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Diastereofacial Selectivity in the Reaction of Chiral *N*-Trimethylsilyl Imines with Ester Enolates: Preparation of *trans* -Azetidin-2-ones in High Stereocontrolled Fashion.

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Abstract: : Highly efficient chiral ester enolate-imine condensation, giving 3,4-disubstituted β-lactams with excellent *trans-syn* or *trans-anti* diastereoselectivity, is reported. The chiral information is included in the electrophilic partner of the condensation, nominally chiral α- , β-silyloxy- or alkoxy-*N*-trimethylsilyl-imines. The high diastereofacial selectivity is determined by the correct choice of the metal cations present in the reaction medium and the very nature of the hydroxy protecting group. By this procedure a number of azetidinones, intermediates in the synthesis of commercially interesting β-lactam antibiotics have been obtained. Fully assigned ^{1}H and ^{13}C NMR spectra of the so obtained azetidinones are reported.

Since its discovery by Gilman[1] in 1943, the interaction between imines and ester enolates to form β-lactams (2-azetidinones) has been one of the most versatile and useful approach to the synthesis of these compounds[2] and hence to the diverse families of β-lactam antibiotics[3] as well as diverse important natural products for which 2-azetidinones constitute key intermediates.[4]

Following the initial Reformatsky approach, particularly developed by Kagan and Gaudemar[5], the ester enolates-imines route to azetidinone ring received new attention from the studies by Bergbreiter and Newcomb that reported the reaction between lithium enolates of esters and imines in 1980[6]. Although the synthetic utility of the ester enolates-imines condensation has been extensively explored and the first claimed limitations (mainly fail of enolizable aldimines to afford β-lactams) have been got through[7], one of the most challenging goals currently under active research is the development of methodologies that lead to an effective chiral control in the formation of the corresponding β-lactam. This control can be induced from the two original moieties of the β-lactam ring: chiral esters or chiral imines.[8,9] The first attempts to prepare optically active β-lactams using ester enolate-imine condensations were reported by Kagan and Luche which obtained, starting from chiral menthyl α-bromo propionate only racemic products[5b]. Similar results were obtained by Furukawa[10], whereas Bergbreiter and Newcomb were able to obtain β-lactams with up to 60% *ee* starting from lithium enolates of menthyl esters[6]. Better results (91% *ee*) were reported by Hart[11] in the synthesis of β-lactam antibiotic PS-5 using as chiral ester enolates that derived from isoborneol 10-diisopropylsulfonamide.[12] More recently the identification of chiral 3-hydroxy-4-aryl-β-lactam as precursor of the C-13 side chain of taxol[13] has promoted research in this area and very high *ee* (98%) have been obtained starting from chiral ester enolates.[14]

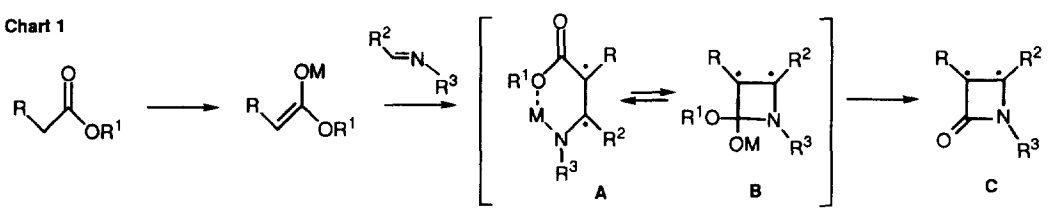
In the past few years the need of chiral (*R*-)-3-hydroxyethyl azetidinone, to be used as intermediate in the synthesis of penems and carbapenems[15,16] has been responsible for the explosion of interest in the title reaction. It did not take long for several groups to recognise that the use of enantiopure β-hydroxybutyrate, available in both optical antipodes, as the ester component would lead to β-lactams with α-hydroxyethyl substitution at C(3). Several research groups[17,18,19,20] including ours[21], have been involved in the materialisation of this approach (*Chiral nucleophile-achiral electrophile*), since by this way it is possible to synthesise, using as ester the (*3S*)-hydroxy butanoate, the enantiopure 3-hydroxy-ethyl-4-acetoxy-azetidin-2-one. An alternative possibility consists in the use of chiral imines and non-chiral ester enolates (*Achiral nucleophile-chiral electrophile*). This approach results particularly useful to introduce, in the position 3 of the β-lactam ring, an amidic group, crucial for the synthesis of monobactam antibiotics.[22] The first attempt to use chiral imines was described by Furukawa, who was able to obtain 18-28% diastereomeric excess (*de*) in reactions between Reformatsky reagents and *N*-(α-methylbenzyl)imines.[23] This approach has been used with greater success by Overman and Osawa.[24] In some recent papers from our laboratories[25] we have reported the complete diastereoselection observed in the cycloaddition reaction using imines derived from chiral α-silyloxy aldehydes. It is noteworthy that all these methodologies lead to β-lactams which can be elaborated at the C4 position to give useful precursors in the chemical synthesis of β-lactams antibiotics.

In view of the above precedents and within the context of our interest in the study of the synthesis, through *N*-metallo imines, of chiral biological significant nitrogen containing molecules, it is the aim of this work to have a better look inside on the condensation reaction between non-chiral esters and chiral *N*-trimethylsilylimines in which the chiral information is constituted by an imine bearing at the α- or β-position of the imine carbon atom a silyloxy or alkoxy group. Our final goal is to develop methodologies that allow the preparation of β–lactams in high diastereoselectivity.

Results and Discussion.

The formation of the β-lactam ring from an ester enolate and an imine is analogous to the well-known aldol condensation, but includes an additional ring-closure step. The first step of the reaction is activation of the incoming imine by coordination of the imine nitrogen to the metal atom of the enolate.[26] This coordination makes the C=N bond more polarized and the carbon becomes a better electrophilic center. Moreover by the evaluation of the ^{13}C chemical shift, it has been shown that the presence of a trimethylsilyl group as substituent of the iminic nitrogen, increases the electrophilicity of the iminic carbon itself compared to that of *N*-alkyl or *N*-aryl imines.[27] The next step is a nucleophilic attack of the enolate anion on the electrophilic carbon of the imine. During this C-C bond formation, leading to an acyclic amino ester intermediate **A** in equilibrium with the corresponding four membered cyclic structure **B**, two new chiral centres are formed and the stereochemistry of the final product is determined.[28,29] Elimination of the metal alkoxide finally leads to the end product **C**. (Chart 1)

Chart 1



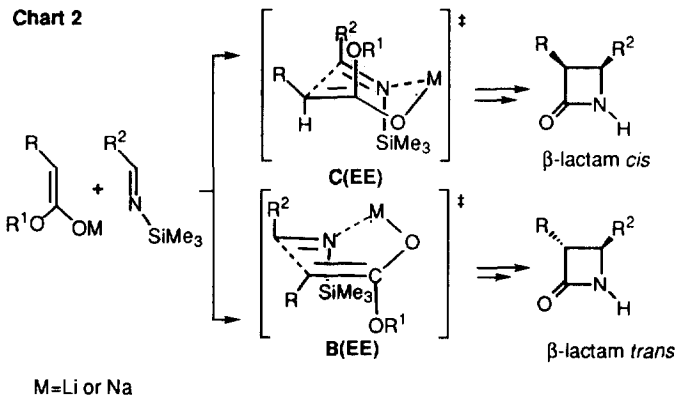
Simple diastereoselection

The formation of *trans*- and *cis*- β-lactams can be explained by taking into account the transition states as shown in Chart 2. We can assume that under the conditions used, as ample literature suggests, treatment of esters with strong bases affords the E enolate[30,31] and that the imine should exist predominantly as the E geometric isomer[11]. In our studies *N*-trimethylsilylimines have been generated by treatment with LiHMDSA

whereas LDA (Method A) or sodium hexamethyldisilylamide (Method B) were used in the generation of the enolates (Scheme 1). As we will see on the subsequent discussion the two methods give rise to a different facial diastereoselectivity of the reaction[32]. Moreover we can also assume that under our conditions (-78°C, THF as solvent) the reaction proceeds under kinetic control[21a]. Keeping fixed the structure of the imine and of the enolate and using the Evans transition state descriptors,[29] two possible transition state models, chair like transition state **C(EE)** and boat like transition state **B(EE)** can be invoked to rationalise the stereochemical outcome (from the simple diastereoselection point of view) of the cycloaddition (Chart 2).

