-(*p*-toluenesulfonyl) α-chloroaldimines **9** was studied under different base conditions with ethyl ester **10a** and the aldimine **9a** derived from isobutyraldehyde (**11a**) as model compounds.[31] In the presence of KOtBu in THF or under

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SCHEME 3. Synthesis of Diamino Esters 13 and 14 from *N*-Tosyl Aldimines 9 and Benzophenone Imine Glycinates 10

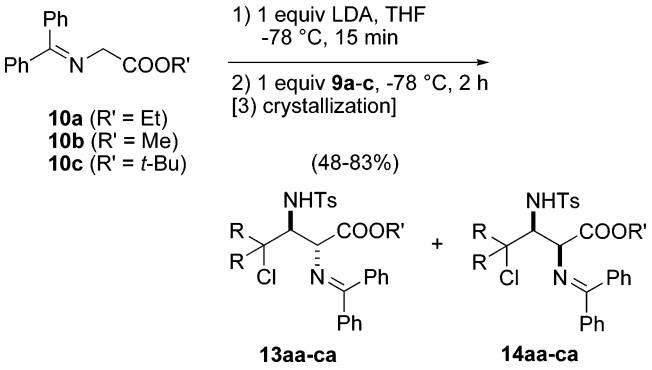


TABLE 1. Addition of Glycinates 10 to Aldimines 9[a]

entry	9	10	dr (13:14)[b] (yield)	13 (%)[c]	14 (%)[c]
1	9a	10a	13aa/14aa = 2:1 (66%)	43	22
2	9a	10b	13ab/14ab = 2.5:1 (57%)	40	17
3	9a	10c	13ac/14ac = 1:1 (48%)	24	
4	9b	10a	13ba/14ba = 2:1 (83%)	46	22
5	9b	10b	13bb/14bb = 3.5:1 (68%)		
6	9c	10a	13ca/14ca = 2:1 (80%)		

[a] All reactions were performed at −78 °C in THF for 2 h using 1 equiv of **9**, 1 equiv of **10**, and 1 equiv of LDA. [b] Determined by ^{1}H NMR analysis (300 MHz) of the crude reaction mixtures. [c] Isolated yield of pure diastereomers after crystallization.

phase transfer conditions (NaOH, benzyltriethylammonium chloride, toluene/water), the reaction failed to give the desired 1,2-adducts. In the presence of $LiClO_4$ and Et_3N in THF,[15k] the two possible *anti* and *syn* diastereomers **13aa** and **14aa** unfortunately were formed only in low yield in 2:1 ratio together with unreacted starting material. However, when the reaction of ethyl glycinate **10a** with *N*-tosylimine **9a** was effected by initial deprotonation of the ester with lithium diisopropylamide (LDA) in THF at −78 °C, a mixture of *syn* and *anti* diastereomers **13aa** and **14aa** was formed in good yield with moderate diastereoselectivity (dr 2:1) (Scheme 3 and Table 1, entry 1). Under the latter reaction conditions, the addition to the *N*-tosylimine **9a** was also accomplished in acceptable yield by using the methyl and *tert*-butyl glycine esters **10b** and **10c** (Table 1, entries 2 and 3). The sterical bulk of the ester **10** had moderate influence on the diastereoselectivity of the reaction with the *anti*/*syn* ratio decreasing from 2.5:1 to 1:1 in the order Me:Et:*t*-Bu. The scope of the nucleophilic addition of glycine ethyl ester **10a** was extended to the larger alkyl-substituted α-chloroimines **9b** (R−R = Cy) and **9c** (R = Et) (Table 1, entries 4 and 6). In both cases, the ratio of the *anti* **13ba**,**ca** and *syn* **14ba**,**ca** Mannich adduct was determined to be 2:1, demonstrating that the sterical bulk of the aldimine **9** had little influence on the diastereoselectivity of the Mannich reaction. However, a higher *anti* diastereoselectivity was observed again when the methyl ester adducts **13bb**/**14bb** were synthesized (Table 1, entry 5). Determination of the diastereomeric ratios was based on the relative integration values of the distinguishable *β*-hydrogens of the *anti* and *syn* adducts **13** and **14** in the crude reaction mixtures. The chemical shifts or the values of coupling constants of acyclic α-(diphenylmethylene)amino-*β*-(*p*-toluenesulfonyl)amino carboxylic esters **13**/**14** cannot be used for an unambiguous determination of their relative stereochemistry. However, comparison with closely related stereochemically defined α-(diphenylmethylene)amino-*β*-(*p*-toluenesulfonyl)-amino carboxylic esters in literature allows a preliminary stereochemical determination.[15k] For analogous *β*-aryl-α-(diphenylmethylene)amino-*β*-(*p*-toluenesulfonyl)amino carboxylic esters, the H_β hydrogen of the *syn* isomer appears at higher chemical shift as compared to the *anti* isomer. Additionally, the vicinal coupling constant $^3J_{H\alpha-H\beta}$ for the *syn* isomer shows a smaller value than the *anti* isomer. These chemical correlations are in agreement with the minor isomers **14** obtained by us, and the relative stereochemistry of the minor isomers **14** was thus tentatively assigned as being *syn*. Moreover, the vicinal coupling constant $^3J_{H\alpha-H\beta}$ for the *syn* isomers **14ab** ($^3J_{H\alpha-H\beta}$ = 1.1 Hz) and **14bb** ($^3J_{H\alpha-H\beta}$ = 0.83 Hz) has a comparable small value as the observed vicinal coupling constant $^3J_{H\alpha-H\beta}$ of the closely related nonchlorinated *β*-isopropyl- ($^3J_{H\alpha-H\beta}$ = 1.6 Hz) and *β*-cyclohexyl-α-(diphenylmethylene)amino-*β*-(*p*-toluenesulfonyl)amino carboxylic esters ($^3J_{H\alpha-H\beta}$ = 1.2 Hz).[15k]

