Enantioselective Synthesis of 3-Amino-2-azetidinones via the Ester Enolate–Imine Condensation

Fred H. van der Steen, Henk Kleijn, George J. P. Britovsek, Johann T. B. H. Jastrzebski, and Gerard van Koten*

Debye Research Institute, Department of Metal-Mediated Synthesis, University of Utrecht, Padualaan 8, 3584 CH Utrecht, The Netherlands

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Three approaches to the enantioselective synthesis of 3-amino-4-substituted-2-azetidinones by condensation of α-amino ester enolates with imines are described: (i) application of chiral ester derivatives of *N,N*-diethylglycine; (ii) application of chiral *N*-(α-methylbenzyl)imines; and (iii) application of chiral imines derived from (2*R*)-2,3-*O*-isopropylideneglyceraldehyde. Zinc and aluminum enolates of (–)-menthyl- and (–)-bornyl *N,N*-diethylglycine esters react with simple imines to selectively afford *trans*-3-(diethylamino)-2-azetidinones, but with a low chiral induction (ee 0–35%). However, reactions of the metal (Li, Zn, Al) ester enolates of (2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopent-1-yl)acetic acid ethyl ester (**1c**) with *N*-(α-methylbenzyl)imines yield N-protected 3-amino-2-azetidinones in excellent yields and with very high diastereo- and enantioselectivities. The best results are obtained for the zinc-mediated reactions. For example, *trans*-(3*R*,4*S*)-1(*R*)-(α-methylbenzyl)-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-[*N*-(*R*)-(α-methylbenzyl)imino]-2-azetidinone (**4a**), a fully protected key intermediate (having the unnatural C-3 configuration) for the synthesis of known monobactam and bicyclic β-lactam antibiotics, was synthesized in 91% yield with an ee of 91%. Application of chiral imines derived from acetaldehyde and propionaldehyde enable, depending on the solvent, the selective high yielding synthesis (de 60–99%; ee >95%) of any one of the four stereoisomers of 3-amino-4-alkyl-2-azetidinones, which are key intermediates for the synthesis of Aztreonam and related antibiotics. In Et_2O, a weakly polar solvent, the trans isomers are formed, whereas the use of a polar THF/HMPA solvent mixture results in formation of the cis isomers. Reaction of the zinc enolate of **1c** with the *N*-(4-methoxyphenyl)imine derivative **2i** of (2*R*)-2,3-*O*-isopropylidene glyceraldehyde affords *trans*-(3*R*,4*S*)-3-amino-4-[(1′*S*)-1′,2′-*O*-isopropylideneethyl]-2-azetidinone (**10a**) in excellent yield (de 86%; ee >98%), whereas reaction of the lithium enolate of **1c** with the *N*-(trimethylsilyl)imine derivative **2l** affords the *cis*-(3*S*,4*S*) isomer **10d** (key intermediate for the synthesis of Carumonam) in good yield (de >90%; >90%). A rationale for the observed stereoselectivities in terms of highly ordered transition states is presented.

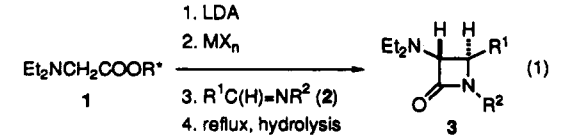
Introduction

Since the discovery of the antibiotic activity of penicillin,[1] numerous examples of naturally occurring and synthetic 2-azetidinones have been described in literature.[2] The latest development has been the discovery of synthetic monocyclic β-lactam antibiotics (monobactams),[3] e.g., Nocardicine, Aztreonam, and Carumonam. These compounds combine a relatively high stability and low toxicity with selective antibiotic activity.

Over the last decade, the condensation of metal ester enolates with imines has become one of the major routes by which the 2-azetidinone ring is constructed.[4] Recently, we reported on a diastereoselective synthesis of 3-amino-2-azetidinones that is characterized by the in situ preparation of α-amino metal ester enolates (the metal being zinc,[5a-f] aluminum,[6] or lithium[5d-f]) and their subsequent reactions with imines. Studies of the influence of substituents and solvents on the stereoselectivity of the condensation step of these reactions, as well as of the properties of the intermediate metal enolates, have provided new insights into how one can control the diastereoselectivity of these reactions; i.e., by a proper choice of metal, solvent(s), and substituents, *cis*- or *trans*-3-amino-2-azetidinones can be selectively synthesized in high yields.[6,7] Since in most cases it is one specific enantiomer of the β-lactam compound that shows antibacteriological activity, we set out to find ways to control the enantioselectivity of our reactions. Preliminary accounts of some experiments have already been presented in two papers.[5a,d]

Results

Chiral Induction Using Chiral Ester Derivatives of *N,N*-Diethylglycine. The most obvious solution for an enantioselective synthesis of 2-azetidinones is to start from readily available chiral esters. This approach has the benefit that the chiral auxilliary is not present in the final 2-azetidinone product and can be recycled by acidic work-up. Hence, two chiral *N,N*-diethylglycine esters **1a** and **1b** were tested as starting materials (eq 1; see Table I).



Although the diastereoselectivity of the reactions shown in eq 1 is excellent, only a poor enantioselectivity is observed. Surprisingly, substitution of the bulky bornyl group for the less bulky menthyl group decreases the enantioselectivity (compare entries 1 and 4). Furthermore, with the reactive imine **2b**, the chiral induction decreases

(1) *The Chemistry of Penicillin*; Clarke, H. T., Johnson, J. R., Robinson, R., Eds.; Princeton University Press: Princeton, 1949.

(2) For recent reviews, see for example: (a) *Chemistry and biology of β-lactam antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vols. 1-3. (b) Koppel, G. A. *In Small Ring Heterocycles—Azetidines, β-Lactams, Diazetidines and Diaziridines*; Hassner, A., Ed.; Wiley: New York, 1982.

(3) Dürckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem.* **1985**, *97*, 183.

(4) For recent literature reviews of the ester enolate imine condensation, see: (a) Brown, M. J. *Heterocycles* **1989**, *29*, 2225. (b) Hart, D. J.; Ha, D-C. *Chem. Rev.* **1989**, *89*, 1447.

(5) (a) Jastrzebski, J. T. B. H.; van der Steen, F. H.; van Koten, G. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 516. (b) van der Steen, F. H.; Jastrzebski, J. T. B. H.; van Koten, G. *Tetrahedron Lett.* **1988**, *29*, 2467. (c) van der Steen, F. H.; Kleijn, H.; Jastrezebski, J. T. B. H.; van Koten, G. *Ibid.* **1989**, *30*, 765. (d) van der Steen, F. H.; Kleijn, H.; Spek, A. L.; van Koten, G. *J. Chem. Soc., Chem. Commun.* **1990**, 503. (e) van der Steen, F. H.; Kleijn, H.; Jastrezbski, J. T. B. H.; van Koten, G. *J. Org. Chem.* **1991**, *56*, 5147. (f) van der Steen, F. H.; Kleijn, H.; Spek, A. L.; van Koten, G. *J. Org. Chem.* **1991**, *56*, 5868.

(6) van der Steen, F. H.; van Mier, G. P. M.; Spek, A. L.; Kroon, J.; van Koten, G. *J. Am. Chem. Soc.* **1991**, *113*, 5742.

(7) (a) van der Steen, F. H.; Boersma, J.; Spek, A. L.; van Koten, G. *J. Organomet. Chem.* **1990**, *390*, C21. (b) van der Steen, F. H.; Boersma, J.; Spek, A. L.; van Koten, G. *Organometallics* **1991**, *10*, 2467.

0022-3263/92/1957-3906$03.00/0

Table I. Enantioselective Synthesis of *trans*-2-Azetidinones 3 Starting from Chiral $Et_2NCH_2COOR^*$ (1a: R = (−)-*l*-Menthyl; 1b: R* = (−)-*l*-Bornyl)

entry	ester	imine[a]	R^1	R^2	MX_n	yield[b] (%)	de[c] (%)	ee[c] (%)
1	1a	2a	Ph	Me	$ZnCl_2$	84	>95[d]	35
2	1a	2a	Ph	Me	Me_2AlCl[e]	92	>95[d]	0
3	1a	2b	Ph	$SiMe_3$[f]	$ZnCl_2$	93	>95[d]	<5
4	1b	2a	Ph	Me	$ZnCl_2$	81	>95[d]	10

[a] Imine is $R^1C(H)=NR^2$. [b] Yields of the crude products. [c] Determined by ^1H NMR integration of the characteristic proton signals of the crude products; the ee's were determined by addition of a chiral shift reagent, Eu(tfc)$_3$. [d] The cis isomer could not be detected with ^1H NMR spectroscopy. [e] Using 1.2 equiv, see ref 6. [f] Replaced by a proton upon hydrolysis.

Table II. Enantioselective Synthesis of (3*R*,4*S*)-1-(α-Methylbenzyl)-3-(disilylamino)-4-(functional group)-2-azetidinones 4 (R^2 = (*R*)-α-Methylbenzyl)

entry	imine[a]	R^1	MX_n	solvent	yield[b] (%)	de[c] (%)	ee[c] (%)
1	2c	C(H)=NR^2	$ZnCl_2$	Et_2O	65	>98[d]	>95[d]
2				THF	91	>98[d]	91
3				toluene	75	>98[d]	>95[d]
4			Li[e]	Et_2O	52[f]	>95[d]	≈40
5				THF	43[g]	>95[d]	≈40
6	2d	2-pyridyl	$ZnCl_2$	Et_2O	68	>98[d]	>95[d,h]
7				THF	98	>98[d]	>95
8			Me_2AlCl[i]	Et_2O	93	86	90
9				THF	97	84	88
10			Li[e]	THF	67	>95[d]	≈50
11	2e	2-furyl	$ZnCl_2$	Et_2O	53	>95[d]	≈30
12			$ZnCl_2$	THF	82	78[j]	>95[k]
13			Me_2AlCl[i]	Et_2O	0		

[a] Imine is $R^1C(H)=NR^2$. [b] Yields of the crude products, based upon the amount of ester 1c. [c] Determined by ^1H NMR integration of the characteristic proton signals of the crude products. [d] The other isomers were not detected with ^1H NMR spectroscopy. [e] No additional metal salt was applied. [f] An additional 8% of the noncyclized product was isolated. [g] An additional 22% of the noncyclized product was isolated. [h] The absolute 3*R*,4*S* configuration of **4b** was confirmed by an X-ray structure determination, see ref 5d. [i] Using 1.2 equiv, see ref 6. [j] The cis isomer is produced in excess. [k] The ee, of the trans isomer is ca. 35%.

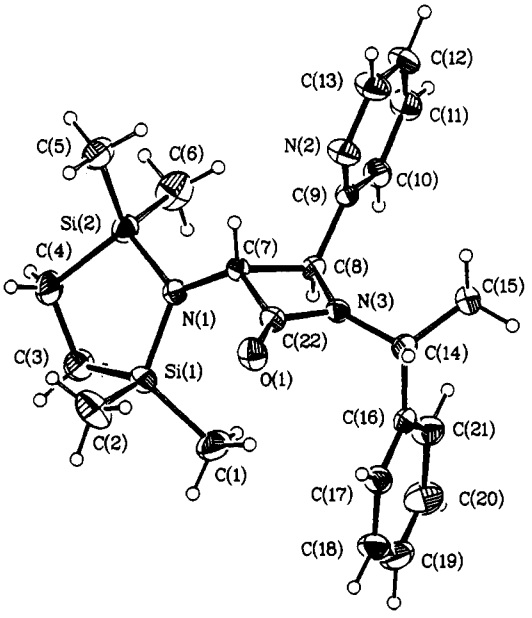
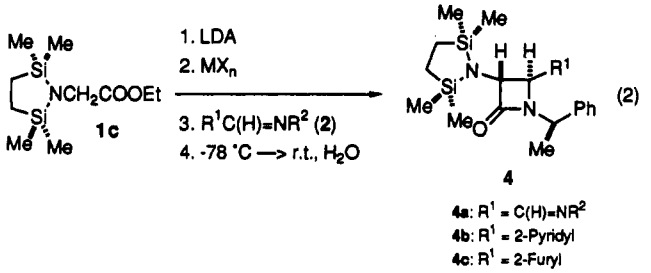


Figure 1.

considerably. The use of aluminum instead of zinc as the metal center[8] led to a complete loss of chiral induction (entry 2). It is noteworthy that recently Ojima et al. have obtained good to excellent enantioselectivity from the reactions of lithium enolates of chiral *N*,*N*-disilyl-protected glycine esters with imines (see Discussion).[9]

Chiral Induction Using *N*-(α-Methylbenzyl)-Substituted Imines. Several research groups have applied imines, N-substituted with a chiral auxiliary, in the ester enolate–imine condensation with varying results,[10a,b] and many examples of this application in the ketene–imine cycloaddition have been reported.[10c] The use of chiral imines derived from α-methylbenzylamine is an excellent choice, since both enantiomers of α-methylbenzylamine are relatively cheap and, moreover, the α-methylbenzyl group can be later transformed into a hydrogen atom in the final product (vide infra). Recently, we showed that reactions of the zinc enolate of (2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopent-1-yl)acetic acid ethyl ester (1c) with 1-aza-4-hetero-1,3-butadiene systems proceed with excellent diastereoselectivity.[5f] Therefore, we started our current investigations with reactions of *N*-(*R*)-α-methylbenzyl-substituted 1-aza-4-hetero-1,3-butadienes **2c–e**, which are easily prepared by condensation of (*R*)-α-methylbenzylamine with the respective aldehydes, with in situ prepared ester enolates (eq 2). Results are gathered in Table II.



(2)

In general, the zinc-mediated reactions are far superior to the lithium- or aluminum-mediated ones, since they combine high yields with excellent stereoselectivity. For the lithium-mediated reactions (entries 4, 5, and 10), 2-

(8) Zinc is four-coordinated in the transition state,[5e] whereas aluminum is five-coordinated in the transition state.[6]

(9) Ojima, I.; Habus, I. *Tetrahedron Lett.* **1990**, *31*, 4289.

