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Isoxazolidin-5-one - Isoxazolidine Rearrangement, an Entry to 3-Amino-3-deoxy Sugars

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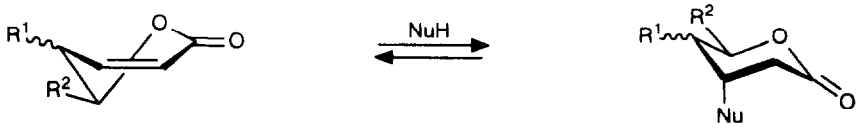
Abstract. Conjugate addition - rearrangement of N-benzylhydroxylamine to α,β-unsaturated lactones **1** provides a short and effective route to 3-substituted isoxazolidin-5-ones. High and defined stereochemistry of this reaction with simultaneous liberation of the 5-OH group of the sugar chain, while all other groups remain protected, creates a possibility to switch from sugars of the D-configurational series to those of the L-series, thus providing a very attractive entry to important 3-amino-2,3-dideoxy sugars. Mesylation of the 2'-OH group of the isoxazolidin-5-one skeleton or introduction of an epoxide ring to C-2',3' carbon atoms and subsequent treatment of the molecule with a nucleophile causes isoxazolidin-5-one - isoxazolidine rearrangement with inversion of the configuration at the C-2 carbon atom.

Conformationally stable α,β-unsaturated sugar δ-lactones **1** undergo, exclusively, conjugated addition of nucleophiles *anti* to the terminal substituent (Scheme 1). This axial approach of nucleophiles is well documented in the literature and has been proved for azide anion,[1,2] aziridine,[3] methoxyl anion,[3] alkyl cuprates,[4] *O*-benzylhydroxylamine,[5] *N*-benzylhydroxylamine[6] and hydrazine[7]. The observed high stereoselectivity of the nucleophilic 1,4-addition to compounds **1** is controlled by the stereoelectronic effect and does not depend on substitution (hydrogen or oxygen atom) and configuration at the C-4 carbon atom. The explanation of the axial approach phenomenon, based on a number of examples that followed the rule, has been provided by Deslongchamps.[8] In the case of azide anion or *O*-benzylhydroxylamine the Michael addition to compounds **1** is reversible.[5] Adducts **2** are unstable, upon attempted purification they easily undergo *retro* addition.

Scheme 1

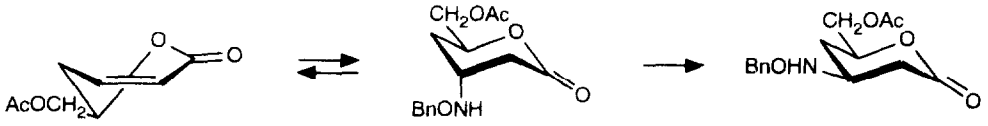


1 **2**

The low energy of activation of the conjugate addition to **1**, which is manifested by the easy *retro* reaction should allow one to perform addition under thermodynamic control. Heating of the lactone **3**, at 50°C

in methanol-d_4 with an excess of *O*-benzylhydroxylamine in an NMR test tube for one week, showed that the initially formed *trans* adduct **4** underwent epimerization slowly to afford the more stable *cis* adduct **5**.

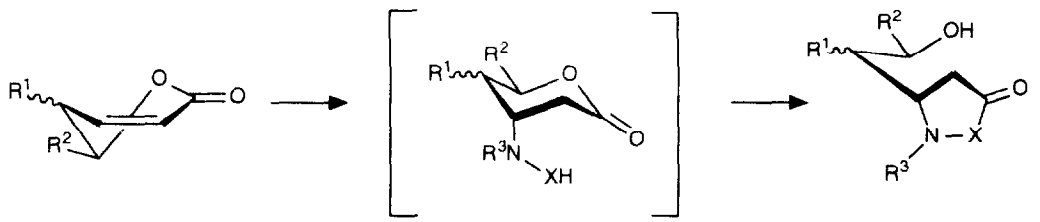
Scheme 2



3 **4** **5**

Addition of *N*-substituted hydroxylamines[6] or hydrazine[7] to lactones **1** is not a reversible process. Kinetic control of the Michael reaction leads to formation of the *anti* adduct which immediately rearranges to the isoxazolidin-5-one or pyrazolidin-3-one skeleton, respectively. Owing to the axial location of the hydroxylamine or hydrazine group in the Michael adduct **6**, opening of the six membered lactone ring is a faster process than the conjugate addition in the first step of the reaction (Scheme 3). Similar addition - rearrangement has been found for reaction of hydrazines with butenolides.[9]