Adducts **13aa**,**ab**,**ac**,**ba** and **14aa**,**ab**,**ba** could be isolated as single diastereomers by crystallization from mixtures of hexane/EtOAc in good yields. The minor *syn* isomers **14aa**,**ab**,**ba** crystallized first from the reaction mixtures and the major *anti* isomers **13aa**,**ab**,**ba** could be subsequently recovered as solid compounds almost quantitatively from the filtrate by concentration. Only *anti* isomer **13ac** crystallized from the 1:1 mixture **13ac**/**14ac** which made it impossible to isolate the *syn* isomer **14ac** as a stereochemically pure compound. All attempts to separate diastereomers **13bb**/**14bb** and **13ca**/**14ca** via selective crystallization failed, and therefore these mixtures were used as such in the subsequent ring closing step, after which separation of the diastereomers would be attempted again (vide infra).

The *anti* stereoselectivity of the Mannich addition reaction of the glycine enolates **15** with the *N*-tosylimines **9** can be explained on the basis of the conformational arrangement in the proposed transition state of the reaction (Figure 1). Due to intramolecular chelation, the enolates **15** are expected to have the *Z*-geometry.[15h,32] When considering a cyclic chelated six-membered chairlike transition state, such as the Zimmerman−Traxler model,[33] in aldol reactions, one can apply as a rule of thumb that (*Z*)-enolates result in *syn*-aldol products. However, in Mannich reactions, the *E*-geometry of the electrophilic aldimines, such as *N*-tosylimines **9**, restricts the latter compounds to only one binding conformation in the Zimmerman−Traxler model,[34] which results in the formation of *anti*-Mannich adducts from (*Z*)-enolates. Therefore, the obtained *anti* stereoselectivity in adducts **13** is in accordance with the chairlike transition state model **TS-1**, in analogy to a model proposed by Davis.[15h] Despite the disfavoring 1,3-diaxial interaction between the haloalkyl group ($CClR_2$) and the alkoxy function (OR′), which explains the better *anti* diastereoselectivity with smaller R′ groups, **TS-1** is likely to be favored due to the coordinating ability of the chlorine atom and, to a lesser extent, one of the oxygen atoms on sulfur with lithium.[35] However, a less sterically congested open transition state **TS-2** cannot be excluded to explain the formation of the *anti* adducts **13**. The formation of

(32) Ezquerra, J.; Pedregal, C.; Merino, I.; Florez, J.; Barluenga, J.; Garcia-Granda, S.; Llorca, M. A. *J. Org. Chem.* **1999**, *64*, 6554.
(33) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.
(34) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.
(35) For the stereochemical explanation of Grignard additions to α-chloro-*tert*-butanesulfinyl aldimines via the coordinating ability of the α-chloro atom with magnesium, see: Denolf, B.; Mangelinckx, S.; Törnroos, K. W.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 3129.