(10) (a) Furukawa, M.; Okawara, Y.; Noguchi, Y.; Terawaki, Y. *Chem. Pharm. Bull.* **1978**, *26*, 260. (b) Overman, L. E.; Osawa, T. *J. Am. Chem. Soc.* **1985**, *107*, 1698. (c) For a recent literature survey concerning the syntheses of 3-amino-2-azetidinones see: Van der Steen, F. H.; van Koten, G. *Tetrahedron* **1991**, *47*, 7503.

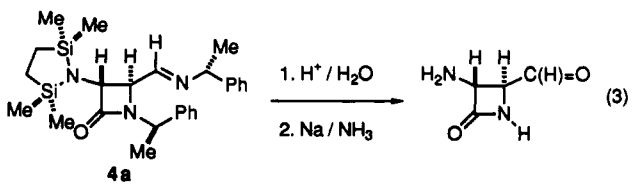
Table III. Enantioselective Synthesis of 1-(α-Methylbenzyl)-3-(disilylamino)-4-substituted-2-azetidinones 5 (R^2 = α-Methylbenzyl)

entry	imine[a]	R^1	MX_n	solvent	yield[b] (%)	3R,4S[c]	3S,4R[c]	3R,4R[c]	3S,4S[c]
1	**2f**[d]	C≡CSiMe$_3$	$ZnCl_2$	Et_2O	93	10	2	69	19
2				THF	92	25	25	30	20
3				toluene	60	11	2	70	17
4			Me_2AlCl[e]	Et_2O	95	21	9	47	23
5			Li[f]	THF	70	25	25	25	25
6	**2g**	Me	$ZnCl_2$	Et_2O	91	10	10	80	g
7				Et_2O[h]	88	10	10	–	80
8				THF	97	85	–	11	4
9				THF[i]	96	78	22	–	–
10			Li[f]	THF	25	70		30	
11	**2h**[h]	Et	$ZnCl_2$	Et_2O	92	2.5	2.5	–	95
12				Et_2O[i]	93	–	70	–	30
13				THF	92	7	8	–	85
14				THF[i]	95	–	99	–	–

[a] Imine is $R^1C(H)=NR^2$. [b] Yields of the crude products. [c] Determined by ^1H NMR integration of the characteristic proton signals of the crude products; the absolute configuration of the products is tentatively assigned on basis of the solid-state structure of **4b**. [d] The imine is a mixture of *E*- and *Z*-isomers (*E*:*Z* = 70:30; see Experimental Section). [e] Using 1.2 equiv, see ref 6. [f] No additional metal salt was used. [g] Isomer not detected with ^1H NMR spectroscopy. [h] The imine was prepared from (–)-(*S*)-α-methylbenzylamine. [i] Containing 20 vol % of HMPA.

azetidinones **4a** and **4b** are obtained in modest yields and only a moderate chiral induction is obtained (ee 40–50%). The aluminum-mediated reaction with imine **2d** gave good results (entries 8 and 9), but surprisingly, no reaction was observed with imine **2e** (entry 13). When the zinc-mediated reactions are performed in weakly polar (Et_2O) or apolar solvents (toluene), lower yields of 2-azetidinones are observed, which is most likely caused by the formation of insoluble complexes of the imine substrates with the inorganic salts present.[11] This explanation is substantiated by the fact that after workup no imines or aldehydes are found among the isolated material. The assignment of the 3*R*,4*S* configuration of *trans*-2-azetidinones **4a–c** is based on a X-ray structure determination of **4b** (see Figure 1).[5d] The use of the (*R*)-α-methylbenzyl group results in the unnatural C^3-configuration, and it is to be expected that when the (*S*)-α-methylbenzyl group is employed, the 2-azetidinones will be formed with the natural 3S configuration (vide infra).

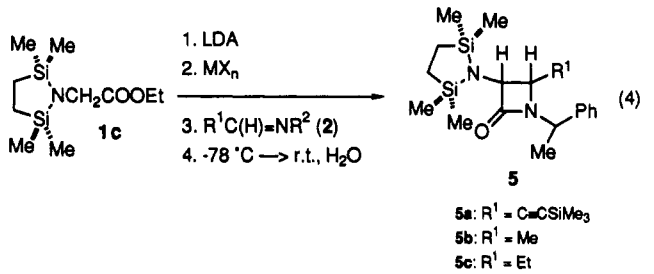
As was previously reported,[5f] reactions with imines **2c** and **2d**, which contain a nitrogen functionality, are far more selective than reactions with imine **2e**, which contains an oxygen functionality. Interestingly, when the zinc-mediated reaction with imine **2e** is carried out in THF, *cis*-2-azetidinone **4c** is formed in a good yield with reasonable selectivity (entry 12). The same reaction in Et_2O displays an excellent trans stereoselectivity, but a modest enantioselectivity (entry 11). *trans*-(3*R*,4*S*)-1(*R*)-(α-Methylbenzyl)-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-[*N*-(*R*)-(α-methylbenzyl)imino]-2-azetidinone **4a** is the synthetically most interesting product, since it represents a 3-fold protected intermediate for the synthesis of known monobactam and bicyclic β-lactam antibiotics (see eq 3). The 3-disilacyclopentane ring is readily



(3)

removed by acid- or base-catalyzed hydrolysis,[12] the 1-α-methylbenzyl group can be removed under mildly reducing conditions (vide infra),[13] and the 4-imino function can be converted by acid-catalyzed hydrolysis into an aldehyde function,[14] which is suitable for further derivatization.[15]

In order to test whether the presence of a potentially coordinating heteroatom in the imino-carbon substituent is necessary to obtain a high chiral induction, reactions with imines **2f–h** were carried out under the same conditions as those used for the reactions with imines **2c–e** (see eq 4; Table III).



(4)

Again, the zinc-mediated reactions are far superior to the lithium- or aluminum-mediated ones. Whereas the lithium enolate reacts poorly with *N*-(α-methylbenzyl)-substituted imines (entries 5 and 9), the zinc enolate usually provides quantitative conversion of the imines into 2-azetidinones **5**. The (trimethylsilyl)ethynyl group at the 4-position in **5a** can be easily converted into an acetoxy group,[16] suitable for further derivatization.[4,17] Unfortunately, **5a** is formed with only a modest diastereo- and enantioselectivity (entries 1–3), most likely because the imine **2f** is present as a mixture of *E*- and *Z*-isomers (70:30), which is detrimental for obtaining a high diastereoselectivity (see Discussion).

With the alkyl-substituted imines **2g** and **2h** interesting results are obtained. Depending on the polarity of the solvent(s), either the *trans*- (in weakly polar diethyl ether) or *cis*-2-azetidinone product (in polar THF/HMPA) is selectively formed. As noted before, the use of the (*R*)-α-methylbenzyl group results in the unnatural 3*R*-configuration, whereas with (*S*)-α-methylbenzyl the natural 3*S*-

(11) Upon addition of the pure imine substrates, white precipitates are formed immediately when the reactions are carried out in Et_2O.

(12) Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.* **1981**, *22*, 1787.

(13) (a) *Protective Groups in Organic Synthesis*; Greene, T. W., Ed.; Wiley: New York, 1981. (b) Shibasaki, M.; Ishida, Y.; Iwasaki, G.; Iimori, T. *J. Org. Chem.* **1987**, *52*, 3488.

(14) Alcaide, B.; Gómez, A.; Plumet, J.; Rodríguez-López, J. *Tetrahedron* **1989**, *45*, 2751.

(15) Evans, D. A.; Williams, J. M. *Tetrahedron Lett.* **1988**, *29*, 5065 and references cited therein.

(16) Chiba, T.; Nagatsuma, M.; Nakai, T. *Chem. Lett.* **1984**, 1927.

(17) Georg, G. I. In *Studies in Natural Product Chemistry*; Rahman, A-ur, Ed.; Elsevier Science: Amsterdam, 1988; Vol. 2.

Table IV. Enantioselective Synthesis of 2-Azetidinones 9, Containing a (1*R*)-1,2-*O*-Isopropylideneethyl Group (R^1) at the 4-Position

entry	imine[a]	R^2	solvent	yield[b] (%)	3*R*,4*S*[c]	3*S*,4*R*[c]	3*R*,4*R*[c]	3*S*,4*S*[c]
1[d]	**2i**	4-MeOPh	Et_2O	81	66	*e*	17	17
2[f]				96	93	–	3.5	3.5
3[d]			THF	91	61	–	27	12
4[f,g]				93	12	–	18	70
5[d]			toluene	50	68	–	26	10
6[d]	**2j**	2,4-$(MeO)_2$Bn	Et_2O	90[h]		trans-(*R*,*S*)[i]		
7[d]	**2k**	Me	Et_2O	30[j]		trans-(*R*,*S*)[i]		
8[k]	**2l**	$SiMe_3$ (H)[l]	THF	≈70[m]		cis-(*R*,*R*)[i]		
9[g,k]				≈95[m]				≈90

[a] Imine is $R^1C(H)=NR^2$. [b] Yields of the crude products, determined by ^1H NMR. [d] Determined by ^1H NMR integration of the characteristic signals. [d] Imine added neat. [e] Not observed with ^1H NMR spectroscopy. [f] Imine added as a 0.5 M solution in Et_2O. [g] Reaction performed without addition of $ZnCl_2$. [h] Based on the amount of pure imine that was present in solution. [i] Mixture of several isomers; the given isomer was present in a large excess in the isolated material. [j] Because of the low conversion, the 2-azetidinones could not be isolated. [k] Imine **2l** was prepared in situ in THF and was directly added to a solution containing the enolate. [l] Upon hydrolysis the trimethylsilyl group is replaced by a hydrogen. [m] Based on the amount of unconverted ester **1c**.

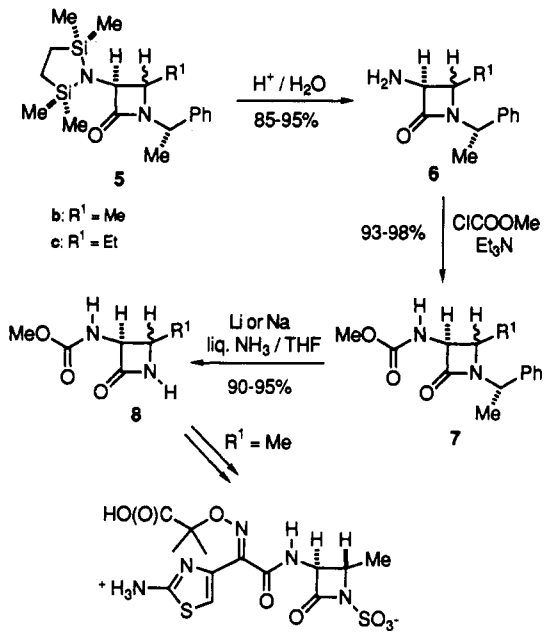
configuration results. In principle, all four stereoisomers of 2-azetidinones **5b** (R^1 = Me) and **5c** (R^1 = Et) can be selectively obtained (de 60–99%; ee >95%) in high yields.

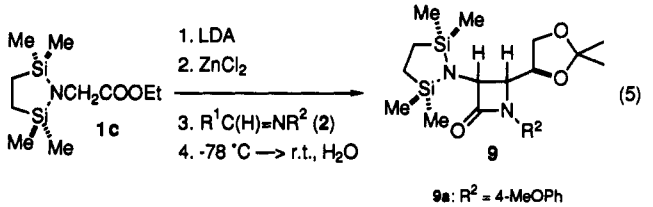
2-Azetidinone **5b** is a protected key intermediate for the synthesis of Aztreonam,[18] and **5c** for the 4-ethyl derivative of Aztreonam, which is more stable to β-lactamase, but which has a lower antibiotic activity.[18] The disilyl moiety of **5b** and **5c** is readily removed by acidic hydrolysis to afford 1-(α-methylbenzyl)-3-amino-4-alkyl-2-azetidinones **6b** and **6c** in nearly quantitative yields. Reprotection of the amino function as a carbamate **7** and then removal of the α-methylbenzyl group with lithium or sodium in a mixture of liquid ammonia and THF affords 3-[(methoxycarbonyl)amino]-4-alkyl-2-azetidinones **8b** and **8c** in excellent yields as crystalline solids. These can be readily converted into Aztreonam and its ethyl analogue by known chemistry (see Scheme I).[18]

Chiral Induction Using Imines Derived from (2*R*)-2,3-*O*-Isopropylideneglyceraldehyde. A third approach to an enantioselective ester enolate–imine route to 2-azetidinones is one where a chiral auxiliary is put into the imino-carbon substituent. However, the synthon must be easily convertible to a useful functionality, e.g., an aldehyde or acetoxy group. Recently, Cainelli et al. have applied chiral imines, derived from (*S*)-lactic aldehyde, in the synthesis of optically active *trans*-carbapenems via their condensation with lithium ester enolates,[19] while Evans et al. have applied chiral imines, derived from chiral α,β-epoxyaldehydes, in the synthesis of *cis*-3-amino-4-formyl-2-azetidinone via a ketene–imine cycloaddition reaction.[20] For the latter reaction chiral imines, derived from glyceraldehyde,[21] are more frequently used and several *cis*-3-amino-2-azetidinones have been obtained with high chiral induction (with the natural 3*S*-configuration) in good yields.[22]

The fact that both enantiomers of 2,3-*O*-isopropylideneglyceraldehyde are available,[21] and the use of its imine derivatives in the enolate–imine condensation has not been reported, prompted us to apply these chiral imine derivatives in our synthetic route to 3-amino-2-azetidinones (eq 5). Successful application would result in 2-azetidinones with a multifunctional substituent at the 4-position. Generally, imines derived from 2,3-*O*-isopropylideneglyceraldehyde are prepared in situ and used directly in solution for subsequent reactions.[21,22] Our attempts to obtain the pure imines were hampered because, upon isolation, these imines **2i–l** tend to polymerize. Therefore, the reactions displayed in eq 5 were carried out with crude imine **2j** and in situ prepared **2l**. However, pure **2i** could be obtained by crystallization from hexane at −30 °C and imine **2k** could be purified by rapid distillation at reduced pressure.