Scheme 3

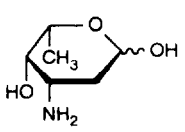


1 X= O, NH **6** **7**

Contrary to this well recognized stereochemical course of the Michael addition, which is under kinetic control providing *anti* adduct only, conjugate addition-rearrangement of *N*-benzylhydrazine to lactone **1** is under control of both kinetic and thermodynamic factors.[10] This has been manifested by the formation of stereo - and regioisomers in the case of addition to lactone **1** of the D-*erythro* and D-*threo* configuration (R^1= OAc, R^2= CH_2OAc).[2]

High and defined stereochemistry of the conjugate addition-rearrangement of *N*-benzyl- hydroxylamine to the lactone **1** with simultaneous liberation of the 5-OH group of the sugar chain while all other groups remain protected creates a unique possibility to switch from sugars of the D-series to those of L-series, thus providing a very attractive entry to important 3-amino-2,3-dideoxy sugars having *cis* located 3-amino function and the C-6 carbon atom, such as components of anthracycline antibiotics: daunosamine **8**, [11] acosamine (**9**),[12] or negamycin

lactone (**10**),[13] the latter being the main fragment of the antibiotics negamycin **11**.[14]



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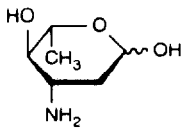

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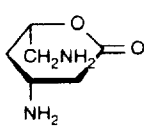

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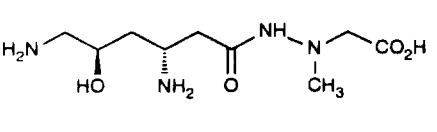

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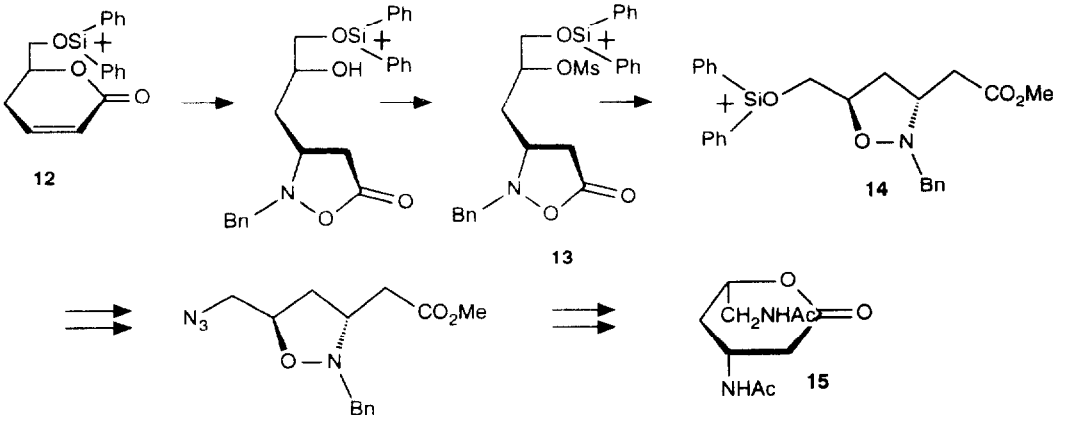
Very recently, we have reported the synthesis of *N,N*-diacetyl-negamycin lactone **15**, which has illustrated the above presented idea (Scheme 4).[15] The sequence of transformations involving the conjugate addition-rearrangement followed by isoxazolidin-5-one - isoxazolidine rearrangement has offered simplicity and full stereocontrol of the synthesis.[15] The concept exemplified in the course of negamycin lactone synthesis has prompted us to investigate more carefully the transformations shown in Scheme 4. For this work we selected lactones **3**, **16-18**.

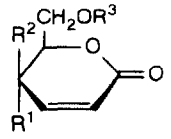
Scheme 4

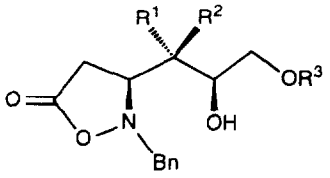


Addition of *N*-benzylhydroxylamine to lactones **3**, **16-18** according to the known procedure[6] afforded respective isoxazolidin-5-ones **19-27** which become substrates for our investigations.