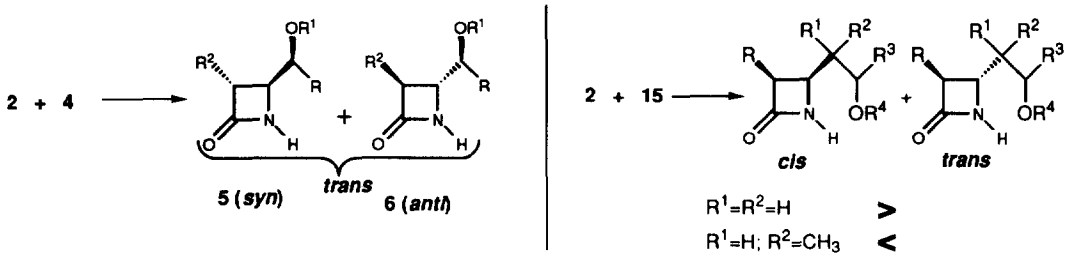
Scheme 1

Chart 2



The chair-like transition state affords the *cis* azetidinone, the boat-like transition state the *trans* one.[33] In the chair-like transition state **C(EE)** an important 1,3 diaxial non bonded interaction between the enolate alkoxy group and the imine side chain can be observed. In the boat-like transition state **B(EE)** the enolate alkoxy group and the imine side chain are remote from each other. In the case of *N*-trimethylsilylimines the 1,4 apical interaction between the alkoxy group and the trimethylsilyl group appears to be of moderate degree since the two groups are relatively far away because of the *N-Si* bond length of about 1.8 Å. From the two transition-states above reported it appears clear why the simple diastereoselection is largely influenced by the sterical hindrance of the imine side chain: small groups, as linear side chains, give preponderant formation of *cis* azetidinones whereas branched chains give as major isomer *trans* azetidinones . This behaviour is in agreement with the hypothesis that with large imine side chain the non bonded 1,3 interaction in the chair-like transition state becomes too large so that the boat-like transition state corresponds to the lowest energy and leads to the preponderant formation of the *trans* isomer. As a matter of fact, the *N*-trimethylsilylimine of lactal, protected on the hydroxy functionality as alkyl or trialkylsilyl ether, upon addition of enolates affords *exclusively syn-trans* or *anti-trans* azetidinones, aside from the *O*-protecting group (Scheme 2), while *N*-trimethylsilylimines of β-silyloxy aldehydes *gives rise to a mixture of cis and trans isomers* depending on the very nature of the substituent in α-position of the iminic carbon atom (Scheme 2, Table 1, 3, 5).

Scheme 2

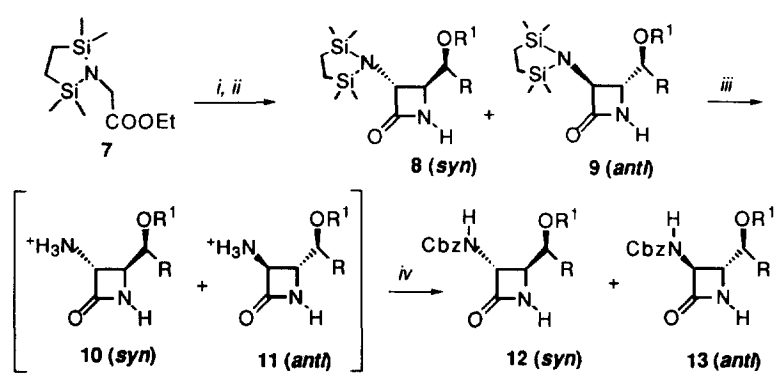


Concerning the 3-amino derivatives (Table 3), because the *N*-protecting disilyl moiety[34] is very susceptible to hydrolysis, the separation by chromatographic techniques was usually accompanied by partial deprotection of the amine function with decomposition of the azetidinone ring. To overcome this problem the crude mixture was hydrolysed in NH_4Cl/HCl. After removal of the disilyl moiety, the amine functionality was protected as carbobenzoxy derivative. The NMR of crude azetidinones before and after the protection shown the same diastereomeric ratio (Scheme 3, Table 3).

N-trimethylsilyl imines of β-silyloxy aldehydes, instead, give a mixture of the *cis* and *trans* isomers (Scheme 4, Table 5) the ratio being determined by the substitution on the α-position of the imine side chain. Linear side chains afforded a larger amount of *cis* azetidinone.

For the all azetidinones reported, the relative *cis-trans* stereochemistry has been determined by the coupling constant of the H_3 and H_4 at ^1H NMR, the *J* of the *cis* isomer being always larger that the *trans* one (Tables 2 and 4).[35]

Scheme 3

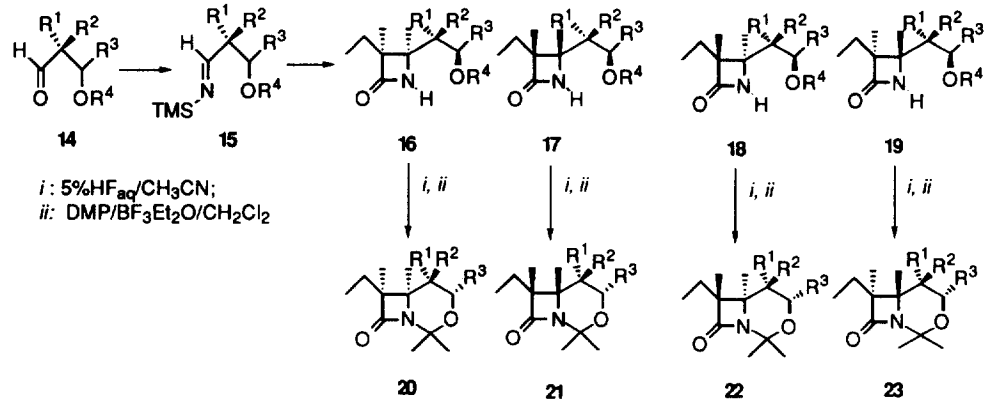


Reagents and conditions: i: LDA, THF, -78°C; *ii* : 2; *iii*: HCl 1N (pH 1.5),2 hrs; *iv*: CbzCl, $NaHCO_3$,(pH8-9), acetone/H_2O.