Scheme I





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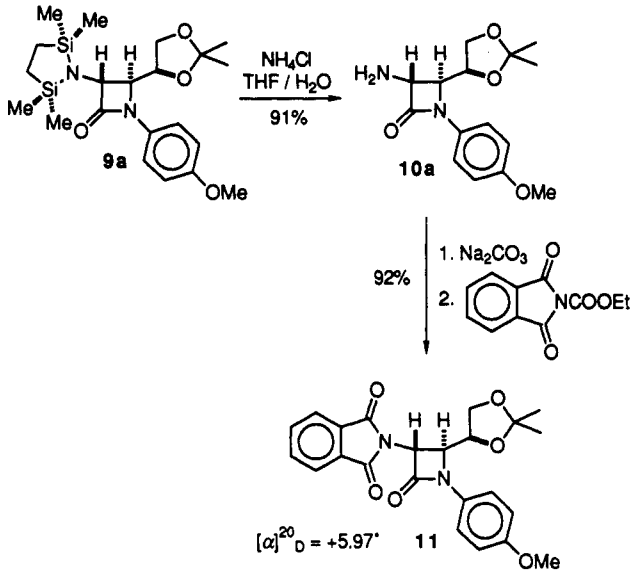
Scheme II



The best results were obtained with imine **2i** that contains the 4-methoxyphenyl group as protective group (entries 1–5). Imine **2k** is apparently not reactive enough, and its conversion is low (entry 7). Although imine **2j**, which contains the 2,4-dimethoxybenzyl protective group, is completely converted into 2-azetidinone **6c** (entry 6), the difficulty to obtain pure **2j** prompted us to focus our attention to reactions with **2i**. Both the 4-methoxyphenyl and the 2,4-dimethoxybenzyl substituent can be readily removed under mild oxidizing conditions (CAN reduction).[23] Because of the poor stability of the *N*-(trimethylsilyl)-substituted imine **2l**, the reactions can only be performed with in situ prepared imine. Since this preparation has to be carried out in THF, only a moderate chiral induction (low diastereoselectivity) is observed for the zinc-mediated reaction. A further complication is that the yields of 2-azetidinones obtained thus far from zinc-mediated reactions with in situ prepared *N*-(trimethylsilyl)imines are not very high.

Depending on the reaction conditions, it is possible to selectively obtain *trans*-(3*R*,4*S*)-**9a** (de 86% and ee > 98%) in a high yield (entry 2) and *cis*-(3*S*,4*S*)-**9a** but with modest selectivity (de 76% and ee 58%; entry 4). The 3*R*,4*S* configuration of *trans*-**9a** has been determined by its transformation into the 3-phthaloylamido derivative **11** (see Scheme II) and comparison of its optical rotation with that previously reported for the 3*S*,4*R* isomer ($[\alpha]^{20}_D$ + 11.6°).[22a] The absolute configuration of both cis isomers of **9a** has been tentatively assigned on the basis of ^{1}H NMR data and correlation thereof with molecular models. The zinc-mediated reaction with imine **2l** (entry 8) afforded 2-azetidinone **9d** in a reasonable yield, but with a moderate enantioselectivity. The lithium-mediated reactions with in situ prepared *N*-(trimethylsilyl)imines usually give better results than we have obtained for our zinc-mediated reactions.[19,24] This observation is illustrated by the enantioselective synthesis of *cis*-2-azetidinone **9d**, a key intermediate in the synthesis of Carumonam, in excellent yield (entry 9).

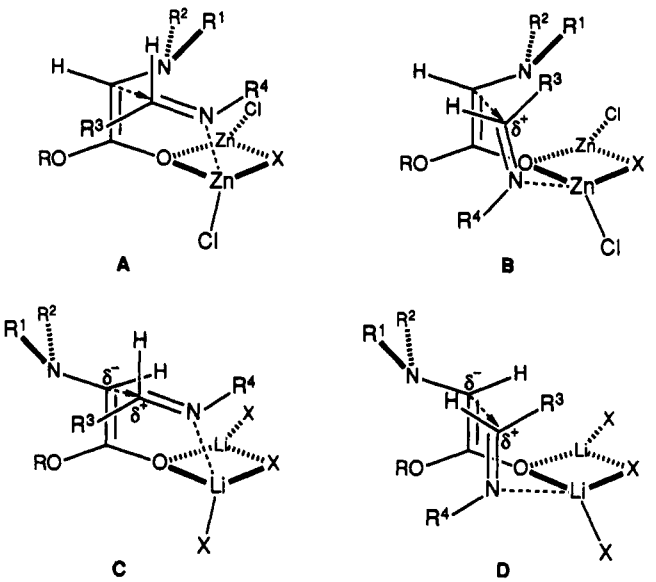


Figure 2.

Discussion

General. The stereochemistry of 3-amino-2-azetidinones is determined during the C–C bond formation between the ester enolate and imine.[25] From the structures of the transition states of this reaction, which are dependent on the configuration (*E* or *Z*) of both the enolate and imine, one may deduce whether the use of a particular chiral auxiliary will result in chiral induction of the C–C bond formation. Several transition states for aldol-type reactions have been proposed.[26] On the basis of the original proposal by Zimmerman and Traxler,[26d] and the recent structural information of the zinc and aluminum enolates,[6,7] we have put forward two highly ordered transition states (**A** and **B**, Figure 2). These transition states, constructed from (*Z*)-enolates and (*E*)-imines, allow a good explanation for the stereoselectivities we have observed thus far in the zinc- and aluminum-mediated reactions of α-amino ester enolates with imines.[5,6] Since the lithium enolate of **1c** has the *E*-configuration,[7b,10b,27] two more transition states are put forward to rationalize the results of the lithium-mediated reactions (**C** and **D**, Figure 2).

Chiral Ester Enolates. We have shown that the zinc- and aluminum-mediated reactions are chelation-controlled;[5-7] i.e., these reactions proceed through either transition state **A** or **B**, leading to *trans*- and *cis*-2-azetidinones, respectively. It is therefore not surprising that with chiral ester enolates (e.g., R = menthyl, bornyl) low chiral inductions are obtained, since the chiral center is too far away to cause a large energy difference between the two enantiotopic faces of the ester enolate. The lithium-mediated reactions, which are non-chelation-controlled, proceed through either transition state **C** or **D**. Depending on the relative bulkiness of the R^3 and R^4 substituent, these reactions afford *cis*- or *trans*-2-azetidinones when bulky chiral ester enolates are employed.[9] From the transition states given in Figure 2 it can be deduced that

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(24) (a) Cainelli, G.; Giacomini, D.; Panunzio, M.; Martelli, G.; Spunta, G. *Tetrahedron Lett.* **1987**, *28*, 4347. (b) Andreoli, P.; Cainelli, G.; Contento, M.; Giacomini, D.; Martelli, G.; Panunzio, M. *Tetrahedron Lett.* **1987**, *28*, 5369. (c) Andreoli, P.; Cainelli, G.; Contento, M.; Giacomini, D.; Martelli, G.; Panunzio, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 945.

(25) Although the loss of stereochemistry as a result of retro-aldolization cannot be ruled out, previous experiments have shown that the occurrence of retro-aldolization in our reactions is not very probable.[5e]

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(27) Dr. R. O. Duthaler of Ciba-Geigy AG, personal communication.

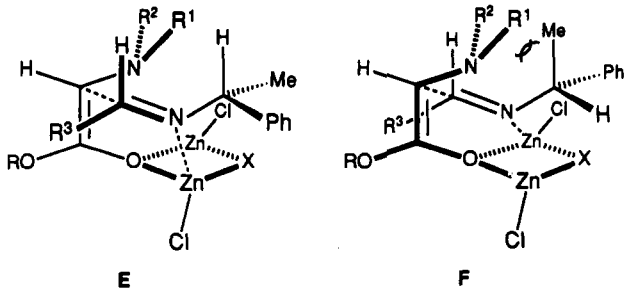

Figure 3.

the reactions going via transition state **C** will lead to *cis*-2-azetidinones with a low to moderate enantioselectivity and that the reactions via transition state **D** will lead to *trans*-2-azetidinones with far higher chiral induction. This is in concordance with the results obtained by Ojima et al.,[9] who suggest that the *trans*-2-azetidinones are formed by a chelation-controlled reaction, i.e., via transition state **A**. However, we and others have shown that the lithium enolate of **1c** has exclusively the *E*-configuration.[7b,10b,27]

***N*-(α-Methylbenzyl)imines.** At first glance, the chiral center present in *N*-(α-methylbenzyl)imines seems to be far from the site where the two new chiral centers are formed (see Figure 2) to cause any chiral induction. However, since the first step of the reaction is coordination of the imino-nitrogen to the metal center,[5e,f,7] and the mode of coordination determines the stereochemical outcome of the reaction (compare transition states **A** and **B** in Figure 2), the chiral center is actually close enough to cause the observed high chiral inductions. Two proposed diastereomeric coordination complexes (based on transition state **A**) between *N*-(α-methylbenzyl)imines and zinc ester enolates are shown in Figure 3.

The energy difference between these two complexes is dependent on the steric strain caused by the amino-nitrogen substituents with either a hydrogen (in **E**) or a methyl group (in **F**). Apparently the energy difference is large enough to cause a good chiral induction (vide supra).

As noted in previous papers,[5] the polarity of the solvent, and hence coordinating ability, has a large influence on the stereoselectivity of the reactions. Especially for the C-alkyl-substituted imines (see Table III) this effect is striking. Since the polarity of the solvent has almost no effect on the configuration of the α-amino zinc ester enolates,[7a,b] the shift of diastereoselectivity is caused by (small) changes in the conformation of the respective transition states. This is supported by the fact that for the relatively small methyl group (R^3 in **A** and **B**) already a small change of solvent polarity has a strong effect on the diastereoselectivity, whereas for the larger ethyl group a large change of solvent polarity is necessary for a complete reversal of the diastereoselectivity.

***C*-(2,3-*O*-Isopropylidenepropyl)imines.** The chiral center of the *C*-(2,3-*O*-isopropylidenepropyl)imines is very close to the site where the two new chiral centers are formed. Therefore, high 1,2-chiral induction is to be expected for the reactions of the ester enolates with imines; i.e., the energy difference between the enantiotopic faces of the ester enolates in transition states **A**–**D** is large. An additional feature is that the imine can have two preferred conformations as shown in Figure 4.

For example, when conformation **G** is combined with transition state **A** a 3*S*-configuration of the 2-azetidinone will result, whereas **H** combined with **A** will result in a 3*R*-configuration. Although NOE-difference experiments have been carried out with the *N*-(2,4-dimethoxybenzyl)-imine **2j**,[22d] these experiments were used only to confirm

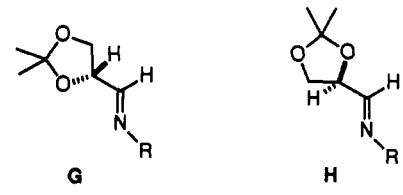

Figure 4.

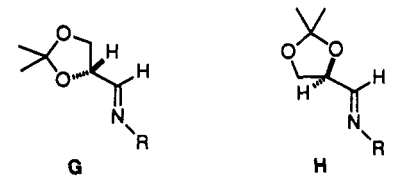

Figure 5.

the *E*-configuration of the imine. Unfortunately, no indication about the conformation of the isopropylidene moiety was given. Since we have proven that with the *N*-(4-methoxyphenyl)imine **2l** a 3*R*,4*S*-configuration of the 2-azetidinone results, we assume that in our case the imine reacts primarily in conformation **H**. Therefore, reaction of imine **2l** with the lithium enolate of **1c** via transition state **C** should result in a 3*S*,4*S*-configuration of the 2-azetidinone product, which seems to be the case on the basis of NMR spectra.

Concluding Remarks

The application of chiral ester enolates in the synthesis of 3-amino-2-azetidinones is limited to enolates that have an *E*-configuration, since in the transition states for (*Z*)-enolates the chiral auxiliary is too far away from the site where the two new chiral centers are formed to cause a high chiral induction. Ojima et al. have demonstrated that chiral esters indeed may result in a high enantioselectivity for a lithium enolate that has an *E*-configuration.[9]

The application of imines N-substituted with a chiral α-methylbenzyl group is limited to strong Lewis-acidic metal enolates, e.g., zinc and aluminum enolates, because the lithium enolates are not reactive enough. α-Amino zinc enolates (and to a lesser extent aluminum enolates) react with chiral 1,4-diaza-1,3-butadiene systems to afford *trans*-3-amino-2-azetidinones in excellent yields with a high enantioselectivity. When *C*-(alkyl)imines are employed, the stereoselectivity of the zinc-mediated reactions can be tuned by changing the polarity of the solvent(s). The use of (highly) polar solvents results in enantioselective syntheses of *cis*-3-amino-4-alkyl-2-azetidinones, whereas in apolar or weakly polar solvents the trans isomers are formed with a high enantioselectivity.

The application of imines, C-substituted with the chiral 2,3-*O*-isopropylidene group, is more general, provided that the imino-nitrogen is substituted with an electron-withdrawing group. Hence, employing our zinc-mediated route, useful *trans*-3-amino-2-azetidinones are obtained enantioselectively, whereas via the lithium-mediated route the cis-isomers are obtained with a high enantioselectivity.