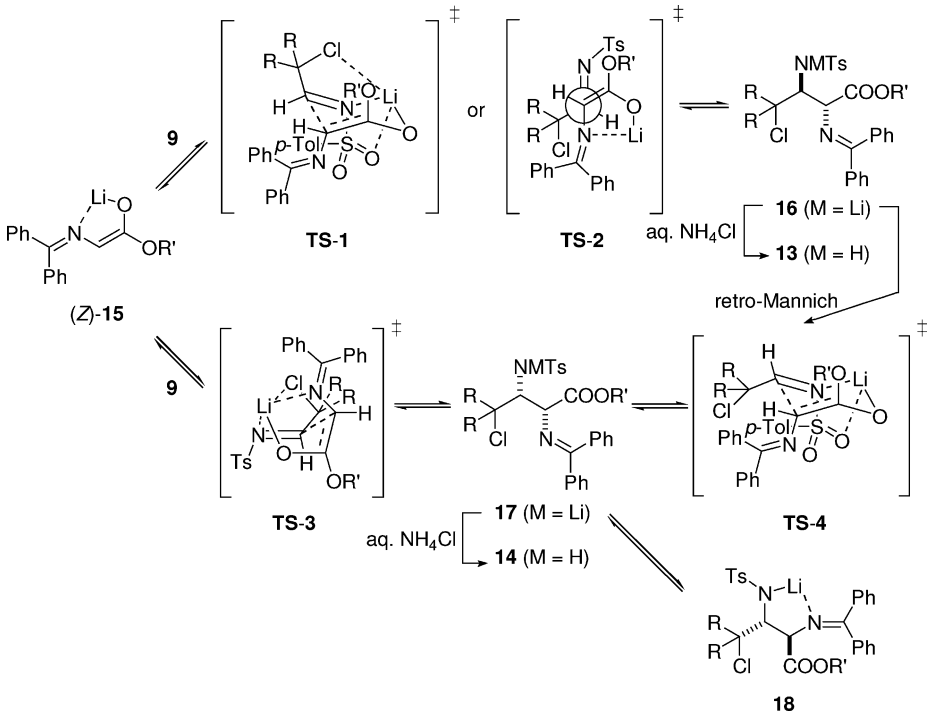


FIGURE 1. Possible transition states in the formation of the *anti* and *syn* diastereomers **13** and **14**.

SCHEME 4. Formation and Isomerization Reaction of the *anti* Adduct 13ab

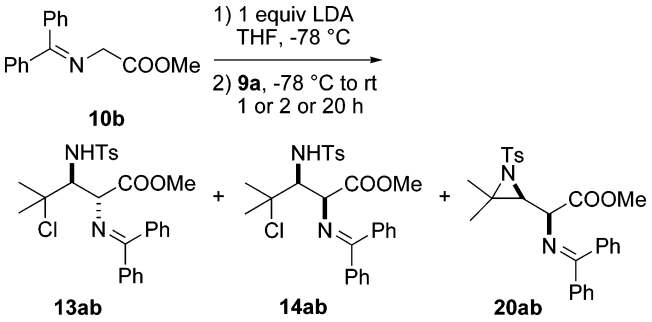


TABLE 2. Formation and Isomerization Reaction of the *anti* Adduct 13ab (Scheme 4)

entry	reaction time (h)	ratio[a] **13ab**:**14ab**	yield[b] **13ab** (%)	yield[b] **14ab** (%)	recovery[b] **10b** (%)	ratio[a] **14ab**:**20ab**
1	1	9:1	37		24	
2	2	2.5:1	40	17	10	
3	20		0			1:1

[a] Determined by ^{1}H NMR analysis (300 MHz) of the crude reaction mixtures. [b] Isolated yields of pure compounds.

the *syn* adducts **14**, especially in the derivatives with the larger R′ groups, can be explained via a boatlike transition state **TS-3** involving the (*E*)-*N*-tosylimines **9**.[36]

In order to get some better insight in the mechanism of the Mannich addition, the reaction of benzophenone imine glycine **10b** and the α-chloroimine **9a** was performed under thermodynamic control (Scheme 4 and Table 2), that is, extended reaction time (20 h) at room temperature. The fact that the *syn* isomer **14ab**, together with the *syn*-aziridine **20ab** (vide infra), instead of the kinetically favored *anti* adduct **13ab**, was formed upon stirring for 20 h gives support for an alternative six-membered chelate chairlike transition state **TS-4**, resulting from the retro-Mannich fragmentation of the initially formed lithiated *anti* adduct **16**. Via the retro-Mannich fragmentation, the formation of imine **9** with *Z*-stereochemistry, as present in transition state **TS-4**, is possible.[37] Very recently, the group of Davis also described that the kinetically favored *anti*-2,3-diamino ester, resulting from the addition of benzophenone imine glycinate **10a** across (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide, isomerized via retro-Mannich fragmentation to the more stable *syn*-2,3-diamino ester under thermodynamic reaction conditions.[15y] In further analogy with suggestions of the group of Davis, it is believed that lithiated *syn* adduct **17** is thermodynamically favored due to the occurrence of an equilibrium with the intramolecular chelated complex **18** which is sterically favored due to the *trans* configuration of the five-membered complex.[15y]

Furthermore, an isomerization of the isolated *anti* isomer **13ab** into the thermodynamically more stable *syn* isomer **14ab** and *syn*-aziridine **20ab** was observed upon stirring under mild base conditions (^{i}Pr$_2$NH, LiCl, rt) (Scheme 5 and Table 3).