With β-silyloxy derivatives, for diagnostic purpose, the diastereomeric ratio has been determined on the crude reaction mixture and the configurations have been assigned by elaboration to the corresponding cyclic acetonides (see experimental section). Nevertheless, since in our hands the chromatographic separation of compounds **22** and **23** from **21** resulted a difficult task, the diastereomeric ratio was assigned on the basis of HPLC and ^1H NMR techniques by integration of the characteristic protons C-3 and C-4 on the crude reaction mixture. The structures of **22** and **23** was tentatively assigned on the basis of combinative coupling constants

evaluation (in the case obtained by irradiation) COSY and NOE techniques at 500 MHz instrument. (Scheme 4, Table 5)

Scheme 4



14a, 15a: R^1=R^2=H; R^3=CH$_3$; R^4=TBDMS. 14b, 15b: R^1=CH$_3$ R^2=H; R^3=H; R^4=TBDMS
14c, 15c: R^1=H; R^2=CH$_3$; R^3=H; R^4=TBDMS

Diastereoface selectivity.

More intriguing appears to be the facial-diastereoselectivity on varying the nature of the *O*-protecting group and the nature of the metal cation used in the formation of *N*-trimethylsilyl imines.

The 1,2-facial diastereoselectivity observed in a given reaction is generally explained by a partitioning of the reaction path *via* a chelated transition state, which exclusively gives the *syn* isomer, and an unchelated one of comparable activation energy that affords a preponderant amount of the *anti* diastereoisomer. This partition has been named by Reetz[36] chelation and non chelation control.

Let us take into account the three factors that seem, in the present case, to play a crucial role in determining the 1,2-diastereoselectivity:[37]

1. The nature of the cations present in the reaction medium.
2. The sterical demanding of the *O*-protecting group of the α-hydroxy functionality.
3. The distance of the silyloxy group from the imine carbon.

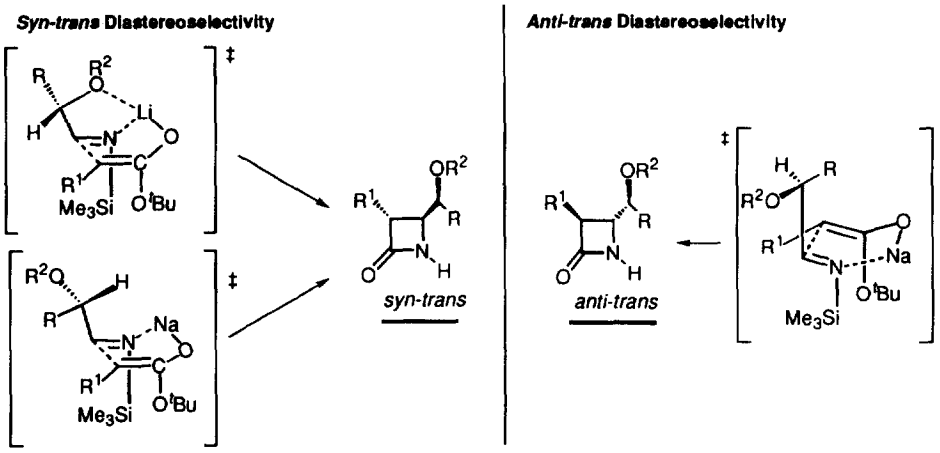
1. *The nature of the cations present in the reaction medium.*

The ester enolates have been generated using as metallating agent lithium diisopropyl amide, lithium or sodium hexamethyldisilyl amide. The use of lithium amides results in a very remarkable *syn-trans* diastereoselectivity whereas using sodium hexamethyldisilylamide the *trans*-diastereoselectivity remains unchanged, as previously discussed, but the *syn* diastereoselectivity decreases. In the case of lithium enolates the observed very high 1,2-*lk* induction of the stereocenter present in the side chain of the imine upon C$_4$ stereocenter of the azetidinone could be explained *via* a Cram cyclic model by assuming coplanarity between oxygen and nitrogen atoms of the imine due to chelation by lithium cations so that the nucleophile attacks from the less hindered face of the diastereotopic plane. In contrast a lower diastereoselectivity is observed using the sodium enolate as nucleophile (Chart 3).

It is known that the sodium cation is a weaker Lewis acid and cannot efficiently coordinate the two heteroatoms of imine ensuing partition between chelated (highly stereoselective) and unchelated (poorly stereoselective) transition states. Therefore the reaction leads to a significant formation of the *anti* isomer. However the more basic imine nitrogen atom still coordinates the sodium cation so that the simple

diastereoselectivity still proceeds *via* a closed boat-like transition state leading exclusively to the formation of *trans* azetidinone as previously emphasised. The very high *syn* diastereoselectivity invariable shown by the alkoxy derivatives, even in the case of sodium enolates, could be originated by the higher basicity of alkoxy groups in comparison with silyloxy groups so that the chelated model is still operating[38].

Chart 3



2. The sterical demanding of the O-protecting group of the α-hydroxy functionality. A careful analysis of the results reported in Table 1 and 2 may be interpreted in terms of ability of the *O*-protecting group to form chelated cyclic structure through the coordination as has been recently assumed in an elegant paper by Eliel and Frye. This ability seems strictly correlated to the sterical demanding of the groups directly linked to the silicon[39]. With the relatively small triethylsilyloxy group the *syn* selectivity is complete, whereas, to an increasing size of the *O*-protecting group corresponds an increasing of *anti* isomer amount. With the big triisopropylsilyloxy group the *syn:anti* ratio becomes 73/27 (Method A) and 17/83 (Method B). (Entries 1, 2 Table 1. See also entries 1, 2 Table 3). Even from this point of view, alkoxy groups show a very high *syn* diastereoselectivity apart from the metal cations used and steric hindrance of the *O*-protecting group itself (See entries 9, 10, 11, 12 Table 1and entries 9 and 10 Table 3) as a further proof that, with alkoxy groups, the chelated model is still operative.

3. The distance of the silyloxy group from the iminic carbon: β-Alkoxy imines.

As we have already seen the control in simple distereoselectivity for the β-silyloxy imines is less stringent than for the α-silyloxy ones. Examples are known in literature on similar behaviour.[31] In an oversimplification it has been attributed to a larger freedom degree of the six membered chelated ring compared with the corresponding five-membered cyclic structure.[40] Because this, different mechanistic pathways and different transition states are involved in determining the stereochemical outcome of the reaction. As result almost all possible stereoisomers are obtained, of course in different ratio depending from substituents and reaction conditions.

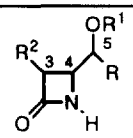
In conclusion it must be pointed out that by a careful choice of the enolate cations and of the *O*-protecting groups the configuration of the two contiguous carbon centres on the azetidinone ring can be controlled by the configuration of the stereogenic centre of the starting imine.

Table 1. Asymmetric Synthesis of β-Lactams trough Chiral Imines-Alkyl Ester Enolates Condensation.