Experimental Section

General Data. All manipulations with air-sensitive reagents were carried out under a dry, oxygen-free, nitrogen atmosphere using standard Schlenk techniques. Solvents were dried and distilled from sodium/benzophenone prior to use. The *N*,*N*-diethylglycine esters **1a** and **1b** were prepared by condensation of *l*-menthol (**1a**) or *l*-borneol (**1b**) with bromoacetyl bromide and subsequent condensation of the bromo acetates with diethylamine as described previously.[7b] (2,2,5,5-Tetramethyl-1-aza-2,5-disilacyclopent-1-yl)acetic acid ethyl ester (**1c**) was prepared according

to a literature procedure.[12] Imines **2a** and **2b** were prepared by standard methods.[28] 2,3-*O*-Isopropylidene-D-glyceraldehyde was prepared from D-mannitol according to literature procedures.[29] (*R*)- and (*S*)-α-methylbenzylamine with an optical purity of 98+% were purchased from Janssen Chimica and amines with an optical purity of 99+% were purchased from Fluka Chemika. Absolutely dry $ZnCl_2$ was prepared as described previously.[5e] ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer in chloroform-d, benzene-d_6, or acetone-d_6 using TMS as an external standard (0.0 ppm). All coupling constants are presented in hertz (Hz). Boiling and melting points are uncorrected. Preparative HPLC was performed on a Philips-4100 system using a Supelcosil PLC-18 column. Optical rotations were determined using a Perkin-Elmer-241 polarimeter. Elemental analyses were performed by the Institute of Applied Chemistry (TNO), Zeist, The Netherlands.

Synthesis of *N*-(α-Methylbenzyl)imines 2. Imine **2c** was prepared according to a modified literature procedure.[28c] Imines **2g** and **2h** were prepared according to a modified procedure described for *N*-ethylidenebenzylamine.[30] Imines **2d–f** were prepared according to the standard procedure given for **2d**: To a stirred and cooled (0 °C) solution containing 10.7 g (0.1 mol) of freshly distilled 2-pyridinecarbaldehyde in 100 mL of Et_2O was added 12.1 g (0.1 mol) of freshly distilled (+)-(*R*)- or (−)-(*S*)-α-methylbenzylamine and subsequently 5 g of Na_2SO_4. Stirring was continued for 2 h at 0 °C, and then the solid was removed by filtration. After removal of the volatile material in vacuo at ambient temperature, the product was purified by distillation in vacuo.

***N*-(*R*)-(α-Methylbenzyl)(2-pyridyl)formaldimine (2d).** Pale yellow liquid. Yield: 20.0 g (95%). Bp 121 °C/0.5 mmHg. $[\alpha]^{20}_D$ −62.19° (*c* 1.3, ethanol). ^1H NMR ($CDCl_3$): δ 8.62 (m, 1 H, pyr*H*), 8.46 (s, 1 H, C*H*=N), 8.04, 7.71 (m, 1 H, pyr*H*), 7.47–7.19 (m, 6 H, pyr*H* and Ar*H*), 4.64 (q, 1 H, C(*H*)(CH_3)Ph), 1.62 (d, 3 H, C(H)(C*H*$_3$)Ph).

***N*-(*R*)-(α-Methylbenzyl)(2-furyl)formaldimine (2e).** Colorless liquid. Yield: 89%. Bp 110 °C/0.5 mmHg. $[\alpha]^{20}_D$ −90.20° (*c* 2.0, ethanol). ^1H NMR ($CDCl_3$): δ 8.12 (s, 1 H, C*H*=N), 7.51–7.21 (m, 6 H, Ar*H* and fur*H*), 6.73, 6.45 (m, 1 H, fur*H*), 4.52 (q, 1 H, C(*H*)(CH_3)Ph), 1.65 (d, 3 H, C(H)(C*H*$_3$)Ph).

***N*-(*R*)-(α-Methylbenzyl)-3-(trimethylsilyl)prop-2-ynaldimine (2f).** Pale yellow liquid. Yield: 92%. Bp 95–100 °C/0.5 mmHg. $[\alpha]^{20}_D$ +104.35° (*c* 1.4, ethanol). The ^1H NMR spectrum revealed that the product was a mixture of two isomers (*E* to *Z* ratio = 70:30). ^1H NMR ($CDCl_3$): *E*, δ 7.51 (d, 1 H, *J* = 0.4, C*H*=N), 7.40–7.20 (m, 5 H, Ar*H*), 4.36 (q, 1 H, C(*H*)(CH_3)Ph), 1.53 (d, 3 H, C(H)(C*H*$_3$)Ph), 0.23 (s, 9 H, Si(C*H*$_3$)$_3$); *Z*, δ 7.53 (d, 1 H, *J* = 0.4, C*H*=N), 5.16 (q, 1 H, C(*H*)(CH_3)Ph), 0.27 (s, 9 H, Si(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$): *E*, δ 143.66 (*C*H=N), 141.18, 128.57, 127.23, 126.72 (Ar*C*), 101.68 (*C*≡CSiMe$_3$), 98.09 (C≡*C*SiMe$_3$), 70.69 (*C*(H)(CH_3)Ph), 24.37 (C(H)(*C*H$_3$)Ph), −0.41 (Si(*C*H$_3$)$_3$); *Z*, δ 144.60 (*C*H=N), 141.18, 128.46, 127.01, 126.83 (Ar*C*), 104.18 (*C*≡CSiMe$_3$), 96.64 (C≡*C*SiMe$_3$), 64.47 (*C*(H)(CH_3)Ph), 23.82 (C(H)(*C*H$_3$)Ph), −0.41 (Si(*C*H$_3$)$_3$).

***N*-Ethylidene-(*R* or *S*)-α-methylbenzylamine (2g).** Colorless liquid. Yield: 83%. Bp 32 °C/0.1 mmHg. ^1H NMR ($CDCl_3$): δ 7.80 (q, 1 H, *J* = 5.1, C*H*=N), 7.35–7.15 (m, 5 H, Ar*H*), 4.28 (q, 1 H, *J* = 7.4 C(*H*)(CH_3)Ph, 1.98 (d, 3 H, *J* = 5.1, C*H*$_3$C(H)=N), 1.50 (d, 3 H, *J* = 7.4, C(H)(C*H*$_3$)Ph).

***N*-Propylidene-(*R* or *S*)-α-methylbenzylamine (2h).** Colorless liquid. Yield: 81%. Bp 61 °C/0.6 mmHg. ^1H NMR ($CDCl_3$): δ 7.75 (t, 1 H, *J* = 5.0, C*H*=N), 7.40–7.15 (m, 5 H, Ar*H*), 4.28 (q, 1 H, *J* = 7.4, C(*H*)(CH_3)Ph, 2.29 (dq, 2 H, *J* = 5.0 and 7.0, CH_3CH_2C(H)=N), 1.50 (d, 3 H, *J* = 7.4, C(H)(C*H*$_3$)Ph), 1.10 (t, 3 H, *J* = 7.0, C*H*$_3$CH$_2$C(H)=N).

(1*S*)-1-[*N*-(4-Methoxyphenyl)imino]-1,2-*O*-isopropylideneethane (2i). Colorless oil. Yield: 95%. The impurities were removed by crystallization at −30 °C in hexane. ^1H NMR ($CDCl_3$): δ 7.81 (d, 1 H, *J* = 5.0, C*H*=N), 7.06 (m, 2 H, Ar*H*), 6.83 (m, 2 H, Ar*H*), 4.71 (ddd, 1 H, *J* = 6.8, 6.1 and 5.0, −C(O)*H*CH$_a$H$_b$O), 4.23 (dd, 1 H, *J* = 8.3 and 6.8, −C(O)HC*H*$_a$H$_b$O), 4.02 (dd, 1 H, *J* = 8.3 and 6.8, −C(O)HCH$_a$*H*$_b$O), 3.74 (s, 3 H, OC*H*$_3$), 1.45, 1.40 (s, 3 H, C(C*H*$_3$)$_2$). ^{13}C NMR ($CDCl_3$): δ 161.05 (*C*=N), 158.52, 143.47, 122.01, 114.26 (Ar*C*), 110.33 (*C*(CH$_3$)$_2$), 77.44 (−*C*(O)HCH$_2$O), 67.33 (−C(O)*H*CH$_2$O), 55.28 (OCH$_3$), 26.52, 25.41 (C(*C*H$_3$)$_2$).

(1*S*)-1-(*N*-Methylimino)-1,2-*O*-isopropylideneethane (2k). Colorless liquid. Yield: 73%. Bp 53 °C/12 mmHg. ^1H NMR ($CDCl_3$): δ 7.51 (br d, 1 H, C*H*=N), 4.52 (br q, 1 H, *J* = 6.7, −C(O)*H*CH$_a$H$_b$O), 4.14 (dd, 1 H, *J* = 7.9 and 6.7, −C(O)HC*H*$_a$H$_b$O), 3.86 (dd, 1 H, *J* = 7.9 and 6.7, −C(O)HCH$_a$*H*$_b$O), 3.37 (s, 3 H, NC*H*$_3$), 1.40, 1.33 (s, 3 H, C(C*H*$_3$)$_2$).

Enantioselective Synthesis of *trans*-3-(Diethylamino)-2-azetidinones 3a and 3b. The reactions shown in eq 1 were carried out according to a standard procedure as described previously.[5] The contents of the crude materials were analyzed by NMR spectroscopy and determined by comparison of the NMR spectra of authentic samples.[5] The enantiomeric excess was determined by ^1H NMR integration of the characteristic proton signals in the presence of a chiral shift reagent (tris[3-((trifluoromethyl)-hydroxymethylene)-*d*-camphorato]Eu(III); Eu(tfc)$_3$).

General Procedure for the (One-Pot) Synthesis of 3-(2,2,5,5-Tetramethyl-1-aza-2,5-disilacyclopentyl)-2-azetidinones. To a stirred solution containing *i*-Pr$_2$NH (1.01 g, 10 mmol) in 30 mL of solvent (Et_2O, toluene, or THF), at −78 °C was added 10 mmol of *n*-BuLi (6.67 mL of a 1.5 M solution in hexanes). The solution was stirred for 10 min at −78 °C, and then glycine ester **1c** (2.45 g, 10 mmol) was added. The reaction mixture was stirred for an additional 15 min at −78 °C, and then 10 mmol of $ZnCl_2$ (10.0 mL of a 1.0 M solution in Et_2O) was added, and after stirring for 30 min 10 mmol of an appropriate imine **2** was added at −78 °C. Then the reaction mixture was stirred for 1 h at −78 °C, after which the reaction mixture was allowed to warm to room temperature and quenched with 20 mL of a saturated aqueous NH_4Cl solution. The precipitated salts were filtered off through a sintered-glass fritt. The aqueous layer was separated and extracted with two portions of Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to afford the crude 2-azetidinone products. The contents of these crude products were examined with ^1H NMR before performing any purification step. Whenever possible,[31] the products were purified by recrystallization, flash chromatography, or HPLC techniques.

***trans*-(3*R*,4*S*)-1(*R*)-(α-Methylbenzyl)-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-[*N*-(*R*)-(α-methylbenzyl)imino]-2-azetidinone (4a).** Pale yellow oil. Yield: 4.22 g (91%). The ^1H NMR spectrum revealed that the product was a mixture of two diastereomeric trans isomers, comprising the 3*R*,4*S* isomer in an excess of 91%. ^1H NMR ($CDCl_3$): δ 7.53 (d, 1 H, *J* = 7.6, C*H*=N), 7.41–7.13 (m, 10 H, Ar*H*), 4.85 (q, 1 H, *J* = 7.2, C(*H*)(CH_3)Ph), 4.34 (q, 1 H, *J* = 6.6, C(*H*)(CH_3)Ph), 4.18 (d, 1 H, *J* = 1.9, NC*H*CHCH=N), 3.67 (dd, 1 H, *J* = 7.6 and 1.9, NCH*C*HCH=N), 1.50 (d, 3 H, *J* = 6.6 C(H)(C*H*$_3$)Ph), 1.39 (d, 3 H, *J* = 7.2, C(H)(C*H*$_3$)Ph), 0.76–0.52 (m, 4 H, SiC*H*$_2$C*H*$_2$Si), 0.05, −0.05 (s, 6 H, Si(C*H*$_3$)$_2$). ^{13}C NMR ($CDCl_3$): δ 168.74 (C=O), 161.10 (*C*=N), 143.81, 139.84, 128.70, 128.54, 127.87, 127.37, 127.22, 126.63 (Ar*C*), 69.82, 66.16 (*C*(H)(CH_3)Ph), 65.56 (NCHCHCH=N), 52.47 (NCH*C*HCH=N), 24.18, 19.88 (C(H)(*C*H$_3$)Ph), 7.94 (SiCH$_2$CH$_2$Si), 0.66, −0.09 (Si(*C*H$_3$)$_2$). $[\alpha]^{20}_D$ +4.17° (*c* 0.7, ethanol). Anal. Calcd for $C_{26}H_{37}N_3OSi_2$: C, 67.48; H, 7.84; N, 9.08. Found: C, 66.44; H, 7.86; N, 8.65.

***trans*-(3*R*,4*S*)-1(*R*)-(α-Methylbenzyl)-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-(2-pyridyl)-2-azetidinone (4b).** Pale yellow solid. Yield: 4.02 g (98%). The ^1H NMR spectrum revealed that the product was a mixture of two diastereomeric trans isomers, comprising the 3*R*,4*S* isomer in an

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(29) (a) Kuszmann, J.; Tomori, E.; Meerwald, I. *Carbohydr. Res.* **1984**, *128*, 87. (b) Hubschwerlen, C. *Synthesis* **1986**, 962.

(30) Campbell, K. N.; Sommers, A. H.; Campbell, B. K. *J. Am. Chem. Soc.* **1944**, *66*, 82.