Having partially solved the separation of the two diastereomers **13** and **14** by crystallization from a hexane/ethyl acetate mixture, the aziridine ring at the β,γ-position was constructed by intramolecular 1,3-displacement of the chloride under basic condition. The reaction of the pure diastereomers **13aa**,**ab**,**ac**,**ba** and **14aa**,**ab**,**ba** was performed easily with K_2CO_3 in refluxing acetone for 5 h giving the β,γ-aziridino-α-(*N*-diphenylmethylidene)amino esters **19aa**,**ab**,**ac**,**ba** and **20aa**,**ab**,**ba** in 58−87% yield (Scheme 6). As presented above, the complete separation of adducts **13ca** and **14ca** proved impossible. Noteworthy, the aziridine formation from the mixture of adducts **13ca**/**14ca** gave a mixture of diethyl-substituted aziridines **19ca**/**20ca** which

(36) For similar discussions on chair- and boatlike transition states in addition reactions of enolates to imines, see ref 17c and: Bernardi, A.; Gennari, C.; Raimondi, L.; Villa, M. B. *Tetrahedron* **1997**, *53*, 7705.

(37) Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *32*, 5287.

SCHEME 5. Isomerization Reaction of the *anti* Adduct 13ab

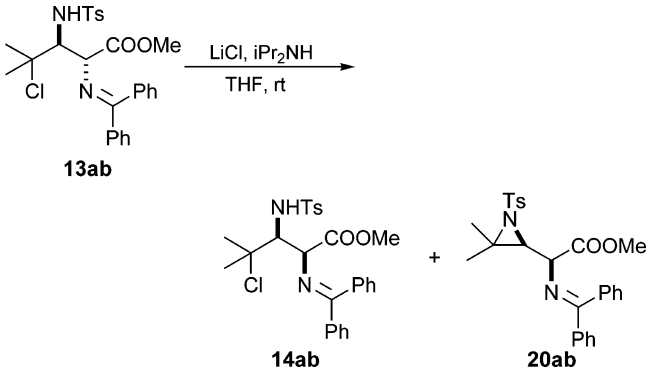
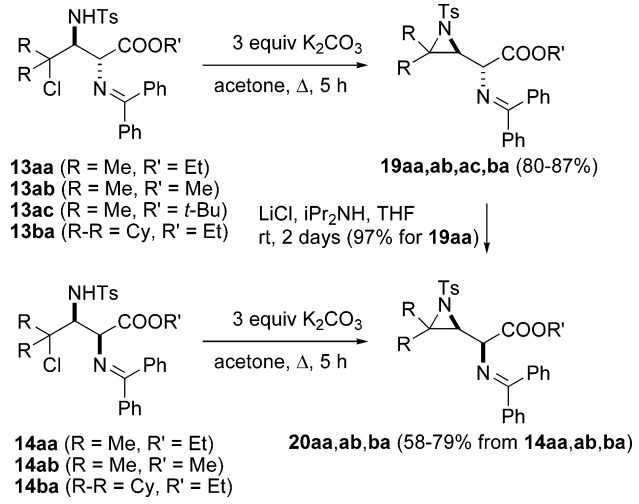


TABLE 3. Isomerization Reaction of the *anti* Adduct 13ab upon Treatment with LiCl/^{i}Pr$_2$NH in THF at rt (Scheme 5)

entry	reaction time	ratio **13ab**:**14ab**:**20ab**[a]
1	15 h	2:1:0
2	35 h	1:1.2:traces
3	3 days	1:2:2
4	5 days	1:5:5

[a] Determined by ^{1}H NMR analysis (300 MHz) of the crude reaction mixtures.

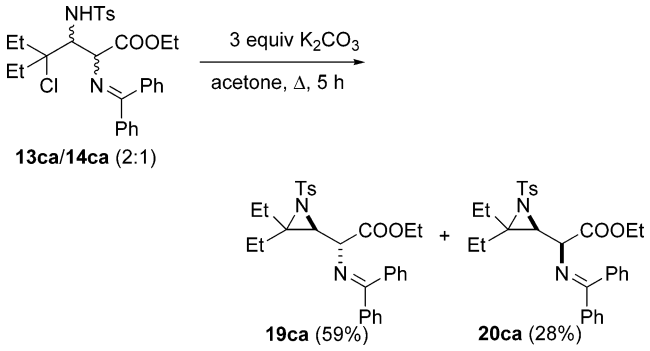
SCHEME 6. Synthesis of the Aziridino Amino Esters 19aa,ab,ac,ba and 20aa,ab,ba



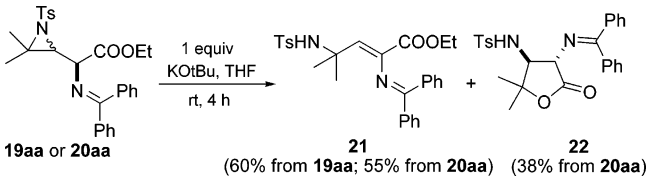
could be separated by crystallization from a hexane/EtOAc solvent system in good yield (Scheme 7). The vicinal coupling constant $^3J_{H\alpha-H\beta}$ for the *anti* isomers **19** shows a smaller value (J = 8.53−8.81 Hz) than the *syn* isomers **20** (J = 9.08−9.36 Hz). The structure and the stereochemical arrangement of the aziridino derivatives **19aa**, **19ab**, **19ac**, **19ca**, and **20aa** were unambigously determined by their X-ray diffraction analysis (see presented ORTEP figures in the Supporting Information), which also confirms the *anti* and *syn* assignments of adducts **13** and **14**.