Entry	R	R^1	R^2	Method	β-Lactams (*Trans* 100%)	Isolated Yield (%)	Product ratio *Syn/Anti*	Ref
1	CH_3	TIPS	C_2H_5	A	**5a/6a**	60	73 /27	
2	CH_3	TIPS	C_2H_5	B	**5a/6a**	51	17/83	
3	CH_3	TBDPS	C_2H_5	A	**5b/6b**	53	90/10	
4	CH_3	TBDPS	C_2H_5	B	**5b/6b**	31	7/93	
5	CH_3	TBDMS	C_2H_5	A	**5c/6c**	63	96/4	25g, j
6	CH_3	TBDMS	C_2H_5	B	**5c/6c**	38	70/30	25i
7	CH_3	TES	C_2H_5	A	**5d/6d**	40	>98/<2	
8	CH_3	TES	C_2H_5	B	**5d/6d**	35	90/10	
9	CH_3	*tert*-Bu	C_2H_5	A	**5e/6e**	25	>98/<2	
10	CH_3	*tert*-Bu	C_2H_5	B	**5e/6e**	20	>98/<2	
11	CH_3	Bn	C_2H_5	A	**5f/6f**	42	>98/<2	
12	CH_3	Bn	C_2H_5	B	**5f/6f**	10	>98/<2	
13	C_2H_5	TBDMS	C_2H_5	A	**5g/6g**	41	93/7	
14	CH_3	TBDMS	*i*-Pr	A	**5h/6h**	61	>98/<2	25g
15	CH_3	TBDMS	*tert*-Bu	A	**5i/6i**	68	>98/<2	
16	Ph	TBDMS	C_2H_5	A	**5j/6j**	84	>98/<2	
17	Ph	TBDMS	*i*-Pr	A	**5m/6m**	70	>98/<2	

TIPS=Triisopropylsilyl; **TBDPS**: tert-Butyldiphenylsilyl; **TBDMS**: tert-Butyldimethylsilyl; **TES**: Triethylsilyl.

Table 2 ^1H and ^{13}C NMR data for Azetidinones 5, 6 .



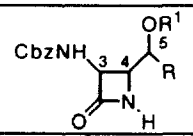
Comp.	H-3	H-4	H-5	C-2	C-3	C-4	C-5
5a	2.70 m	3.20 (dd, J=2.35; 7.52)	3.90 (dq, J=6.22; 7.52)	170.91	54.40	60.25	71.21
6a	3.00 m	3.25 (dd, J=2.23; 3.84)	4.05 (dq, J=3.84; 6.22)	171.83	53.60	59.78	68.61
5b	2.65 m	3.30 (dd, J=2.26; 7.33)	3.80 (dq, J=6.25; 7.33)	170.62	50.34	60.00	72.09
6b	2.95 m	3.15 (dd, J=2.10; 3.92)	3.95 (dq, J=3.90; 6.24)	171.22	53.50	59.34	68.81
5c	2.71 (dt, J=2.57; 7.03)	3.18 (dd, J=2.57; 8.86)	3.75 (quintet, J=8.86)	168.80	52.40	57.80	68.90
6c	2.85 (dt, J=2.52; 721)	3.15 (dd, J=2.53; 5.64)	3.85 m	171.55	53.80	56.60	68.60
5d	2.68 m	3.15 (dd, J=2.23; 7.81)	3.73 (quintet, J=6.35)	170.58	54.60	59.93	71.20
6d	2.94 m	3.19 (dd, J=2.10; 4.65)	3.87 (quintet, J=6.52)	171.44	54.18	59.61	68.60
5e	2.70 m	3.20 (dd, J=2.25; 8.04)	3.60 (dq, J=6.2; 8.04)	170.73	54.71	58.65	70.13
5f	2.70 m	3.20 (dd, J=2.28; 8.04)	3.45 (dq, J=6.1; 8.04)	170.72	55.05	58.32	70.86
5g	2.75 m	3.30 (dd, J=2.33; 7.52)	3.55 (m, J(4-5)=7.52)	170.55	54.62	57.84	75.83
6g	3.00 m	3.30 (dd, J=2.10; 3.92)	3.70 (m, J(4-5)=3.92)	171.52	53.64	57.51	73.19
5h	2.58 (dt, J=2.24; 7.65)	3.22 (dd, J=2.24; 7.65)	3.75 (quintet, J=7.65)	170.31	58.10	59.90	71.30
5i	2.50 (t, J=1.75)	3.14 (dd, J=2.10; 6.20)	3.65 (quintet, J=6.31)	169.71	56.51	63.41	70.92
5j	2.70 m	3.33 (dd, J=2.26; 7.53)	4.50 (d, J=7.53)	170.63	54.19	60.40	77.87
5m	2.62 (ddd, J=2.23; 2.04; 7.85)	3.41 (dd, J=2.22; 7.51)	4.50 (d, J=7.501)	170.05	58.60	59.60	78.36

Table 3. Asymmetric Synthesis of β-Lactams trough Chiral Imines-STABASE Enolate Condensation.

Entry	R	R^1	Method	β-Lactams (*Trans* 100%)	Yield (%)*	*Syn/Anti* ratio	Ref.
1	CH_3	TIPS	A	**12a/13a**	56	90/10	25b
2	CH_3	TIPS	B	**12a/13a**	65	15/85	25b
3	CH_3	TBDPS	A	**12b/13b**	20	>98/<2	
4	CH_3	TBDPS	B	**12b/13b**	36	9/91	
5	CH_3	TBDMS	A	**12c/13c**	85	>98/<2	25h
6	CH_3	TBDMS	B	**12c/13c**	73	40/60	25h
7	CH_3	TES	A	**12d/13d**	54	>98/<2	
8	CH_3	TES	B	**12d/13d**	40	96/4	
9	CH_3	*tert*-Bu	A	**12e/13e**	39	>98/<2	
10	CH_3	*tert*-Bu	B	**12e/13e**	55	>98/<2	
11	Ph	TBDMS	A	**12f/13f**	40	>98/<2	25h

*Determined on the isolated Cbz derivatives. **TIPS**=Triisopropylsilyl; **TBDPS**: tert-Butyldiphenylsilyl; **TBDMS**: tert-Butyldimethylsilyl; **TES**: Triethylsilyl.

Table 4 ^1H and ^{13}C NMR data for Azetidinones 12, 13 .



Comp.	H-3	H-4	H-5	C-2	C-3	C-4	C-5
12a	4.50 (dd, J=2.10; 8.35)	3.50 (dd, J=2.10; 6.52)	4.00 (quintet, J=6.03)	168.58	60.32	63.59	66.99
13a	4.75 (dd, J=2.10; 8.62)	3.60 m	4.15 m	167.73	58.73	62.47	66.69
12b	4.35 (dd, J=2.02; 8.30)	3.60 (dd, J=2.04; 6.92)	3.85 (quintet, J=6.90)	167.12	66.99	63.14	60.33
13b	4.75 (dd, J=1.00; 8.63)	3.50 m	3.95 m	167.10	67.22	62.16	59.05
12c	4.60 (d, J=7.65)	3.65 m	4.80 m	167.80	59.90	63.25	74.15
13c	4.75 (dd, J=2.10; 8.65)	3.60 m	4.15 m	167.73	58.73	62.47	67.06
12d	4.5 (dd, J=2.02; 9.01)	3.45 (dd, J=2.02; 7.45)	3.85 (quintet, J=6.93)	167.48	67.13	63.61	60.60
13d	4.70 (dd, J=2.03; 8.64)	3.55 m	3.93 m	167.40	65.50	62.59	60.40
12e	4.63 (dd, J=1.83, 9.45)	3.55 m	3.55 m	169.41	60.58	63.15	66.73

Table 5. Asymmetric Synthesis of β-Lactams trough β-silyloxy Chiral Imines-Ester Enolates Condensation.