(31) Because the protecting disilyl moiety is very susceptible to hydrolysis, the separation by chromatographic techniques was usually accompanied by partial deprotection of the amine function. Therefore, it was not always possible to obtain analytically pure samples. Furthermore, elemental analyses of 3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-2-azetidinones proved difficult because of partial hydrolysis during sampling.

excess of more than 95%. ^{1}H NMR ($CDCl_3$): δ 8.62–8.59 (m, 1 H, pyr*H*), 7.67–7.58 (m, 1 H, pyr*H*), 7.32–7.09 (m, 7 H, Ar*H* and pyr*H*), 5.01 (q, 1 H, *J* = 7.2, C(*H*)(CH_3)Ph), 4.36 (d, 1 H, *J* = 2.0, NC*H*CH-pyr), 4.04 (d, 1 H, *J* = 2.0, NCHC*H*-pyr), 1.26 (d, 3 H, *J* = 7.2, C(H)(C*H*$_3$)Ph), 0.70–0.56 (m, 4 H, SiC*H*$_2$C*H*$_2$Si), –0.09, –0.13 (s, 6 H, Si(C*H*$_3$)$_2$). ^{13}C NMR ($CDCl_3$): δ 170.14 (*C*=O), 158.24, 149.74, 139.76, 136.42, 128.56, 127.78, 127.52, 122.97, 121.94 (Ar*C* and pyr*C*), 69.89 (*C*(H)(CH_3)Ph), 66.90 (N*C*HCH-pyr), 52.27 (NCH*C*H-pyr), 18.79 (C(H)(*C*H$_3$)Ph), 7.93 (Si*C*H$_2$*C*H$_2$Si), 0.43, –0.04 (Si(*C*H$_3$)$_2$). The enantiomerically pure trans-(3*R*,4*S*) isomer was obtained as colorless crystals after one crystallization from Et_2O/pentane (1:1 v/v), mp 132 °C. $[\alpha]^{20}_D$ +53.36° (*c* 0.33, ethanol). Anal. Calcd for $C_{22}H_{31}N_3OSi_2$: C, 64.50; H, 7.63; N, 10.26; Si, 13.71. Found: C, 64.13; H, 7.28; N, 10.26; Si, 13.54.

***trans*-(3*R*,4*S*)-1(*R*)-(α-Methylbenzyl)-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-(2-furyl)-2-azetidinone (4c).** Yellow oil. Yield: 2.11 g (53%). The ^{1}H NMR spectrum revealed that the product was a mixture of two diastereomeric trans isomers, comprising the 3*R*,4*S* isomer in 30% excess. ^{1}H NMR ($CDCl_3$): trans-(3*R*,4*S*), δ 7.39–7.19 (m, 6 H, Ar*H* and fur*H*), 6.34–6.31 (m, 1 H, fur*H*), 6.20–6.18 (m, 1 H, fur*H*), 4.98 (q, 1 H, *J* = 7.2, C(*H*)(CH_3)Ph), 4.42 (d, 1 H, *J* = 2.2, NC*H*CH-fur), 3.88 (d, 1 H, *J* = 2.2, NCHC*H*-fur), 1.25 (d, 3 H, *J* = 7.2 C(H)(C*H*$_3$)Ph), 0.77–0.51 (m, 4 H, SiC*H*$_2$C*H*$_2$Si), –0.88, –0.10 (s, 6 H, Si(C*H*$_3$)$_2$). ^{13}C NMR ($CDCl_3$): δ 169.19 (*C*=O), 150.98, 142.71, 139.55, 128.55, 127.74, 127.47, 110.62, 109.17 (Ar*C* and fur*C*), 67.25 (*C*(H)(CH_3)Ph), 58.72 (N*C*HCH-fur), 51.33 (NCH*C*H-fur), 17.76 (C(H)(*C*H$_3$)Ph), 7.92 (Si*C*H$_2$*C*H$_2$Si), 0.47, –0.06 (Si(*C*H$_3$)$_2$).

^{1}H NMR ($CDCl_3$): trans-(3*S*,4*R*), δ 7.38–7.20 (m, 6 H, Ar*H* and fur*H*), 6.23–6.21 (m, 1 H, fur*H*), 6.11–6.09 (m, 1 H, fur*H*), 4.37 (d, 1 H, *J* = 2.0 NC*H*CH-fur), 3.99 (d, 1 H, *J* = 2.0 NCHC*H*-fur), 3.60 (q, 1 H, *J* = 7.2, C(*H*)(CH_3)Ph), 1.65 (d, 3 H, *J* = 7.2, C(H)(C*H*$_3$)Ph), 0.68–0.45 (m, 4 H, SiC*H*$_2$C*H*$_2$Si), 0.38, 0.08 (Si(C*H*$_3$)$_2$). The enantiomerically pure trans-(3*R*,4*S*) isomer **4c** was obtained as colorless crystals after one crystallization from hexane, mp 92 °C. $[\alpha]^{20}_D$ +37.95° (*c* 0.26, ethanol). Anal. Calcd for $C_{21}H_{30}N_2O_2Si_2$: C, 63.27; H, 7.59; N, 7.03. Found: C, 63.28; H, 7.43; N, 7.18.

***cis*-(3*R*,4*R*)-1(*R*)-(α-Methylbenzyl)-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-(2-furyl)-2-azetidinone (4c).** The reaction was carried out according to the standard procedure in THF. Pale yellow oil. Yield: 3.28 g (82%). The ^{1}H NMR spectrum revealed that the product was a mixture of three diastereomeric compounds: cis-(3*R*,4*R*), trans-(3*R*,4*S*), and trans-(3*S*,4*R*) in a ratio of 89:7:4. ^{1}H NMR ($CDCl_3$): cis, δ 7.30–7.17 (m, 6 H, Ar*H* and fur*H*), 6.28–6.26 (m, 1 H, fur*H*), 6.15–6.13 (m, 1 H, fur*H*), 4.59 (d, 1 H, *J* = 4.6, NC*H*CH-fur), 4.46 (d, 1 H, *J* = 4.6, NCHC*H*-fur), 4.38 (q, 1 H, *J* = 7.2, C(*H*)(CH_3)Ph), 1.72 (d, 3 H, *J* = 7.2, C(H)(C*H*$_3$)Ph), 0.68–0.47 (m, 4 H, SiC*H*$_2$C*H*$_2$Si), 0.12, –0.13 (s, 6 H, Si(C*H*$_3$)$_2$). Attempts to obtain enantiomerically pure *cis*-**2c** by recrystallization and chromatographic separation were unsuccessful.[31]

1(*R*)-(α-Methylbenzyl)-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-[1-(trimethylsilyl)ethynyl]-2-azetidinone (5a). Yellow oil. Yield: 3.99 g (93%). The ^{1}H NMR spectrum revealed that the product was a mixture of four diastereomeric products: cis-(3*R*,4*S*), cis-(3*S*,4*R*), trans-(3*R*,4*R*), and trans-(3*S*,4*S*), in a ratio of 10:2:69:19. ^{1}H NMR ($CDCl_3$): trans-(3*R*,4*S*), δ 7.52 (m, 5 H, Ar*H*), 5.07 (q, 1 H, *J* = 6.9, C(*H*)(CH_3)Ph), 4.25 (d, 1 H, *J* = 2.0 NC*H*CHC≡C), 3.61 (d, 1 H, *J* = 2.0 NCHC*H*C≡C), 1.70 (d, 3 H, *J* = 6.9, C(H)(C*H*$_3$)Ph), 0.95–0.55 (m, 4 H, SiC*H*$_2$C*H*$_2$Si), 0.21–0.00 (s, 21 H, Si(C*H*$_3$)$_2$ and Si(C*H*$_3$)$_3$); trans-(3*S*,4*S*), δ 5.03 (q, 1 H, *J* = 7.2, C(*H*)(CH_3)Ph), 4.25 (d, 1 H, *J* = 2.0 NC*H*CHC≡C), 3.43 (d, 1 H, *J* = 2.0 NCHC*H*C≡C), 1.73 (d, 3 H, *J* = 7.2, C(H)(C*H*$_3$)Ph); cis-(3*R*,4*S*), δ 4.73 (q, 1 H, *J* = 6.7, C(*H*)(CH_3)Ph), 4.48 (d, 1 H, *J* = 4.7 NC*H*CHC≡C), 4.13 (d, 1 H, *J* = 4.7, NCHC*H*C≡C), 1.69 (d, 3 H, *J* = 6.7, C(H)(C*H*$_3$)Ph); cis-(3*S*,4*R*), δ 4.69 (q, 1 H, *J* = 6.7, C(*H*)(CH_3)Ph), 4.40 (d, 1 H, *J* = 4.7, NC*H*CHC≡C), 3.92 (d, 1 H, *J* = 4.7, NCHC*H*C≡C), 1.69 (d, 3 H, *J* = 6.7, C(H)(C*H*$_3$)Ph). The diastereomers could not be separated by crystallization or chromatography.[31]

***trans*-(3*R*,4*R*)-1(*R*)-(α-Methylbenzyl)-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-methyl-2-azetidinone (5b).** The reaction was performed according to the standard procedure in Et_2O, and after the reaction mixture was warmed up to room temperature, Et_2O was replaced by THF and refluxed for 1 h to complete the cyclization reaction. After being cooled to room temperature and the standard workup procedure, 3.16 g (91%) of the crude product was isolated as a yellow oil. The ^{1}H NMR spectrum revealed that the product was a mixture of three diastereomeric products: cis-(3*R*,4*S*), cis-(3*S*,4*R*), and trans-(3*R*,4*R*) in a ratio of 10:10:80. ^{1}H NMR ($CDCl_3$): trans, δ 7.40–7.10 (m, 5 H, Ar*H*), 4.87 (q, 1 H, *J* = 7.2, C(*H*)(CH_3)Ph), 3.69 (d, 1 H, *J* = 1.9, NC*H*CHCH$_3$), 3.18 (dq, 1 H, *J* = 6.3 and 1.9, NCHC*H*CH$_3$), 1.63 (d, 3 H, *J* = 7.2 C(H)(C*H*$_3$)Ph), 1.24 (d, 3 H, *J* = 6.3, NCHCHC*H*$_3$), 0.76–0.52 (m, 4 H, SiC*H*$_2$C*H*$_2$Si), 0.05, –0.05 (s, 6 H, Si(C*H*$_3$)$_2$). ^{13}C NMR ($CDCl_3$): trans, δ 168.87 (*C*=O), 139.98, 128.66, 127.65, 126.96 (Ar*C*), 61.45 (*C*(H)(CH_3)Ph), 58.72 (N*C*HCHCH$_3$), 51.99 (NCH*C*HCH$_3$), 19.56 (C(H)(*C*H$_3$)Ph), 14.05 (NCHCH*C*H$_3$), 8.88 (Si*C*H$_2$*C*H$_2$Si), 0.28, –0.72 (Si(*C*H$_3$)$_2$). The trans-(3*S*,4*S*) enantiomer of **5b** was isolated in 88% yield (de 60%; ee >95%) using imine **2g** prepared from (*S*)-α-methylbenzylamine.

***cis*-(3*R*,4*S*)-1(*R*)-(α-Methylbenzyl)-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-methyl-2-azetidinone (5b).** The reaction was carried out following the standard procedure in THF. Yellow oil. Yield: 3.36 g (97%). The ^{1}H NMR spectrum revealed that the product was a mixture of three diastereomeric products: cis-(3*R*,4*S*), trans-(3*R*,4*R*), and trans-(3*S*,4*S*) in a ratio of 85:11:4. ^{1}H NMR ($CDCl_3$): cis, δ 7.40–7.10 (m, 5 H, Ar*H*), 4.62 (q, 1 H, *J* = 7.3, C(*H*)(CH_3)Ph), 4.35 (d, 1 H, *J* = 4.9, NC*H*CHCH$_3$), 3.50 (dq, 1 H, *J* = 6.3 and 4.9, NCHC*H*CH$_3$), 1.69 (d, 3 H, *J* = 7.3, C(H)(C*H*$_3$)Ph), 0.88 (d, 3 H, *J* = 6.3, NCHCHC*H*$_3$), 0.76–0.52 (m, 4 H, SiC*H*$_2$C*H*$_2$Si), 0.05, –0.05 (s, 6 H, Si(C*H*$_3$)$_2$). ^{13}C NMR ($CDCl_3$): cis, δ 168.98 (*C*=O), 141.53, 128.59, 127.52, 126.88 (Ar*C*), 62.52 (*C*(H)(CH_3)Ph), 53.70 (N*C*HCHCH$_3$), 52.22 (NCH*C*HCH$_3$), 18.96 (C(H)(*C*H$_3$)Ph), 13.79 (NCHCH*C*H$_3$), 7.99 (Si*C*H$_2$*C*H$_2$Si), 1.20, 0.36 (Si(*C*H$_3$)$_2$).

***trans*-(3*S*,4*S*)-1(*S*)-(α-Methylbenzyl)-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-ethyl-2-azetidinone (5c).** The reaction was performed according to the standard procedure in Et_2O, and after the reaction mixture was warmed to room temperature, Et_2O was replaced by THF and refluxed for 1 h to complete the cyclization reaction. After the mixture was cooled to room temperature and the standard workup procedure, 3.32 g (92%) of the crude product was isolated as a yellow oil. The ^{1}H NMR spectrum revealed that the product was a mixture of three diastereomeric products: cis-(3*R*,4*S*), cis-(3*S*,4*R*), and trans-(3*S*,4*S*) in a ratio of 2.5:2.5:95. ^{1}H NMR ($CDCl_3$): trans, δ 7.40–7.10 (m, 5 H, Ar*H*), 4.77 (q, 1 H, *J* = 7.2, C(*H*)(CH_3)Ph), 3.75 (d, 1 H, *J* = 2.3, NC*H*CHCH$_a$H$_b$CH$_3$), 3.18 (ddd, 1 H, *J* = 8.5, 3.8, and 2.3, NCHC*H*CH$_a$H$_b$CH$_3$), 1.61 (d, 3 H, *J* = 7.2, C(H)(C*H*$_3$)Ph), 1.80–1.20 (m, 2 H, NCHCHC*H*$_a$*H*$_b$CH$_3$), 0.82 (t, 3 H, *J* = 7.4, NCHCHCH$_a$H$_b$C*H*$_3$), 0.73–0.67 (m, 4 H, SiC*H*$_2$C*H*$_2$Si), 0.02, –0.03 (s, 6 H, Si(C*H*$_3$)$_2$). ^{13}C NMR ($CDCl_3$): trans, δ 170.31 (*C*=O), 140.82, 128.74, 127.68, 127.23 (Ar*C*), 65.32 (N*C*HCHCH$_2$CH$_3$), 63.71 (*C*(H)(CH_3)Ph), 52.53 (NCH*C*HCH$_2$CH$_3$), 26.42 (NCHCH*C*H$_2$CH$_3$), 19.90 (C(H)(*C*H$_3$)Ph), 9.51 (NCHCH*C*H$_2$CH$_3$), 8.04 (Si*C*H$_2$*C*H$_2$Si), 1.03, 0.24 (Si(*C*H$_3$)$_2$).