It was interesting to observe that when the cyclization reaction from the *anti* adduct **13aa** was continued for a longer time (16 h) a mixture of aziridines **19aa**/**20aa** was detected in 5:1 ratio. It was found that, in analogy with the isomerization of **13ab** to **14ab**, the *anti*-aziridine **19aa** could be isomerized under mild base conditions (^{i}Pr$_2$NH, LiCl, THF, rt) to the *syn* isomer **20aa** in 97% yield (Scheme 6).

SCHEME 7. Synthesis of the Aziridino Amino Esters 19ca and 20ca



SCHEME 8. Base-Induced Formation of 4-Aminopentenoate 21 from *anti*- or *syn*-Aziridines 19aa and 20aa



In the presence of a stronger base (KOtBu), both the *anti*- and *syn*-aziridine derivatives **19aa** and **20aa** resulted in the same γ-amino α,β-unsaturated amino ester **21** formed by deprotonation in the α-position of the ester and double bond formation by expulsion of the aziridine nitrogen (1,2-elimination) (Scheme 8). The latter mechanism is analogous to our previously reported mechanism in the synthesis of methyl 2-alkoxy-4-(alkylamino)-pentenoates from intermediate methyl 2-aziridinylacetates.[5] When the ring opening with KOtBu in THF was performed on the *syn*-aziridine **20aa**, *trans*-lactone **22** could be isolated in 38% yield from the reaction mixture as a side product besides allylamine **21**. The determination of the *trans* stereochemistry of lactone **22** is based on observed NOE effects (Figure 2) and supported by the relative large vicinal coupling constant $^3J_{H\alpha-H\beta}$ (J = 9.63 Hz).[38] The 4-aminopentenoate **21** is assumed to possess the *Z*-geometry according to the reaction mechanism via *anti* elimination (Scheme 9). The assumption is made that the *anti*-aziridine **19aa** again isomerizes to the *syn*-aziridine **20aa** under the reaction conditions which subsequently led to the formation of the corresponding (*Z*)-pentenoate **21**. The assumption for the *Z*-geometry is supported by the appearance of the olefinic β-proton at 5.90 ppm in the ^{1}H NMR spectrum ($CDCl_3$, 300 MHz). The latter chemical shift is near to the range of 6.18−6.25 ppm in which the olefinic protons appeared of the analogous (*Z*)-methyl 2-alkoxy-4-(alkylamino)pentenoates, while the chemical shift of the olefinic proton of (*E*)-methyl 2-alkoxy-4-(alkylamino)pentenoates was higher (i.e., 6.55−6.60 ppm).[5]

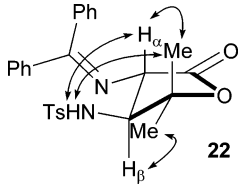
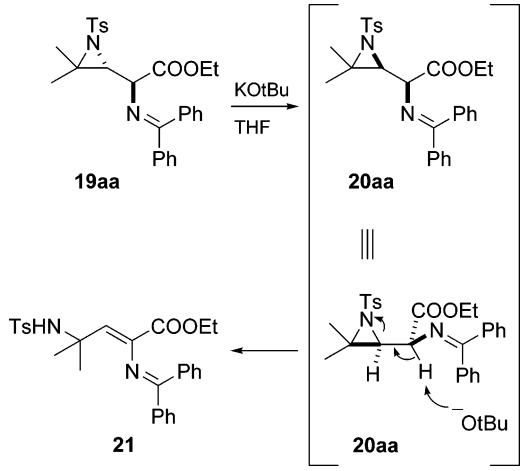
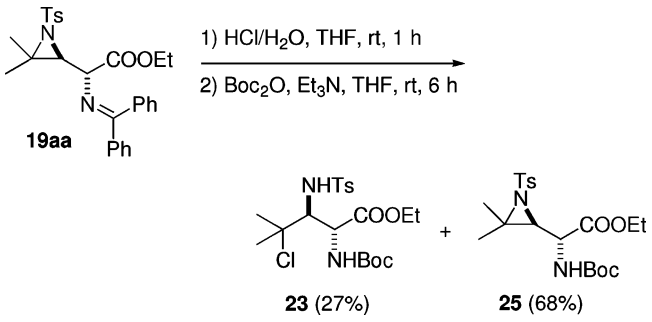


FIGURE 2. Determination of *trans* stereochemistry of lactone **22** via a 2D NOESY experiment.