Entry	Imine	Meth	β-Lactams	R^1	R^2	R^3	Isolated Yield (%)	Product ratio (cis/trans)*	Ref.
1	**15a**	A	**16a:17a:18a:19a**	H	H	CH_3	46	75:8:15:2(83/17)	
2	**15b**	A	**16b:17b:18b:19b**	CH_3	H	H	52	15/2/75/8 (17/83)	25f
3	**15c**	A	**16c:17c:18c:19c**	H	CH_3	H	59	15/0/72/13(15/85)	41

*The products ratio showed to be the same for the open-chains and acetonide derivatives by HPLC analyses

Experimental Section

General: Melting points are uncorrected. All reactions were conducted under nitrogen atmosphere. THF was distilled from Na/benzophenone ketyl and CH_2Cl_2 was distilled from P_2O_5. ^{1}H-NMR spectra were recorded at 200 and 500 MHz in $CDCl_3$ using residual of $CHCl_3$ as internal references. All reactions were performed under argon atmosphere.

General Procedure for the Synthesis of α-Silyloxy aldehydes.
To a solution of hydroxy ester (30 mmol) and imidazole (60 mmol) in anhydrous DMF (30 ml) cooled with ice-water were added 30 mmol of the appropriate silyl-chloride. After ten minutes the bath was removed and the reaction was left at room temperature for three hours. The mixture was poured in ice-water and extracted with hexane (3x50ml) which was washed with brine (2x50ml), dried (Na_2SO_4) and concentrated in vacuo. To a solution of the appropriate ester (20 mmol) in anhydrous ether (80 ml) was added dropwise diisobutylaluminiumhydride (DIBAH) in hexane (30 mmol, 30 ml, 1 M) by a side arm at -78 °C. After being stirred at the same temperature for the time to consume the starting ester (from 15 min to 2 hr) the mixture was poured in ice water and extracted with ether. The solvent was washed twice with diluted cold hydrochloridric acid, brine, dried and concentrated in vacuo. The residue was chromatographed on silica gel (hexane-ethyl acetate 9:1) to give the target aldehyde.

Ethyl (*S*)-2-[(Triisopropylsilyl)oxy]-2-propanoate
$[\alpha]_D^{20}$= -16.5 (*c* 1.95, $CHCl_3$); IR ($CHCl_3$) 1750 cm^{-1}; ^{1}H NMR 1.05 (m, 21H), 1.25 (t, 3H, J=7.1), 1.40 (d, 3H, J=6.70), 4.15 (q, 2H, J=6.70), 4.45 (q, 1H, J=7.1); ^{13}C NMR 174.18, 68.47, 60.59, 21.72, 17.79, 14.14, 12.08.

(*S*)-2-[(Triisopropylsilyl)oxy]-2-propanal
$[\alpha]_D^{20}$=-8.4 (*c* 2.72, $CHCl_3$); IR ($CHCl_3$) 1736 cm^{-1}; ^{1}H NMR 1.08 (m, 21H), 1.30 (d, 3H, J=6.8), 4.20 (dq, 1H, J=1.58, 6.8), 9.65 (d, 1H, J =1.58); ^{13}C NMR 204.06, 73.72, 18.78, 17.76, 12.05.

Ethyl (*S*)-2-(*tert*-Butyloxy)-2-propanoate
$[\alpha]_D^{20}$=-41.0(*c* 2.04, $CHCl_3$); IR ($CHCl_3$) 1745 cm^{-1}; ^{1}H NMR 1.10 (s, 9H), 1.20 (t, 3H, J=7.1), 1.25 (d, 3H, J=6.8), 4.07 (m, 3H); ^{13}C NMR 174.88, 74.62, 67.35, 60.40, 27.56, 20.32, 13.97.

(*S*)-2-(*tert*-Butyloxy)-2-propanal
$[\alpha]_D^{20}$=-77.0(*c* 2.05, $CHCl_3$); IR ($CHCl_3$) 1738 cm^{-1}; ^{1}H NMR 1.16(d, 3H, J=6.9), 1.17 (s, 9H), 3.87 (dq, 1H, J=2.1, 6.9), 9.55 (d, 1H, J=2.1); ^{13}C NMR 205.40, 74.78, 72.85, 28.14, 17.45.

Ethyl (*S*)-2-[(Triethylsilyl)oxy]-2-propanoate
$[\alpha]_D^{20}$=-28.6 (*c* 1.94, $CHCl_3$); IR ($CHCl_3$) 1750 cm^{-1}; ^{1}H NMR 0.60(q, 6H, J=8.10), 0.95 (t, 9H, J=8.10), 1.23 (t, 3H, J=7.1), 1.40 (d, 3H, J=6.72), 4.13 (q, 2H, J=7.1), 4.30 (q, 1H, J=6.7); ^{13}C NMR 173.93, 68.07, 60.60, 21.23, 14.07, 6.52, 4.56.

(*S*)-2-[(Triethylsilyl)oxy]-2-propanal
$[\alpha]_D^{20}$=-11.5 (*c* 1.55, $CHCl_3$); IR ($CHCl_3$) 1735 cm^{-1}; ^{1}H NMR 0.60(q, 6H, J=7.85), 0.95 (t, 9H, J=7.85), 1.25 (d, 3H, J=6.84), 4.05 (dq, 1H, J=1.34, 6.84), 9.60 (d, 1H, J=1.34); ^{13}C NMR 204.12, 73.46, 18.53, 6.59, 4.68.

General Procedure for the Synthesis of *N*-Trimethylsilyl imines.
To a 1 M solution of LiHMDSA in THF (10 ml), under argon atm, 10 mmol of the aldehyde in 30 ml of THF at -40°C were added. The mixture was stirred at the same temperature for 40 min, and the resulting cold solution of *N*-trimethylsilylimine was used directly for the condensation with the ester enolate (see below).

General Procedure for the preparation of Azetidinones .(5a-5m and 6a-6m)
Method A : To a solution of diisopropylamine (1.01 g, 10 mmol) in anhydrous THF (20 ml) was added *n*-butyllithium in hexane (4 ml 2.5 N sol., 10 mmol) at -78°C. The solution was stirred for 10 min followed by addition of ester (10 mmol) in THF (5 ml) at a rate such that the temperature did not exceed -60°C. The solution was stirred for 1 h followed by addition of the *N*-trimethylsilylimine (1eq), prepared as previously reported, *via* cannula over a 5 min period. The mixture was stirred at -78°C for 15 min., the cold bath was

removed, and the mixture was allowed to warm to room temperature followed by stirring overnight. The solution was diluted with 100 ml of ethyl acetate and washed sequentially with 50 mL of a saturated solution of NH_4Cl and 50 ml of water. The combined aqueous washes were extracted with 100 ml portions of ethyl acetate. The organic layers were dried and concentrated in vacuo. Diastereomeric ratio were determined on the crude reaction mixture by a combined HPLC, ^1H and ^{13}C NMR spectra. The residue was purified (hexane/ethyl acetate) to give the β-lactams reported in Table 1 in yields and ratio therein indicated.

Method B : Same protocol of *Method A* but NaHMDSA was used for the preparation of ester enolates.

(3*R*, 4*S*)-3-Ethyl-4-[(*S*)-1-(triisopropylsilyloxy)-ethyl]-2-azetidinone. 5a
I.r. ($CHCl_3$) 1775 cm^{-1}. ^1H NMR 1.05 (m, 21H), 1.20 (d, 3H, J=6.2), 1.75 (m, 2H), 2.70 (m, 1H), 3.20 (dd, 1H, J=2.35, 7.52), 3.90 (dq, 1H, J=6.22, 7.52), 6.00 (s, 1H); ^{13}C NMR 170.91, 71.22, 60.25, 54.40, 21.37, 20.03, 18.04, 12.51, 11.49. Anal. Calcd for $C_{16}H_{33}NO_2Si$: C, 64.16; H, 11.10; N, 4.68. Found: C, 64.35 ; H, 11.15; N, 4.70.