***cis*-(3*S*,4*R*)-1(*S*)-(α-Methylbenzyl)-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-ethyl-2-azetidinone (5c).** The reaction was performed according to the standard procedure in a mixture of THF/HMPA (5:1, v/v). Yellow oil. Yield: 3.43 g (95%). The ^{1}H NMR spectrum showed resonances of the cis-(3*S*,4*R*) isomer only. ^{1}H NMR ($CDCl_3$): cis, δ 7.40–7.10 (m, 5 H, Ar*H*), 4.60 (q, 1 H, *J* = 7.2, C(*H*)(CH_3)Ph), 4.28 (d, 1 H, *J* = 4.9, NC*H*CHCH$_a$H$_b$CH$_3$), 3.21 (ddd, 1 H, *J* = 8.9, 4.9 and 4.0, NCHC*H*CH$_a$H$_b$CH$_3$), 1.68 (d, 3 H, *J* = 7.2, C(H)(C*H*$_3$)Ph), 1.80–1.30 (m, 2 H, NCHCHC*H*$_a$*H*$_b$CH$_3$), 0.76 (t, 3 H, *J* = 7.5, NCHCHCH$_a$H$_b$C*H*$_3$), 0.75–0.60 (m, 4 H, SiC*H*$_2$C*H*$_2$Si), 0.07, 0.03 (s, 6 H, Si(C*H*$_3$)$_2$). ^{13}C NMR ($CDCl_3$): cis δ 169.81 (*C*=O), 141.72, 128.42, 127.31, 126.66 (Ar*C*), 62.33 (*C*(H)(CH_3)Ph), 60.62 (N*C*HCHCH$_2$CH$_3$), 53.31 (NCH*C*HCH$_2$CH$_3$), 22.12 (NCHCH*C*H$_2$CH$_3$), 19.04 (C(H)(*C*H$_3$)Ph), 12.02 (NCHCHCH$_2$*C*H$_3$), 7.94 (Si*C*H$_2$C*H*$_2$Si), 0.83, 0.30 (Si(*C*H$_3$)$_2$).

General Procedure for the Removal of the Disilacyclopentyl Group in Azetidinones 5. Because the 2-azetidinones **5** could not be purified by crystallization or chromatographic separation these compounds were in the first instance converted to their 3-amino derivatives **6**. The crude 2-azetidinones **5** were dissolved in 25 mL of THF. To the solution was added excess aqueous HCl (20 mL of a 1.0 M solution). The solution was stirred

for 1 h at room temperature. After addition of 25 mL of Et_2O, the water layer was separated, washed with 25 mL of Et_2O, and then basicified with ammonia (25% wt solution in water). The water layer was extracted three times with 25 mL of CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated in vacuo to afford the 3-amino-2-azetidinones **6**.

***trans*-(3*R*,4*R*)-1(*R*)-(α-Methylbenzyl)-3-amino-4-methyl-2-azetidinone (6b).** Yellow oil. Yield: 1.88 g (91%). The ^1H NMR spectrum revealed that the product was a mixture of three diastereomeric products: cis-(3*R*,4*S*), cis-(3*S*,4*R*), and trans-(3*R*,4*R*) in a ratio of 10:10:80. ^1H NMR ($CDCl_3$): trans, δ 7.40–7.10 (m, 5 H, Ar*H*), 4.86 (q, 1 H, *J* = 7.2, C(*H*)(CH_3)Ph), 3.53 (d, 1 H, *J* = 2.0, NC*H*CHCH$_3$), 3.13 (dq, 1 H, *J* = 6.2 and 2.0, NCHC*H*CH$_3$), 1.58 (d, 3 H, *J* = 7.2, C(H)(C*H*$_3$)Ph), 1.50 (br s, 2 H, N*H*$_2$), 1.22 (d, 3 H, *J* = 6.2 NCHCHC*H*$_3$).

***cis*-(3*R*,4*S*)-1(*R*)-(α-Methylbenzyl)-3-amino-4-methyl-2-azetidinone (6b).** Yellow oil. Yield: 1.96 g (95%). The ^1H NMR spectrum revealed that the product was a mixture of three diastereomeric products: cis-(3*R*,4*S*), trans-(3*R*,4*R*), and trans-(3*S*,4*S*), in a ratio of 85:11:4. ^1H NMR ($CDCl_3$): cis, δ 7.40–7.10 (m, 5 H, Ar*H*), 4.65 (q, 1 H, *J* = 7.2, C(*H*)(CH_3)Ph), 4.09 (d, 1 H, *J* = 5.0, NC*H*CHCH$_3$), 3.66 (dq, 1 H, *J* = 6.2 and 5.0, NCHC*H*CH$_3$), 1.67 (d, 3 H, *J* = 7.2, C(H)(C*H*$_3$)Ph), 1.50 (br s, 2 H, N*H*$_2$), 0.94 (d, 3 H, *J* = 6.2, NCHCHC*H*$_3$). ^{13}C NMR ($CDCl_3$): cis, δ 170.16 (*C*=O), 141.15, 128.53, 127.48, 126.66 (Ar*C*), 60.68 (*C*(H)(CH_3)Ph), 52.68 (N*C*HCHCH$_3$), 51.84 (NCH*C*HCH$_3$), 18.82 (C(H)(*C*H$_3$)Ph), 13.79 (NCHCH*C*H$_3$).

***trans*-(3*S*,4*S*)-1(*S*)-(α-Methylbenzyl)-3-amino-4-ethyl-2-azetidinone (6c).** Yellow oil. Yield: 1.94 g (88%). The ^1H NMR spectrum revealed that the product was a mixture of three diastereomeric products: cis-(3*R*,4*S*), cis-(3*S*,4*R*), and trans-(3*S*,4*S*) in a ratio of 2.5:2.5:95. ^1H NMR ($CDCl_3$): trans, δ 7.40–7.10 (m, 5 H, Ar*H*), 4.85 (q, 1 H, *J* = 7.2, C(*H*)(CH_3)Ph), 3.63 (d, 1 H, *J* = 2.0, NC*H*CHCH$_a$H$_b$CH$_3$), 3.00 (ddd, 1 H, *J* = 9.3, 3.8, and 2.0, NCHC*H*CH$_a$H$_b$CH$_3$), 1.59 (d, 3 H, *J* = 7.2, C(H)(C*H*$_3$)Ph), 1.80–1.20 (m, 4 H, NCHCHC*H*$_a$*H*$_b$CH$_3$ and N*H*$_2$), 0.85 (t, 3 H, *J* = 7.4, NCHCHCH$_a$H$_b$C*H*$_3$). ^{13}C NMR ($CDCl_3$): trans, δ 170.02 (*C*=O), 140.31, 128.74, 127.68, 127.03 (Ar*C*), 64.54 (N*C*HCHCH$_2$CH$_3$), 63.80 (*C*(H)(CH_3)Ph), 51.73 (NCH*C*HCH$_2$CH$_3$), 26.22 (NCHCH*C*H$_2$CH$_3$), 19.57 (C(H)(*C*H$_3$)Ph), 9.51 (NCHCHCH$_2$*C*H$_3$).

***cis*-(3*S*,4*R*)-1(*S*)-(α-Methylbenzyl)-3-amino-4-ethyl-2-azetidinone (6c).** Yellow oil. Yield: 2.09 g (95%). ^1H NMR ($CDCl_3$): cis, δ 7.35–7.15 (m, 5 H, Ar*H*), 4.58 (q, 1 H, *J* = 7.2, C(*H*)(CH_3)Ph), 4.08 (d, 1 H, *J* = 5.1, NC*H*CHCH$_a$H$_b$CH$_3$), 3.34 (m, 1 H, NCHC*H*CH$_a$H$_b$CH$_3$), 1.61 (d, 3 H, *J* = 7.2, C(H)(C*H*$_3$)Ph), 1.70–1.20 (m, 4 H, NCHCHC*H*$_a$*H*$_b$CH$_3$ and N*H*$_2$), 0.73 (t, 3 H, *J* = 7.4, NCHCHCH$_a$H$_b$C*H*$_3$). ^{13}C NMR ($CDCl_3$): cis, δ 170.50 (*C*=O), 141.47, 128.61, 127.55, 126.63 (Ar*C*), 60.74 (N*C*HCHCH$_2$CH$_3$), 58.70 (*C*(H)(CH_3)Ph), 52.33 (NCH*C*HCH$_2$CH$_3$), 21.48 (NCHCH*C*H$_2$CH$_3$), 19.01 (C(H)(*C*H$_3$)Ph), 10.51 (NCHCHCH$_2$*C*H$_3$).

General Procedure for the Conversion of 3-Amino-2-azetidinones 6 to 3-Carbamates 7. Unfortunately, the 3-amino-2-azetidinones could not be purified by crystallization or chromatographic separation and were therefore converted into their carbamates **7**. The crude 2-azetidinones **6** were dissolved in 25 mL of benzene. To the solution was added an equimolar amount of methyl chloroformate, and subsequently 2 mol equiv of Et_3N were added slowly at room temperature. Immediately a white solid (Et_3N.HCl) started to precipitate. The suspension was stirred for 1 h, and then all volatiles were removed in vacuo. The solid residue was extracted with 75 mL of Et_2O. Concentration of the extracts in vacuo afforded the crude 3-carbamates **7**.

***trans*-(3*R*,4*R*)-1(*R*)-(α-Methylbenzyl)-3-[(methoxycarbonyl)amino]-4-methyl-2-azetidinone (7b).** Off-white solid. Yield: 2.57 g (98%). The ^1H NMR spectrum revealed that the product was a mixture of three diastereomeric products: cis-(3*R*,4*S*), cis-(3*S*,4*R*), and trans-(3*R*,4*R*) in a ratio of 10:10:80. ^1H NMR ($CDCl_3$): trans, δ 7.34–7.24 (m, 5 H, Ar*H*), 5.81 (br d, 1 H, *J* = 6.4, N*H*), 4.88 (q, 1 H, *J* = 7.2, C(*H*)(CH_3)Ph), 4.20 (dd, 1 H, *J* = 6.4 and 1.9 NC*H*CHCH$_3$), 3.62 (s, 3 H, OC*H*$_3$), 3.39 (dq, 1 H, *J* = 6.2 and 1.9, NCHC*H*CH$_3$), 1.61 (d, 3 H, *J* = 7.2, C(H)(C*H*$_3$)Ph), 1.26 (d, 3 H, *J* = 6.2, NCHCHC*H*$_3$). ^{13}C NMR ($CDCl_3$): trans, δ 165.82 (*C*=O), 155.58 (*C*(O)OCH$_3$), 139.71, 128.67, 127.84, 127.02 (Ar*C*), 63.42 (*C*(H)(CH_3)Ph), 57.81 (NCHCHCH$_3$), 52.43 (NCH*C*HCH$_3$), 51.92 (O*C*H$_3$), 19.50 (C(H)(*C*H$_3$)Ph), 18.89 (NCHCH*C*H$_3$). The enantiomerically pure trans isomer was obtained as colorless crystals after one recrystallization from Et_2O/pentane (6:1 v/v) at −30 °C, mp 135 °C. $[\alpha]^{23}_D$ +52.6° (*c* 0.4, chloroform). Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.11; H, 6.92; N, 10.68; O, 18.30. Found: C, 63.55; H, 6.81; N, 10.61; O, 18.77.

The trans-(3*S*,4*S*) enantiomer of **7b** was prepared in a similar way. $[\alpha]^{23}_D$ −51.6° (*c* 1.0, chloroform).

***cis*-(3*R*,4*S*)-1(*R*)-(α-Methylbenzyl)-3-[(methoxycarbonyl)amino]-4-methyl-2-azetidinone (7b).** Off-white solid. Yield: 2.53 g (97%). The ^1H NMR spectrum revealed that the product was a mixture of three diastereomeric products: cis-(3*R*,4*S*), trans-(3*R*,4*R*), and trans-(3*S*,4*S*) in a ratio of 85:11:4. ^1H NMR ($CDCl_3$): cis, δ 7.31–7.24 (m, 5 H, Ar*H*), 5.84 (br d, 1 H, *J* = 8.0, N*H*), 4.92 (dd, 1 H, *J* = 8.0 and 4.9, NC*H*CHCH$_3$), 4.65 (q, 1 H, *J* = 7.1, C(*H*)(CH_3)Ph), 3.76 (dq, 1 H, *J* = 6.3 and 4.9 NCHC*H*CH$_3$), 3.64 (s, 3 H, OC*H*$_3$), 1.67 (d, 3 H, *J* = 7.2, C(H)(C*H*$_3$)Ph), 0.93 (d, 3 H, *J* = 6.2, NCHCHC*H*$_3$). ^{13}C NMR ($CDCl_3$): cis, δ 166.43 (*C*=O), 156.83 (*C*(O)OCH$_3$), 140.70, 128.76, 127.82, 127.60 (Ar*C*), 59.24 (*C*(H)(CH_3)Ph), 53.07 (N*C*HCHCH$_3$), 52.51 (NCH*C*HCH$_3$ and O*C*H$_3$), 19.08 (C(H)(*C*H$_3$)Ph), 14.10 (NCHCH*C*H$_3$). The enantiomerically pure cis isomer was obtained as colorless crystals after one recrystallization from Et_2O/pentane (6:1 v/v) at −30 °C, mp 102 °C. $[\alpha]^{25}_D$ −8.1° (*c* 0.9, chloroform).