SCHEME 9. Mechanism for the Formation of (*Z*)-Pentenoate 21



SCHEME 10. Formation of the *N*-Boc-Protected Aziridino Amino Esters 25



Analogous γ-amino α,β-unsaturated amino esters have proven to be useful synthetic intermediates for Diels−Alder and 1,3-dipolar cycloaddition reactions[39] for the synthesis of chiral α,γ-diamino acid derivatives,[40] as dipeptidyl peptidase inhibitors,[41] and for the synthesis of functionalized pyrrolin-2-ones.[42]

To further demonstrate the synthetic potential of the aziridines **19** and **20**, the deprotection and reprotection of the α-amino-function was investigated. The *anti*-aziridino ester **19aa** could be converted easily into the corresponding *N*-Boc-protected derivative **25** by hydrolysis with aqueous HCl followed by protection with Boc_2O (Scheme 10). During the acidic hydrolysis of **19aa** and, especially, of **20aa**, the three-membered ring was opened by chloride resulting in *anti*- and *syn*-γ-chloro-α,β-diamino esters **23** and **24**. From the *syn* compound **24**, the *N*-Boc-protected aziridine **26** was formed by treatment with K_2CO_3 (Scheme 11).

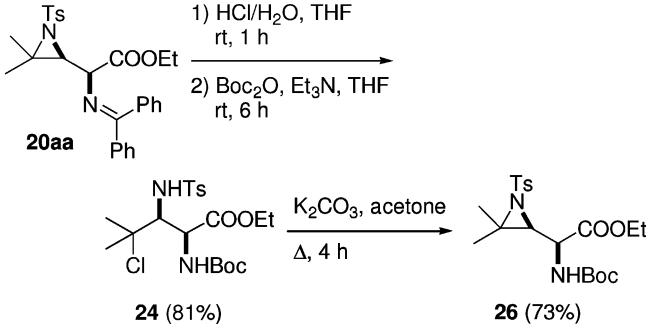
In conclusion, an efficient synthesis of β,γ-aziridino α-amino ester diastereomers has been achieved based on Mannich addition of glycinates across α-chlorinated aldimines and subsequent intramolecular ring closure. The stereochemically pure and synthetically useful *anti*- and *syn*-aziridines were obtained via selective crystallizations. These strained diamino acid derivatives are expected to react via regioselective opening of their aziridine ring, which would allow further stereoselective functionalizations of the corresponding α-amino acid derivatives.

Experimental Section

Imines **12** were prepared according to a literature procedure.[30]

***N*-(2-Ethylbutylidene)-*p*-toluenesulfonamide (12c):** Light yellowish oil; yield 54%; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.85 (t, 6H, J = 7.43 Hz), 1.59 (dq, 4H, J = 7.15 Hz, J = 7.43 Hz), 2.32 (sextet, 1H, J = 6.60 Hz), 2.43 (s, 3H), 7.33 (d, 2H, J = 7.98 Hz), 7.81 (d, 2H, J = 8.26 Hz), 8.44 (d, 1H, J = 6.33 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.4, 21.6, 24.0, 48.2, 128.0, 129.8, 135.0, 144.6, 181.8; IR (NaCl, cm^{-1}) ν = 1626, 1598, 1459, 1325, 1160, 1091, 815, 758, 672; MS (ES, pos) *m*/*z* 254 (M + H$^+$, 100).

SCHEME 11. Formation of the *N*-Boc-Protected Aziridino Amino Esters 26



General Procedure for the Preparation of α-Chloroimines 9. To a solution of *N*-(*p*-toluenesulfonyl)imine **12** (40 mmol) in CCl_4 (50 mL) was added *N*-chlorosuccinimide (1 equiv) in portions after which the mixture was stirred at reflux for 18 h. After cooling of the reaction mixture, the solid was filtered off and the filtrate was concentrated in vacuo giving the *N*-tosyl α-chloroimine **9** (purity >70%) which was used immediately in the next step without purification (if purity was >80%). Alternatively, this imine was taken up in CCl_4 (100 mL), rapidly washed with 0.5 N aq NaOH (1 × 50 mL) and ice−water (3 × 70 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give the *N*-tosyl α-chloroimines **9** which were spectroscopically analyzed (purity ∼ 80−90%).

***N*-(2-Chloro-2-methylpropylidene)-*p*-toluenesulfonamide (9a).** White solid; mp 88−89 °C; yield 96%; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.72 (s, 6H), 2.44 (s, 3H), 7.36 (d, 2H, J = 7.98 Hz), 7.81 (d, 2H, J = 8.26 Hz), 8.45 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.8, 28.3, 66.3, 128.3, 130.1, 133.7, 145.4, 174.5; IR (KBr, cm^{-1}) ν = 3250, 2924, 1704, 1598, 1375, 1159, 1055; MS (ES, pos) *m*/*z* 260/262 (M + H$^+$, 80). Due to the lability of this compound, no acceptable elemental analysis could be obtained.