(3*S*, 4*R*)-3-Ethyl-4-[(*S*)-1-(triisopropylsilyloxy)-ethyl]-2-azetidinone. 6a
I.r. ($CHCl_3$) 1775 cm^{-1}. ^1H NMR 1.05 (m, 21H), 1.20 (d, 3H, J=6.2), 1.75 (m, 2H), 3.00 (m, 1H), 3.25 (dd, 1H, J=2.23, 3.84), 4.05 (dq, 1H, J=3.84, 6.22), 6.00 (s, 1H); ^{13}C NMR 171.83, 68.61, 59.78, 53.60, 21.56, 20.14, 18.06, 12.51, 11.58. Anal. Calcd for $C_{16}H_{33}NO_2Si$: C, 64.16; H, 11.10, N, 4.68. Found: C, 63.98; H, 11.20; N, 4.60.

(3*R*, 4*S*)-3-Ethyl-4-[(*S*)-1-(*tert*-butyldiphenylsilyloxy)-ethyl]-2-azetidinone. 5b
IR ($CHCl_3$) 1765 cm^{-1}; ^1H NMR 1.00 (t, 3H, J=7.3), 1.10 (m, 12H), 1.70 (m, 2H), 2.65 (m, 1H), 3.30 (dd, 1H, J=2.26, 7.33), 3.80 (dq, 1H, J=6.25, 7.33), 6.10 (s, 1H), 7.3-7.7 (m, 10H); ^{13}C NMR 170.62, 135.89, 135.79, 135.62, 133.75, 133.60, 129.98, 129.91, 127.92, 127.74, 72.09, 60.00, 54.35, 27.00, 21.36, 19.84, 19.26, 11.53. *m/z* 323 (M^+-57); 280; 253. Anal. Calcd for $C_{23}H_{31}NO_2Si$: C, 72.40; H, 8.19; N, 3.67. Found: C, 72.60 ; H, 8.21 ; N, 3.58 .

(3*S*, 4*R*-)-3-Ethyl-4-[(*S*)-1-(*tert*-butyldiphenylsilyloxy)-ethyl]-2-azetidinone. 6b
IR ($CHCl_3$) 1765 cm^{-1}; ^1H NMR 1.00 (t, 3H, J=7.3), 1.10 (m, 12H), 1.70 (m, 2H), 2.95 (m, 1H), 3.15 (dd, 1H, J= 2.10, 3.92), 3.95 (dq, 1H, J=3.90, 6.24), 6.15 (s, 1H), 7.3-7.7 (m, 10H); ^{13}C NMR 171.22, 135.93, 135.89, 134.10, 133.43, 129.95, 129.86, 127.92, 127.80, 127.72, 68.81, 59.34, 53.50, 27.00, 21.53, 19.77, 19.22, 11.56. *m/z* 323 (M^+-57); 280; 253. Anal. Calcd for $C_{23}H_{31}NO_2Si$: C, 72.40; H, 8.19; N, 3.67. Found: C, 72.55 ; H, 8.20; N, 3.55 .

(3*R*, 4*S*)-3-Ethyl-4-[(*S*)-1-(triethyllsilyloxy)-ethyl]-2-azetidinone. 5d
IR ($CHCl_3$) 1765 cm^{-1}; ^1H NMR 0.58 (q, 6H); 0.92 (t, 9H); 0.95 (t, 3H); 1.13 (d, 3H, J=6.25); 1.72 (m, 2H); 2.68 (m, 1H); 3.15 (dd, 1H, J=2.23, 7.81); 3.73 (quintet, 1H, J=6.35); 6.0 (bs, 1H). ^{13}C NMR 170.58, 71.20, 59.93, 54.60; 21.32; 20.04; 11.47; 6.76, 4.90. Anal. Calcd for $C_{13}H_{27}NO_2Si$: C, 60.65; H, 10.57; N, 5.44. Found: C, 60.80 ; H, 10.60; N, 5.43 .

(3*S*, 4*R*)-3-Ethyl-4-[(*S*)-1-(triethyllsilyloxy)-ethyl]-2-azetidinone. 6d
IR ($CHCl_3$) 1770 cm^{-1}; ^1H NMR 0.60 (q, 6H); 0.95 (t, 9H); 1.02 (t, 3H); 1.14 (d, 3H, J=6.2); 1.70 (m, 2H); 2.94 (m, 1H); 3.19 (dd, 1H, J=2.10, 4.65); 3.87 (quintet, 1H, J=6.52); 5.90 (bs, 1H). ^{13}C NMR 171.44, 68.60, 59.61, 54.18; 21.59; 20.23; 11.65, 6.77, 4.86. Anal. Calcd for $C_{13}H_{27}NO_2Si$: C, 60.65; H, 10.57; N, 5.44. Found: C, 60.85 ; H, 10.55; N, 5.45.

(3*S*, 4*R*)-3-Ethyl-4-[(*S*)-1-(*tert*-butoxy)-ethyl]-2-azetidinone. 5e
IR ($CHCl_3$) 1755 cm^{-1}; ^1H NMR 1.05 (t, 3H, J=7.4), 1.15 (d, 3H, J=6.2), 1.20 (s, 9H), 1.75 (m, 2H), 2.70 (m, 1H), 3.20 (dd, 1H, J= 2.25, 8.04), 3.60 (dq, 1H, J=6.20, 8.04), 6.55 (s, 1H); *m/z* 199 (M^+); 183; 170; 153. ^{13}C NMR 170.73, 73.72, 70.13, 58.65, 54.71, 28.59, 21.32, 19.27, 11.33. Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62, N, 7.03. Found: C, 66.39 ; H, 10.67; N, 7.00.

(3*R*, 4*S*)-3-Ethyl-4-[(*S*)-1-(benzyloxy)-ethyl]-2-azetidinone. 5f
IR ($CHCl_3$) 1780 cm^{-1};^1H NMR 1.00 (t, 3H), 1.15 (d, 3H, J=7.3), 1.70 (m, 2H), 2.70 (m, 1H), 3.20 (dd, 1H, J=2.28, 8.04), 3.45 (dq, 1H, J=6.10, 8.04), 4.50 (m, 2H), 6.60 (s, 1H), 7.30 (m, 5H). ^{13}C NMR 170.72, 138.27, 128.43, 127.70, 77.47, 70.86, 58.32, 55.05, 21.39, 15.75, 11.49. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21, N, 6.00. Found: C, 72.25; H, 8.25; N, 5.80.

(3*R*, 4*S*)-3-Ethyl-4-[(*S*)-1-(*tert*-Butyldimethylsilyloxy)-propyl]-2-azetidinone. 5g

IR ($CHCl_3$) 1780, 1765 cm^{-1}; ^1H NMR 0.05 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 0.93 (t, 3H, J=7.3), 1.02 (t, 3H, J=7.4), 1.50 (m, 2H), 1.75 (m, 2H), 2.75 (m, 1H), 3.30 (dd, 1H, J=2.33, 7.52), 3.55 (m, 1H, $J_{4,5}$=7.52), 5.80 (s, 1H); ^{13}C NMR 170.55, 75.83, 57.84, 54.62, 26.80, 25.80, 21.32, 18.07, 11.28, 9.07, -4.25, -4.32. *m/z* 199 (M^+-72); 144. Anal. Calcd for $C_{14}H_{29}NO_2Si$: C, 61.94; H, 10.77, N, 5.16. Found: C, 61.74; H, 10.73; N, 5.18.