***trans*-(3*S*,4*S*)-1(*S*)-(α-Methylbenzyl)-3-[(methoxycarbonyl)amino]-4-ethyl-2-azetidinone (7c).** Yellow oil. Yield: 2.56 g (93%). The ^1H NMR spectrum revealed that the product was a mixture of three diastereomeric products: cis-(3*R*,4*S*), cis-(3*S*,4*R*), and trans-(3*S*,4*S*) in a ratio of 2.5:2.5:95. ^1H NMR ($CDCl_3$): trans, δ 7.40–7.20 (m, 5, H, Ar*H*), 5.29 (br d, 1 H, *J* = 7.1, N*H*), 4.87 (q, 1 H, *J* = 7.2, C(*H*)(CH_3)Ph), 4.30 (dd, 1 H, *J* = 7.4 and 2.1, NC*H*CHCH$_a$H$_b$CH$_3$), 3.65 (s, 3 H, OC*H*$_3$), 3.25 (ddd, 1 H, *J* = 9.2, 3.7, and 2.1, NCHC*H*CH$_a$H$_b$CH$_3$), 1.63 (d, 3 H, *J* = 7.2, C(H)(C*H*$_3$)Ph), 1.80–1.20 (m, 2 H, NCHCHC*H*$_a$*H*$_b$CH$_3$), 0.88 (t, 3 H, *J* = 7.4 NCHCHCH$_a$H$_b$C*H*$_3$). ^{13}C NMR ($CDCl_3$): trans, δ 166.11 (*C*=O), 156.14 (*C*(O)OCH$_3$), 139.92, 128.78, 127.78, 127.03 (Ar*C*), 63.41 (*C*(H)(CH_3)Ph), 61.62 (N*C*HCHCH$_2$CH$_3$), 52.53 (NCHCHCH$_2$CH$_3$), 52.11 (O*C*H$_3$), 25.94 (NCHCH*C*H$_2$CH$_3$), 19.70 (C(H)(*C*H$_3$)Ph), 9.31 (NCHCHCH$_2$*C*H$_3$). The enantiomerically pure trans isomer was obtained as off-white crystals after one recrystallization from Et_2O/pentane (6:1 v/v) at −30 °C, mp 82 °C. $[\alpha]^{23}_D$ −27.1° (*c* 1.0, chloroform). Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30, N, 10.14. Found: C, 65.08; H, 7.37; N, 10.13.

***cis*-(3*S*,4*R*)-1(*S*)-(α-Methylbenzyl)-3-[(methoxycarbonyl)amino]-4-ethyl-2-azetidinone (7c).** Yellow oil. Yield: 2.56 g (93%). ^1H NMR ($CDCl_3$): cis, δ 7.40–7.20 (m, 5 H, Ar*H*), 5.32 (br d, 1 H, *J* = 8.4, N*H*), 5.03 (dd, 1 H, *J* = 8.4 and 4.9, NC*H*CHCH$_a$H$_b$CH$_3$), 4.69 (q, 1 H, *J* = 7.1, C(*H*)(CH_3)Ph), 3.66 (s, 3 H, OC*H*$_3$), 3.53 (ddd, 1 H, *J* = 8.9, 4.9, and 4.4, NCHC*H*CH$_a$H$_b$CH$_3$), 1.69 (d, 3 H, *J* = 7.1, C(H)(C*H*$_3$)Ph), 1.44 (ddq, 1 H, *J* = 14.0, 7.4, and 4.4, NCHCHCH$_a$*H*$_b$CH$_3$), 1.28 (ddq, 1 H, *J* = 14.0, 8.9, and 7.4, NCHCHC*H*$_a$H$_b$CH$_3$), 0.72 (t, 3 H, *J* = 7.4, NCHCHCH$_a$H$_b$C*H*$_3$). ^{13}C NMR ($CDCl_3$): trans, δ 166.60 (*C*=O), 156.62 (*C*(O)OCH$_3$), 140.92, 128.78, 127.78, 126.58 (Ar*C*), 59.13 (*C*(H)(CH_3)Ph), 58.67 (N*C*HCHCH$_2$CH$_3$), 52.79 (NCH*C*HCH$_2$CH$_3$), 52.61 (O*C*H$_3$), 22.24 (NCHCH*C*H$_2$CH$_3$), 19.10 (C(H)(*C*H$_3$)Ph), 9.99 (NCHCHCH$_2$*C*H$_3$). The enantiomerically pure cis isomer was obtained as colorless crystals after one recrystallization from Et_2O/pentane (6:1 v/v) at −30 °C, mp 103 °C. $[\alpha]^{23}_D$ −8.0° (*c* 0.7, chloroform). Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14. Found: C, 65.10; H, 7.29; N, 10.00.

General Procedure for the Removal of the α-Methylbenzyl Group. Pure 2-azetidinones **7** were dissolved in 20 mL of THF. After addition of 40 mL of liquid NH_3, small pieces of sodium metal were added until the blue color persisted. Then the NH_3 was evaporated and the residue was quenched with 20 mL of a saturated aqueous NH_4Cl solution. The aqueous layer was extracted twice with 20 mL of CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated in vacuo to afford the almost pure 2-azetidinones **8**.

***trans*-(3*R*,4*R*)-3-[(Methoxycarbonyl)amino]-4-methyl-2-azetidinone (8b).** Off-white solid. Yield: 0.71 g (90%). ^1H NMR (acetone-d_6): δ 7.22 (br s, 1 H, C(O)N*H*), 6.96 (br d, 1 H, N*H*),

4.25 (dd, 1 H, J = 8.6 and 2.2, NC*H*CHCH$_3$), 3.66 (dq, 1 H, J = 6.2 and 2.2, NCHC*H*CH$_3$), 3.61 (s, 3 H, OCH_3), 1.35 (d, 3 H, J = 6.2, NCHCHCH_3). ^{13}C NMR (acetone-d_6): δ 167.09 (*C*=O), 157.11 (*C*(O)OCH$_3$), 66.03 (N*C*HCHCH$_3$), 53.35 (NCH*C*HCH$_3$), 52.22 (O*C*H$_3$), 19.63 (NCHCH*C*H$_3$). The enantiomerically pure trans isomer was obtained as white crystals after one recrystallization from CHCl$_3$/pentane (6:1, v/v) at −30 °C, mp 124 °C. Anal. Calcd for $C_6H_{10}N_2O_3$: C, 45.57; H, 6.37; N, 17.71. Found: C, 45.63; H, 6.59; N, 17.77.

The trans-(3*S*,4*S*) enantiomer of **8b** was prepared in 90% yield. [α]$^{23}_D$ −73.7° (*c* 1.0, methanol).

***cis*-(3*R*,4*S*)-3-[(Methoxycarbonyl)amino]-4-methyl-2-azetidinone (8b).** Off-white solid. Yield: 0.74 g (93%). ^{1}H NMR (acetone-d_6): δ 7.31 (br s, 1 H, C(O)N*H*), 7.02 (br d, 1 H, N*H*), 4.94 (dd, 1 H, J = 9.5 and 5.3, NC*H*CHCH$_3$), 3.89 (dq, 1 H, J = 6.1 and 5.3, NCHC*H*CH$_3$), 3.62 (s, 3 H, OCH_3), 1.20 (d, 3 H, J = 6.1, NCHCHCH_3). ^{13}C NMR (acetone-d_6): δ 167.73 (*C*=O), 157.45 (*C*(O)OCH$_3$), 61.75 (N*C*HCHCH$_3$), 52.33 (O*C*H$_3$), 50.30 (NCH*C*HCH$_3$), 16.21 (NCHCH*C*H$_3$). The enantiomerically pure cis isomer was obtained as white crystals after one recrystallization from CHCl$_3$/pentane (6:1, v/v) at −30 °C, mp 184 °C. [α]$^{23}_D$ +34.0° (*c* 0.2, acetone).

***trans*-(3*S*,4*S*)-3-[(Methoxycarbonyl)amino]-4-ethyl-2-azetidinone (8c).** Yellow oil. Yield: 0.82 g (95%). ^{1}H NMR (acetone-d_6): δ 7.36 (br s, 1 H, C(O)N*H*, 6.99 (br d, 1 H, N*H*), 4.32 (dd, 1 H, J = 8.8 and 2.4, NC*H*CHCH$_2$CH$_3$), 3.61 (s, 3 H, OCH_3), 3.48 (dt, 1 H, J = 6.7 and 2.4, NCHC*H*CH$_2$CH$_3$), 1.67 (dq, 2 H, J = 7.4 and 6.7, NCHCHCH_2CH$_3$), 0.97 (t, 3 H, J = 7.4, NCHCHCH$_2$CH_3). ^{13}C NMR (acetone-d_6): δ 167.39 (*C*=O), 157.04 (*C*(O)OCH$_3$), 64.53 (N*C*HCHCH$_2$CH$_3$), 59.18 (NCH*C*HCH$_2$CH$_3$), 52.20 (O*C*H$_3$), 27.82 (NCHCH*C*H$_2$CH$_3$), 10.51 (NCHCHCH$_2$*C*H$_3$). The enantiomerically pure trans isomer was obtained as white crystals after one recrystallization from CHCl$_3$/pentane (6:1, v/v) at −30 °C, mp 134 °C. [a]$^{23}_D$ −43.6° (*c* 1.0, methanol). Anal. Calcd for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.02; N, 16.27. Found: C, 48.65; H, 7.20; N, 16.15.

***cis*-(3*S*,4*R*)-3-[(Methoxycarbonyl)amino]-4-ethyl-2-azetidinone (8c).** Yellow oil. Yield: 0.82 g (95%). ^{1}H NMR (acetone-d_6): δ 7.50 (br s, 1 H, C(O)N*H*, 7.02 (br d, 1 H, N*H*), 4.98 (ddd, 1 H, J = 9.6, 5.1, and 1.4 NC*H*CHCH$_2$CH$_3$), 3.65 (dt, 1 H, J = 6.7 and 5.1, NCHC*H*CH$_2$CH$_3$), 3.62 (s, 3 H, OCH_3), 1.67 (dq, 2 H, J = 7.4 and 6.7, NCHCHCH_2CH$_3$), 0.92 (t, 3 H, J = 7.4, NCHCHCH$_2$CH_3). ^{13}C NMR (acetone-d_6): δ 168.01 (*C*=O), 157.54 (*C*(O)OCH$_3$), 61.39 (N*C*HCHCH$_2$CH$_3$), 56.44 (NCH*C*HCH$_2$CH$_3$), 52.30 (O*C*H$_3$), 24.62 (NCHCH*C*H$_2$CH$_3$), 10.53 (NCHCHCH$_2$*C*H$_3$). The enantiomerically pure cis isomer was obtained as white crystals after one recrystallization from CHCl$_3$/pentane (6:1, v/v) at −30 °C, mp 206 °C. [α]$^{23}_D$ +57.8° (*c* 0.8, methanol). Anal. Calcd for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.02; N, 16.27. Found: C, 48.42; H, 7.07; N, 15.92.

***trans*-(3*R*,4*S*)-1-(4-Methoxyphenyl)-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-[(1′*S*)-1′,2′-*O*-isopropylideneethyl]-2-azetidinone (9a).** The optimum result (selectivity, yield) was obtained when the reaction was carried out with low concentrations of reactants: i.e., [*c*] enolate ≈ 0.25 M and the imine **2i** was added dropwise as a 0.5 M solution in Et$_2$O. Pale brown solid. Yield: 4.18 g (96%). The ^{1}H NMR spectrum revealed that the product was a mixture of three diastereomeric compounds: cis-(3*S*,4*S*), cis-(3*R*,4*R*), and trans-(3*R*,4*S*) in a ratio of 3.5:3.5:93. ^{1}H NMR (CDCl$_3$): δ 7.36 (d, 2 H, J = 9.0, Ar*H*), 6.86 (d, 2 H, J = 9.0, Ar*H*), 4.52 (ddd, 1 H, J = 6.9, 6.8, and 3.2, −C(O)*H*CH$_a$H$_b$O), 4.31 (d, 1 H, J = 2.3, NC*H*CHR*), 4.06 (dd, 1 H, J = 8.2 and 6.9, −C(O)HC*H*$_a$H$_b$O), 3.99 (dd, 1 H, J = 3.2 and 2.3, NCHC*H*R*), 3.78 (s, 3 H, OCH_3), 3.75 (dd, 1 H, J = 8.2 and 6.9, −C(O)HCH$_a$*H*$_b$O), 1.37, 1.31 (s, 3 H, C(CH_3)$_2$), 0.76 (s, 4 H, SiCH_2CH_2Si), 0.16, 0.13 (Si(CH_3)$_2$). ^{13}C NMR (CDCl$_3$): δ 167.74 (*C*=O), 156.54, 130.52, 119.88, 114.40 (Ar*C*), 109.81 (*C*(CH$_3$)$_2$), 73.45 (−*C*(O)HCH$_2$O), 65.68 (N*C*HCHR*), 63.00 (NCH*C*HR*), 62.39 (−C(O)H*C*H$_2$O), 55.45 (O*C*H$_3$), 26.08, 24.81 (C(*C*H$_3$)$_2$), 7.98 (SiCH$_2$*C*H$_2$Si), 0.93, 0.03 (Si(*C*H$_3$)$_2$). The enantiomerically pure trans isomer was obtained as white crystals after recrystallization from Et$_2$O in 85% yield, mp 164 °C. [α]$^{20}_D$ +9.21° (*c* 0.9, benzene). Anal. Calcd for $C_{21}H_{34}N_2O_4Si_2$: C, 58.03; H, 7.88; N, 6.44; Si, 12.92. Found: C, 57.49; H, 7.85; N, 6.44; Si, 13.01.