General Procedure for the Addition Reaction of Benzophenone Imine Glycine Esters 10 to α-Chloro *N*-Tosylimines 9. To a solution of LDA (15 mmol) in dry THF (10 mL) was added benzophenone imine glycine ester **10** (15 mmol) in dry THF (25 mL) at −78 °C and stirred for 15 min. Then a solution of *N*-tosyl α-chloroimine **9** (15 mmol) in dry THF (30 mL) was added dropwise, and the mixture was stirred at −78 °C. After 2 h, a solution of saturated NH_4Cl (25 mL) was added to the reaction mixture and extracted with EtOAc (3 × 80 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The diastereomers **13aa**,**ab**,**ac**,**ba** and **14aa**,**ab**,**ba** were isolated after crystallization of the crude mixture from hexane/EtOAc by which the minor isomers **14aa**,**ab**,**ba** and the isomer **13ac** crystallized first and the major isomers **13aa**,**ab**,**ba** were obtained by crystallization from the filtrate. Adducts **13bb**,**ca** and **14bb**,**ca** were isolated as mixtures of diastereomers.

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***anti*-Ethyl 4-Chloro-2-(diphenylmethylenamino)-4-methyl-3-(*p*-toluenesulfonylamido)pentanoate (13aa).** Yellow solid; mp 114−116 °C; yield 43% (after crystallization); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.19 (t, 3H, J = 7.15 Hz), 1.46 (s, 3H), 1.49 (s, 3H), 2.37 (s, 3H), 3.88 (dd, 1H, J = 3.03 Hz, J = 9.08 Hz), 4.04 (q, 2H, J = 7.15 Hz), 4.57 (d, 1H, J = 3.03 Hz), 6.33 (d, 1H, J = 9.08 Hz), 7.11−7.49 (m, 12H), 7.76−7.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.8, 21.6, 30.6, 30.8, 61.4, 64.8, 65.5, 71.9, 126.9, 127.5, 127.9, 128.6, 128.8, 129.1, 129.4, 130.6, 135.8, 138.8, 139.0, 142.7, 171.1, 172.3; IR (KBr, cm^{-1}) ν = 3327, 2975, 1743, 1627, 1446, 1322, 1088; MS (ES, pos) *m*/*z* 527/529 (M + H$^+$, 100). Anal. Calcd for $C_{28}H_{31}ClN_2O_4S$: C, 63.80; H, 5.93; N, 5.31; S, 6.08. Found: C, 63.67; H, 5.89; N, 5.23; S, 6.01.

General Procedure for the Formation of β,γ-Aziridino α-Amino Esters 19 and 20. A solution of α,β-diamino ester **13** or **14** (3 mmol) in acetone (30 mL) was treated with K_2CO_3 (3 equiv), and the mixture was stirred at reflux for 5 h. After cooling of the reaction mixture, the solid was filtered off and the filtrate was concentrated in vacuo. The residue was taken up in EtOAc (100 mL) and washed with H_2O (3 × 60 mL). The organic layer was dried ($MgSO_4$) and then concentrated under reduced pressure. The crude product was purified by crystallization from hexane/EtOAc.

***anti*-Ethyl 2-(3,3-Dimethyl-1-tosylaziridin-2-yl)-2-(diphenylmethyleneamino)acetate (19aa).** White crystals; mp 147−148 °C; yield 82%; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.03 (s, 3H), 1.10 (t, 3H, J = 7.15 Hz), 1.73 (s, 3H), 2.40 (s, 3H), 3.71 (d, 1H, J = 8.53 Hz), 3.74−3.93 (m, 2H), 3.84 (d, 1H, J = 8.53 Hz), 7.10−7.83 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.0, 21.5, 21.61, 21.64, 50.2, 53.1, 61.4, 65.2, 127.8, 128.1, 128.2, 128.6, 129.1, 129.2, 129.3, 130.9, 135.7, 138.2, 139.3, 143.7, 169.9, 171.9; IR (KBr, cm^{-1}) ν = 3443, 2981, 2937, 1733, 1615, 1322, 1186, 1157, 1086. MS (ES, pos) *m*/*z* 491 (M + H$^+$, 100). Anal. Calcd for $C_{28}H_{30}N_2O_4S$: C, 68.55; H, 6.16; N, 5.71; S, 6.54. Found: C, 68.42; H, 6.28; N, 5.61; S, 6.50.

General Procedure for the Isomerization of Adduct 13ab and Aziridine 19aa. Adduct **13ab** or aziridine **19aa** (0.4 mmol) was dissolved in 10 mL of THF. To this solution were added 17 mg (1 equiv) of LiCl and 40 mg (1 equiv) of diisopropylamine, and the mixture was stirred at room temperature for the period of time as mentioned in the Discussion. Water (15 mL) was added to this mixture, and the reaction mixture was extracted with EtOAc (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure.