(3*S*, 4*R*)-3-Ethyl-4-[(*S*)-1-(*tert*-Butyldimethylsilyloxy)-propyl]-2-azetidinone. 6g
IR ($CHCl_3$) 1785, 1760 cm^{-1}; ^1H NMR 0.05 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 0.92 (t, 3H, J=7.3), 1.00 (t, 3H, J=7.4), 1.48 (m, 2H), 1.73 (m, 2H), 3.00 (m, 1H), 3.30 (dd, 1H, J=2.1, 3.9), 3.70 (m, 1H, $J_{4,5}$=3.92), 6.00 (s, 1H); ^{13}C NMR 171.52, 73.19, 57.51, 53.64, 27.37, 25.81, 21.55, 18.05, 11.51, 9.43, -4.43, -4.47. Anal. Calcd for $C_{14}H_{29}NO_2Si$: C, 61.94; H, 10.77, N, 5.16. Found: C, 61.84; H, 10.63; N, 5.20.

(3*R*, 4*S*)-3-*tert*-Butyl-4-[(*S*)-1-(*tert*-butyldimethylsilyloxy)-ethyl]-2-azetidinone. 5i
IR ($CHCl_3$) 1760 cm^{-1}; ^1H NMR -0.06 (s, 6H), 0.88 (s, 9H), 0.92 (s, 9H), 1.07 (d, 3H, J=6.0), 2.50 (t, 1H, J=1.7), 3.14 (dd, 1H, J=2.10, 6.20), 3.65 (quintet, 1H, J=6.31), 6.35 (s, 1H); ^{13}C NMR 169.71, 70.92, 63.41, 56.51, 30.34, 27.38, 25.62, 20.17, 17.77, -4.48, -4.89. Anal. Calcd for $C_{15}H_{31}NO_2Si$: C, 63.10; H, 10.94, N, 4.91. Found: C, 63.24; H, 10.98; N, 4.88.

General procedure for the preparation of azetidinones. (12a-12e)
To a 1 M solution of LiHMDSA (*syn-adduct procedure*, *Method A*) or NaHMDS (*anti-adduct procedure*, *Method B*) in THF (33.7 ml) were added, a -78°C, 8.3 g (33.7 mmol) of STABASE 2 in 10 ml of THF. The mixture was stirred for 2 h followed by addition of *N*-(trimethylsilyl)imine **2** (1 eq) *via* cannula over a 10 min period. The mixture was allowed to warm, spontaneously, to room temperature and stirred overnight. To this brown solution, at 0°C, 50 ml of NH_4Cl_{aq} were added and the pH was adjusted to 4 by addition of 1 N solution of HCl, followed by addition of 5.0 g of $NaHCO_3$ (pH 8). Benzylchloroformate (6.8 g, 40 mmol), dissolved in 20 ml of acetone, was added dropwise. After stirring at room temperature (3 hrs), the reaction mixture was extracted with ethyl acetate (500 ml) and the organic layers were washed with brine, dried and concentrated in vacuo. The residue was purified by flash chromatography (hexane-ethyl acetate 1:1)

(*3R,4S*)-3-(Benzyloxycarbonylamino)-4-[(*S*)-1-(*tert*-butyldiphenylsilyloxy)-ethyl]-2-azetidinone 12b
IR ($CHCl_3$) 1764, 1720 cm^{-1}; ^1H NMR 1.05 (s, 9H), 1.15 (d, 3H, J=6.3), 3.60 (dd, 1H, J=2.04, 6.92), 3.85 (quintet, 1H, J=6.90), 4.35 (dd, 1H, J=2.02, 8.30), 5.10 (s, 2H), 5.65 (d, 1H, J=8.3), 6.05 (s, 1H), 7.3-7.8 (m, 15H); ^{13}C NMR 167.12, 155.40, 135.67, 135.48, 133.46, 133.41, 129.85, 129.75, 128.33, 128.14, 128.01, 127.94, 127.78, 127.57, 70.88, 66.99, 63.14, 60.33, 26.79, 19.59, 19.06. Anal. Calcd for $C_{29}H_{34}N_2O_4Si$: C, 69.29; H, 6.82, N, 5.57. Found: C, 69.60; H, 6.85; N, 5.52.

(*3S,4R*)-3-(Benzyloxycarbonylamino)-4-[(*S*)-1-(*tert*-butyldiphenylsilyloxy)-ethyl]-2-azetidinone 13b
IR ($CHCl_3$) 1765, 1720 cm^{-1}; ^1H NMR 1.05 (s, 9H), 1.15 (d, 3H, J=6.3), 3.50 (m, 1H), 3.95 (m,1H), 4.75 (dd, 1H, J=1.00, 8.63), 5.10 (s, 2H), 5.60 (d, 1H, J=8.6), 5.70 (s, 1H), 7.2-7.8 (m, 15H); ^{13}C NMR 167.10, 155.39, 135.89, 133.84, 133.38, 129.98, 129.82, 128.51, 128.18, 128.08, 127.83, 127.74, 127.62, 67.22, 62.16, 59.05, 26.97, 19.74, 19.19. Anal. Calcd for $C_{29}H_{34}N_2O_4Si$: C, 69.29; H, 6.82, N, 5.57. Found: C, 69.60; H, 6.85; N, 5.55.

(*3R,4S*)-3-(Benzyloxycarbonylamino)-4-[(*S*)-1-(triethylsilyloxy)-ethyl]-2-azetidinone 12d
IR ($CHCl_3$) 1760, 1720 cm^{-1}; ^1H NMR 0.65 (q, 6H), 1.00 (t, 9H), 1.25 (d, 3H, J=6.1), 3.45 (dd, 1H, J=2.02, 7.45), 3.85 (quintet, 1H, J=6.93), 4.55 (dd, 1H, J=2.02, 9.01), 5.10 (s, 2H), 6.20 (d, 1H, J=9.0), 7.00 (s, 1H), 7.35 (s, 5H); ^{13}C NMR 167.48, 155.62, 128.47, 128.27, 128.14, 128.03, 69.79, 67.13, 63.61, 60.60, 20.10, 6.72, 4.97. Anal. Calcd for $C_{19}H_{30}N_2O_4Si$: C, 60.29, H, 7.99 N, 7.40. Found: C, 60.35; H, 8.03, N, 7.35.

(*3S,4R*)-3-(Benzyloxycarbonylamino)-4-[(*S*)-1-(triethylsilyloxy)-ethyl]-2-azetidinone 13d
IR ($CHCl_3$) 1765, 1725 cm^{-1}; ^1H NMR 0.60 (q, 6H), 0.90 (t, 9H), 1.20 (d, 3H, J=6.10), 3.55 (m, 1H), 3.93 (m, 1H), 4.70 (dd, 1H, J=2.03, 8.64), 5.10 (s, 2H), 6.05 (d, 1H, J=8.60), 6.70 (s, 1H), 7.35 (s, 5H). Anal. Calcd for $C_{19}H_{30}N_2O_4Si$: C, 60.29, H, 7.99 N, 7.40. Found: C, 60.32; H, 7.96, N, 7.43.