***cis*-(3*S*,4*S*)-1-(4-Methoxyphenyl)-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-[(1′*S*)-1′,2′-*O*-isopropylideneethyl]-2-azetidinone (9a).** The reaction was carried out according to the standard procedure in THF, but the addition of ZnCl$_2$ was skipped. Red/orange oil. Yield: 3.95 g (91%). The ^{1}H NMR spectrum revealed that the product was a mixture of three diastereomeric compounds: cis-(3*S*,4*S*), cis-(3*R*,4*R*), and trans-(3*R*,4*S*) in a ratio of 70:18:12. These diastereomers were separated by preparative HPLC techniques (90:10 MeOH/H$_2$O, LC-18 reversed-phase column, 8 mL/min). However, this separation was complicated by the fact that part of the sample (especially the trans isomer) was hydrolyzed to the 3-amino-2-azetidinone (**10a**). The stereoisomers of **10a** could not be separated using reversed-phase techniques as all three isomers do have the same retention time (R_f = 216 s). Despite the hydrolysis, samples of both cis isomers with a purity of more than 90% were obtained as colorless oils that solidified upon standing in air.

Cis-(3*R*,4*R*). R_f = 524 s. ^{1}H NMR (CDCl$_3$): δ 7.62 (d, 2 H, J = 9.2, Ar*H*), 6.84 (d, 2 H, J = 9.2, Ar*H*), 4.55 (d, 1 H, J = 5.4, NC*H*CHR*), 4.32 (ddd, 1 H, J = 8.5, 7.4, and 6.4, −C(O)-*H*CH$_a$H$_b$O), 4.16 (dd, 1 H, J = 8.4 and 6.4, −C(O)HC*H*$_a$H$_b$O), 4.06 (dd, 1 H, J = 8.5 and 5.4, NCHC*H*R*), 3.78 (s, 3 H, OCH_3), 3.65 (dd, 1 H, J = 8.4 and 7.4, −C(O)HCH$_a$*H*$_b$O), 1.46, 1.32 (s, 3 H, C(CH_3)$_2$), 0.78 (s, 4 H, SiCH_2CH_2Si), 0.24, 0.20 (Si(CH_3)$_2$). ^{13}C NMR (CDCl$_3$): δ 166.70 (*C*=O), 156.56, 131.34, 119.77, 114.12 (Ar*C*), 108.42 (*C*(CH$_3$)$_2$), 73.97 (−*C*(O)HCH$_2$O), 65.73 (N*C*HCHR*), 62.52 (NCH*C*HR*), 60.19 (−C(O)H*C*H$_2$O), 55.46 (O*C*H$_3$), 26.45, 25.23 (C(*C*H$_3$)$_2$), 8.01 (SiCH$_2$*C*H$_2$Si), 1.08, 0.26 (Si(*C*H$_3$)$_2$).

Cis-(3*S*,4*S*). R_f = 663 s. ^{1}H NMR (CDCl$_3$): δ 7.45 (d, 2 H, J = 9.1, Ar*H*), 6.84 (d, 2 H, J = 9.1, Ar*H*), 4.68 (d, 1 H, J = 5.1, NC*H*CHR*), 4.40 (ddd, 1 H, J = 7.5, 6.1, and 4.0, −C(O)-*H*CH$_a$H$_b$O), 4.33 (dd, 1 H, J = 5.1 and 4.0, NCHC*H*R*), 3.88 (dd, 1 H, J = 8.3 and 6.1, −C(O)HC*H*$_a$H$_b$O), 3.77 (s, 3 H, OCH_3), 3.72 (dd, 1 H, J = 8.3 and 7.5, −C(O)HCH$_a$*H*$_b$O), 1.33, 1.32 (s, 3 H, C(CH_3)$_2$), 0.75 (m, 4 H, SiCH_2CH_2Si), 0.24, 0.19 (Si(CH_3)$_2$). ^{13}C NMR (CDCl$_3$): δ 167.50 (*C*=O), 156.21, 137.16, 119.64, 113.84 (Ar*C*), 109.21 (*C*(CH$_3$)$_2$), 76.86 (−*C*(O)HCH32O), 67.22 (N*C*HCHR*), 63.26 (NCH*C*HR*), 62.26 (−C(O)H*C*H$_2$O), 55.46 (O*C*H$_3$), 26.56, 25.37 (C(*C*H$_3$)$_2$), 7.88 (SiCH$_2$*C*H$_2$Si), 0.79, 0.64 (Si(*C*H$_3$)$_2$).

***cis*-(3*S*,4*S*)-3-(2,2,5,5-Tetramethyl-1-aza-2,5-disilacyclopentyl)-4-[(1′*S*)-1′,2′-*O*-isopropylideneethyl]-2-azetidinone (9d).** The reaction was carried according to the standard procedure in THF, with the modification that a cooled (−78 °C) solution containing 10 mmol of the in situ prepared lithium enolate of ester **1c** was added slowly to a cooled solution (−78 °C) containing 10 mmol of the in situ prepared imine **2l** in 50 mL of THF.[32] Yellow oil. Yield: 3.12 g (95%). The ^{1}H NMR spectrum revealed that the product was a mixture of at least two compounds: *cis*-**9d** and its partially desilylated form *cis*-**10d** along with some minor impurities (<5%). Purification of the compounds by flash-chromatography (neutral Al$_2$O$_3$, chloroform) afforded *cis*-(3*S*,4*S*)-**9d** with a reasonable purity (>90%) as a pale yellow oil. Attempts to obtain analytically pure samples unfortunately were not successful.[31] ^{1}H NMR (CDCl$_3$): δ 6.33 (br s, 1 H, N*H*), 4.44 (d, 1 H, J = 4.9, NC*H*CHR*), 4.12 (ddd, 1 H, J = 6.9, 6.2, and 5.0, −C(O)*H*CH$_a$H$_b$O), 3.98 (dd, 1 H, J = 8.2 and 6.2, C-(O)HC*H*$_a$H$_b$O), 3.52 (m, 2 H, NCHC*H*R* and −C(O)HCH$_a$*H*$_b$O), 1.35, 1.32 (s, 3 H, C(CH_3)$_2$), 0.70 (s, 4 H, SiCH_2CH_2Si), 0.11 (m, 12 H, 2× Si(CH_3)$_2$). ^{13}C NMR (CDCl$_3$): δ 170.39 (*C*=O), 108.87 (*C*(CH$_3$)$_2$), 76.42 (−*C*(O)HCH$_2$O), 66.98 (N*C*HCHR*), 63.69 (NCH*C*HR*), 58.69 (−C(O)H*C*H$_2$O), 26.75, 25.46 (C(*C*H$_3$)$_2$), 7.84 (SiCH$_2$*C*H$_2$Si), 0.84, 0.61 (Si(*C*H$_3$)$_2$).

***trans*-(3*R*,4*S*)-1-(4-methoxyphenyl)-3-amino-4-[(1′*S*)-1′,2′-*O*-isopropylideneethyl]-2-azetidinone (10a).** To a solution of 1.50 g (3.4 mmol) of optically pure *trans*-**9a** in 50 mL of THF was added 40 mL of a 3.0 M aqueous NH$_4$Cl solution. The reaction mixture was stirred vigorously for 48 h at room temperature and then extracted with three 30-mL portions of Et$_2$O. The organic extracts were dried over Na$_2$SO$_4$ and concentrated in vacuo affording 1.3 g of an off-white solid. This was washed twice with 10 mL of cold (−30 °C) Et$_2$O and dried in vacuo, yielding 0.91 g (91%) of pure 2-azetidinone **10a** as a white solid, mp 162 °C. ^{1}H NMR (CDCl$_3$): δ 7.32 (d, 2 H, J = 9.0, Ar*H*), 6.85

(32) The *N*-(trimethylsilyl)imine **2l** was prepared in situ from the chiral aldehyde and LiHMDS according to a procedure reported by Hart et al.[28b]

(d, 2 H, J = 9.0, ArH), 4.57 (ddd, 1 H, J = 6.8, 6.8, and 3.0, -C(O)HCH$_a$H$_b$O), 4.18 (d, 1 H, J = 2.3, NCHCHR*), 4.11 (dd, 1 H, J = 8.4 and 6.8, -C(O)HCH$_a$H$_b$O), 3.90 (dd, 1 H, J = 3.0 and 2.3, NCHCHR*), 3.83 (dd, 1 H, J = 8.4 and 6.8, -C(O)HCH$_a$H$_b$O), 3.77 (s, 3 H, OCH$_3$), 2.08 (br s, 2 H, NH$_2$), 1.38, 1.30 (s, 3 H, C(CH$_3$)$_2$). ^{13}C NMR ($CDCl_3$): δ 167.25 (C=O), 156.66, 130.17, 119.83, 114.39 (ArC), 110.02 (C(CH$_3$)$_2$), 72.64 (-C(O)HCH$_2$O), 65.83 (NCHCHR*), 63.46 (NCHCHR*), 60.60 (-C(O)HCH$_2$O), 55.49 (OCH$_3$), 26.06, 24.79 (C(CH$_3$)$_2$). This product was converted without purification to 2-azetidinone **11** for comparison of the optical rotation (vide supra).

***cis*-(3*S*,4*S*)-3-Amino-4-[(1′*S*)-1′,2′-*O*-isopropylideneethyl]-2-azetidinone (10d).** Following the same procedure as described above for **10a**, crude **9d** was deprotected to afford 1.47 g (93%) of **10d** as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 5.77 (br s, 1 H, NH), 4.23 (m, 3 H, NCHCHR*, -C(O)HCH$_a$H$_b$O, and C(O)HCH$_a$H$_b$O), 3.75 (dd, 1 H, J = 7.9 and 4.6, NCHCHR*), 3.68 (m, 1 H, -C(O)HCH$_a$H$_b$O), 2.15 (br s, 2 H, NH$_2$), 1.42, 1.33 (s, 3 H, C(CH$_3$)$_2$). ^{13}C NMR ($CDCl_3$): δ 172.60 (C=O), 109.94 (C(CH$_3$)$_2$), 74.93 (-C(O)HCH$_2$O), 66.70 (NCHCHR*), 62.35 (NCHCHR*), 56.71 (-C(O)HCH$_2$O), 26.21, 25.24 (C(CH$_3$)$_2$).

***trans*-(3*R*,4*S*)-1-(4-Methoxyphenyl)-3-phthalimido-4-[(1′*S*)-1′,2′-*O*-isopropylideneethyl]-2-azetidinone (11).** To a solution of 0.88 g (3.0 mmol) of pure *trans*-**10a** in 50 mL of THF was added 10 mL of a saturated aqueous Na_2CO_3 solution and subsequently 1.10 g (5.0 mmol) of Nefkens reagent.[33] The mixture was stirred vigorously for 1 h at room temperature and then extracted three times with 30 mL of EtOAc. The organic extracts were dried over Na_2SO_4 and concentrated in vacuo affording 1.6 g of an off-white solid. This was washed twice with 20 mL of cold (0 °C) Et_2O and dried in vacuo, yielding 1.17 g (92%) of pure **11** as a white solid, mp 154 °C, dec. $[\alpha]^{20}_D$ +5.97 (c 0.7, methanol). ^{1}H NMR ($CDCl_3$): δ 7.87-7.81, 7.78-7.72 (m, 2 H, ArH of phthalim), 7.39 (d, 2 H, J = 8.9, ArH of anisyl), 6.91 (d, 2 H, J = 8.9, ArH of anisyl), 5.58 (d, 1 H, J = 2.6 NCHCHR*), 4.64 (ddd, 1 H, J = 7.0, 6.5, and 2.3, -C(O)HCH$_a$H$_b$O), 4.50 (dd, 1 H, J = 2.6 and 2.3, NCHCHR*), 4.13 (dd, 1 H, J = 8.4 and 6.5, -C(O)HCH$_a$H$_b$O), 3.80 (s, 3 H, OCH$_3$), 3.64 (dd, 1 H, J = 8.4 and 7.0, -C(O)HCH$_a$H$_b$O), 1.54, 1.36 (s, 3 H, C(CH$_3$)$_2$). ^{13}C NMR ($CDCl_3$): δ 166.87, 161.55 (C=O), 157.19, 134.53, 131.72, 123.74, 120.73, 114.55 (ArC), 110.63 (C(CH$_3$)$_2$), 71.96 (-C(O)HCH$_2$O), 66.15 (NCHCHR*), 59.37 (-C(O)HCH$_2$O), 55.52 (OCH$_3$), 54.16 (NCHCHR*), 26.11, 25.43 (C(CH$_3$)$_2$). Anal. Calcd for $C_{23}H_{22}N_2O_6$: C, 65.39; H, 5.25; N, 6.63. Found: C, 64.84; H, 5.45; N, 6.53.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of some of the new compounds (42 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

The Reaction of Glyoxylic Acid with Ammonia Revisited

Anthonius J. Hoefnagel,* Herman van Bekkum, and Joop A. Peters

Laboratory of Organic Chemistry and Catalysis, Delft University of Technology, Julianalaan 136, 2628 BL Delft, The Netherlands

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Upon addition of ammonia or an alkylamine to glyoxylic acid an ammonium derivative of glyoxylic acid precipitates quantitatively. With the use of solid-state ^{13}C and ^{15}N NMR spectroscopy, it is shown that adducts of glyoxylic acid and ammonia or the alkylamine are obtained. These compounds are not stable in aqueous solution. The compositions of the aqueous solutions have been investigated by ^{1}H, ^{13}C, ^{15}N, and ^{17}O NMR. Under basic conditions hexahydro-*s*-triazine-2,4,6-tricarboxylate is the predominant species in a solution of the adduct of ammonia and glyoxylic acid, whereas upon acidification (pH < 6) glyoxylate is the only organic species. In a basic solution of the adduct of ethylamine and glyoxylic acid *N*-ethyliminoacetate is the only species. The *N*-methyl adduct shows an intermediate behavior: both the hexahydrotriazine and the imine are observed. Under acidic conditions deamination to glyoxylate always occurs. Intermediates in the reaction of glyoxylic acid and ammonia could be detected with ^{1}H NMR, when the reaction was performed with an excess of ammonia. The mechanism of these reactions is discussed.

Introduction

Glycine and hydroxyglycine units are occurring in various pharmacologically important compounds, such as amoxicillin- and cephalosporin-type antibiotics. Ammonium derivatives of glyoxylic acid have been proposed as intumescent fire-retarding and heat-insulating materials.[1] Furthermore, iminoacetic acid is thought to be an inter-

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