Ethyl 2-(Diphenylmethyleneamino)-4-methyl-4-(*p*-toluenesulfonylamido)pent-2-enoate (21). To a solution of aziridine **19aa** or **20aa** (1.33 mmol) in 15 mL of dry THF was added in portions 1.33 mmol of KOtBu. After stirring the mixture for 4 h at room temperature, water (25 mL) was added and extraction was performed with EtOAc (3 × 25 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Column chromatography on silica gel (hexanes/EtOAc 2:1) afforded allylamine **21** and lactone **22** when starting from aziridine **20aa**: Yellow oil; yield 60% from **19aa**; 55% from **20aa** (column chromatography on silica gel: hexanes/EtOAc 2:1); R_f = 0.36; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.93 (t, 3H, J = 7.15 Hz), 1.48 (s, 6H), 2.31 (s, 3H), 3.65 (q, 2H, J = 7.15 Hz), 5.90 (s, 1H), 7.06 (d, 2H, J = 7.98 Hz), 7.21−7.57 (m, 8H), 7.61 (d, 2H, J = 8.26 Hz), 7.75−7.78 (m, 2H), 7.82 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.9, 21.5, 28.9, 56.1, 60.9, 127.2, 128.2, 128.6, 129.1, 129.4, 130.0, 130.1, 131.8, 133.9, 136.7, 138.2, 138.7, 140.1, 142.5, 163.4, 170.6; IR (NaCl, cm^{-1}) ν = 3369, 2927, 2971, 1720, 1598, 1321, 1157, 1093; MS (ES, pos) *m*/*z* 491 (M + H$^+$, 100).

***anti*-Ethyl 2-(*tert*-Butoxycarbonylamino)-2-(3,3-dimethyl-1-tosylaziridin-2-yl)acetate (25).** A solution of aziridine **19aa** (1.43 mmol) and 18% aq HCl (0.5 mL) in THF (20 mL) was stirred for 1 h. Then a saturated solution of $NaHCO_3$ in H_2O (40 mL) was added. The mixture was extracted with EtOAc (3 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. To the crude product in THF (25 mL) were added Et_3N (2.9 mmol) and Boc_2O (1.5 mmol), and the mixture was stirred for 6 h. Then it was taken up in EtOAc (60 mL), washed with H_2O, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography over silica gel (hexane/EtOAc 4:1) affording aziridine **25** and diaminoester **23**: White crystals; mp 96−99 °C; yield 68%; R_f = 0.14; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.01 (t, 3H, J = 6.88 Hz), 1.42 (s, 12H), 1.73 (s, 3H), 2.42 (s, 3H), 3.06 (d, 1H, J = 8.81 Hz), 3.48−3.53 (m, 1H), 3.90 (dq, 1H, J = 7.15 Hz, J = 10.46 Hz), 4.01−4.07 (m, 1H), 5.27 (br d, 1H, J = 7.98 Hz), 7.31 (d, 2H, J = 7.98 Hz), 7.81 (d, 2H, J = 8.26 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.9, 21.2, 21.6, 21.8, 28.3, 51.2, 51.9, 52.2, 61.6, 80.4, 127.8, 129.4, 138.0, 143.9, 154.6, 170.4; IR (KBr, cm^{-1}) ν = 3247, 3132, 2977, 1750, 1705, 1324, 1162; MS (ES, pos) *m*/*z* 449 (M + Na$^+$, 8), 371 (100), 327 (58), 200 (36). Anal. Calcd for $C_{20}H_{30}N_2O_6S$: C, 56.32; H, 7.09; N, 6.57; S, 7.52. Found: C, 55.93; H, 6.84; N, 6.60; S, 8.01.

X-ray Crystallographic Study: Crystallographic data were collected at 173 K with a Nonius-Kappa CCD area detector diffractometer using graphite-monochromatized Mo Kα radiation (λ = 0.71073 Å) as reported earlier.[43] The structures were solved by direct methods using of the SHELXS-97 program,[44] and full-matrix, least-squares refinements on F^2 were performed by using the SHELXL-97 program.[44] The CH hydrogen atoms were included at the fixed distances with the fixed displacement parameters from their host atoms. The deposition number CCDC 636457−636461 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at ww.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (int.) + 44-1223-336-033; e-mail deposit@ccdc.cam.ac.uk].

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Supporting Information Available: General information, spectroscopic data for compounds **9b**, **9c**, **13ab**−**ca**, **14aa**−**ca**, **19ab**−**ca**, **20aa**,**ab**,**ba**,**ca**, **22**, and **23**, experimental procedures and spectroscopic data for compounds **24** and **26**, and X-ray diffraction analysis of compounds **19aa**, **20aa**, **19ab**, **19ac**, and **19ca**. This material is available free of charge via the Internet at http://pubs.acs.org.

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