(*3R,4S*)-3-(Benzyloxycarbonylamino)-4-[(*S*)-1-*tert*-butoxy-ethyl]-2-azetidinone 12e
^1H NMR 1.14 (s, 9H), 1.19 (d, 3H, J=5.90), 3.55 (m, 2H), 4.63 (dd, 1H, J=1.83, 9.45), 5.05 (AB, 2H), 6.70 (d, 1H, J=9.45), 7.30 (s, 5H), 8.00 (s, 1H). ^{13}C NMR 169.41, 155.76, 136.24, 128.34, 127.88, 127.71, 73.96, 69.40, 66.73, 63.15, 60.58, 28.58, 19.37. Anal. Calcd for $C_{17}H_{24}N_2O_4$: C, 63.73, H, 7.55, N, 8.74. Found: C, 63.92; H, 7.58, N, 8.72.

(±)-(*3R, 4R,*)-4-[(R)-2-(*tet*-Butyldimethylsilyloxy)propyl]-3-Ethyl-Azetidin-2-one 16a

IR ($CHCl_3$) 1765 cm^{-1}; ^1H NMR 0.04 (s, 3 H), 0.06 (s, 3 H), 0.90 (s, 9 H), 1.05 (t, 3 H, J=5.60), 1.18 (d, 3 H, J=6.22), 1.65 (m, 4 H), 3.12 (m, 1 H), 3.68 (m, 1 H), 3.90 (m, 1 H), 6.10 (bs, 1H). ^{13}C NMR 171.51, 68.61, 54.97, 50.43, 40.40, 25.89, 24.48, 18.32, 17.96, 12.59, -4.38, -4.52. MS *m/z* 271 (M^+). Anal. Calcd for $C_{14}H_{29}NO_2Si$: C, 61.90, H, 10.77, N, 5.16 . Found: C, 61.81; H, 10.70, N, 5.10.

(±)-(*3R, 4S,*)-4-[(*R*)-2-(*tet*-Butyldimethylsilyloxy)propyl]-3-Ethyl-Azetidin-2-one 17a
IR ($CHCl_3$) 1775 cm^{-1}; ^1H NMR 0.04 (s, 3 H), 0.06 (s, 3 H), 0.90 (s, 9 H), 1.05 (t, 3 H, J=5.64), 1.18 (d, 3 H, J=6.22), 1.65 (m, 4 H), 3.12 (m, 1 H), 3.93 (m, 2 H), 5.90 (bs, 1H). ^{13}C NMR 171.88, 66.48, 54.77, 48.42, 39.69, 25.87, 23.86, 18.34, 18.02, 12.60, -4.32, -4.80. Anal. Calcd for $C_{14}H_{29}NO_2Si$: C, 61.94, H, 10.77, N, 5.16. Found: C, 61.88.92; H, 10.73, N, 5.18.

(±)-(*3S, 4R*)4-[(*R*)-2-(*tet*-Butyldimethylsilyloxy)propyl]-3-Ethyl-Azetidin-2-one 18a
IR ($CHCl_3$) 1765 cm^{-1}; ^1H NMR 0.02 (s, 3 H), 0.01 (s, 3 H), 0.85 (s, 9 H), 0.98 (t, 3 H, J=5.72), 1.12 (d, 3 H, J=6.35), 1.68 (m, 4 H), 2.65 (m, 1 H), 3.43 (ddd, 1 H, J=2.32, 4.05, 9.22
), 3.86 (m, 1 H), 6.25 (bs, 1H).

(±)-(*3S, 4S*4-[(*R*)2-(*tet*-Butyldimethylsilyloxy)propyl]-3-Ethyl-Azetidin-2-one 19a
IR ($CHCl_3$) 1765 cm^{-1}; ^1H NMR 0.02 (s, 3 H), 0.01 (s, 3 H), 0.85 (s, 9 H), 0.98 (t, 3 H, J=5.70), 1.13 (d, 3 H, J=6.32), 1.68 (m, 4 H), 2.65 (m, 1 H), 3.33 (ddd, 1 H, J=2.10, 5.82, 6.63), 3.86 (m, 1 H), 6.2 (bs, 1H).

General procedure for the preparations of acetonides (20, 21, 22 and 23)
A solution of azetidinone **16a** (*e.g.*) (1.6 g, 5.9 mmol) in 3 ml of acetonitrile containing 5% of 40% aqueous HF, was stirred at room temperature for 30 min. The mixture was evaporated and flash chromatographed on SiO_2 (eluting with ethyl acetate) to give the alcohol **16a** in quantitative yield. A solution of **16a** (10 mmol) in anhydrous CH_2Cl_2 (15 ml), 2,2-dimethoxypropane (10 mmol) and a catalytic amount of $(Et)_2O$ BF_3 (0.1 ml) was stirred at room temperature for 3 h. The mixture was diluted with ethyl acetate (50 ml), washed with brine, dried (Na_2SO_4), evaporated and the residue was purified on SiO_2 (eluting hexane/ethyl acetate 70/30) to give **20a**.

(±)-(*4R, 6R, 7R*)-7-Ethyl-2,2,4-trimethyl-3-Oxa-Bicyclo [4.2.0.] Octan-8-One 20a
IR ($CHCl_3$) 1745 cm^{-1}. ^1H NMR ($CDCl_3$) 1.04 (t, 3H, J=7.00), 1.21 (d, 3H, J=6.52), 1.39 (s, 3 H), 1.50-1.60 (m, 1 H); 1.68 (s, 3 H), 1.64-1.72 (m, 1 H), 1.73-1.90 (m, 1 H), 1.87 (dt, 1 H, J=3.83, 13.8), 3.04 (ddd, 1 H, J=5.23, 7.61, 9.04), 3.74-3.80 (m, 2 H).

(±)-(*4R, 6S, 7R*)- 7-Ethyl-2,2,4-trimethyl-3-Oxa-Bicyclo [4.2.0.] Octan-8-One 21a
IR ($CHCl_3$) 1743 cm^{-1}.^1H NMR ($CDCl_3$) 0.99 (t, 3 H, J=7.00), 1.22 (d, 3 H, J=6.52), 1.39 (s, 3 H), 1.36 (m, 1H), 1.70-1.82 (m, 1 H), 1.75 (s, 3 H), 3.10 (ddd, 1H, J= 5.37, 6.84, 9.77), 3.69 (dt, 1 H, J=4.82, 12.25), 3.91 (m, 1 H). ^{13}C NMR (C_6D_6) 169.27, 85.64, 64.47, 53.39, 45.52, 32.08, 28.52, 24.13, 21.43, 19.14, 12.62; MS *m/z* 182 (M^+-15).

(±)-(*4R, 6R, 7S*)-7-Ethyl-2,2,4-trimethyl-3-Oxa-Bicyclo [4.2.0.] Octan-8-One 22a
^1H NMR ($CDCl_3$) 3.36 (ddd, 1 H, J=1.43, 4.45, 10.98), 3.88 (m, 1 H)

(±)-(*4R, 6S, 7S*)-7-Ethyl-2,2,4-trimethyl-3-Oxa-Bicyclo [4.2.0.] Octan-8-One 23a
^1H NMR ($CDCl_3$) 3.25 (ddd, 1 H, J=1.43, 4.45, 10.98), 3.78 (dt, 1 H, J=1.45, 12.40)

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