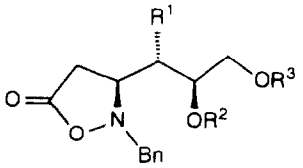
Inversion of configuration at the C-2'carbon atom in **20** (C-5 of the sugar chain) could be achieved according to the Mitsunobu procedure[16] using *p*-nitrobenzoic acid, diethyl azodicarboxylate and triphenylphosphine to afford compound **23** of the lyxo-configuration. Saponification of the p-nitrobenzoyl group in **23** with methanolic potassium carbonate afforded **24**. Compounds **20** and **24** were acetylated to give respective acetates **25** and **26** whose spectral and analytical data were compared. Inversion of configuration at C-2' in **19** and **20** can also be accomplished by a three-step transformation involving mesylation of the free

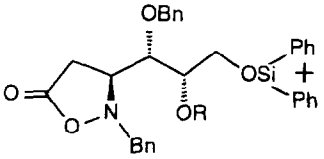
hydroxyl group, deacetylation or desilylation of the terminal substituent and subsequent formation of epoxides of L-*threo* **32** and L-*lyxo* **33** configuration respectively.





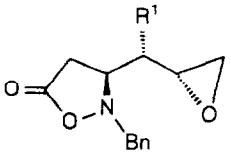
R^1= R^2= H, R^3= Ac	**3**	**19**
R^1= OBn, R^2= H, R^3= $SiPh_2t$-Bu	**16**	**20**
R^1= OBn, R^2= H, R^3= Bn	**17**	**21**
R^1= H, R^2= OBn, R^3= Bn	**18**	**22**



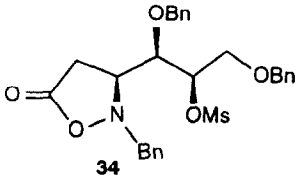


25: R^1= OBn, R^2= Ac, R^3= $SiPh_2t$-Bu
27: R^1= H, R^2= Ms, R^3= Ac
28: R^1= R^3=H, R^2= Ms
29: R^1= OBn, R^2= Ms, R^3= $SiPh_2t$-Bu
30: R^1= OBn, R^2= Ms, R^3= H
31: R^1= OBn, R^2= Ms, R^3= Bn

23: R= PNB
24: R= H
26: R= Ac



32: R^1= H
33: R^1= OBn



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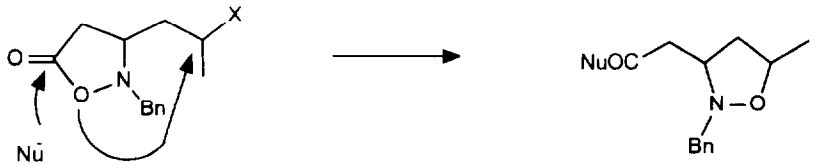
Direct formation of the epoxide **32** by treatment of **27** with sodium methoxide in CH_2Cl_2 afforded the desired product in 22% yield only. Compound **32** was accompanied by isoxazolidine **42**. Formation of the epoxide **33** by treatment of **29** with fluoride anion failed due to the sensitivity of the isoxazolidin-5-one ring to attack of nucleophiles. We succeeded to obtain **33** *via* desilylation of **29** with a HF/Py complex followed by treatment of **30** with Triton-B.

The isoxazolidin-5-one fragment is an "active ester" type grouping which easily undergoes opening upon treatment with various nucleophiles. In the case of weak nucleophiles such as alcohols, owing to the entropy factor, the five membered ring formation is favored and we did not observe opening of the isoxazolidin-5-one

ring. If, however, a stronger nucleophile is used or the alcohol is activated with a base, and a leaving group is present at C-2, for example an *O*-mesyl substituent or an epoxide ring, then the nucleophile attacks the isoxazolidin-5-one carbonyl group causing consequentially a nucleophilic substitution at the C-2' carbon atom and formation of a more stable isoxazolidine ring (Scheme 5). Reaction proceeds with inversion of configuration at the C-2' carbon atom. This tandem reaction has been applied for negamycin lactone **15** synthesis;[15] D-*erythro* compound **13** upon treatment with methanol in the presence of a base such as anhydrous potassium carbonate, sodium hydrogen carbonate, or DABCO, has afforded isoxazolidine **14** with L-*threo* configuration. Similarly D-*ribo* isoxazolidin-5-ones **29** and **31** under the same conditions give L-*lyxo* isoxazolidines **35** and **36**, respectively. On the other hand D-*xylo* compound **34** provides L-*arabino* isoxazolidine **37**.

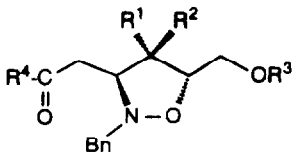
Scheme 5



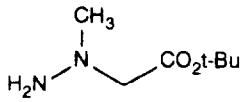
The isoxazolidin-5-one ring can also be opened upon treatment with benzylamine to afford the respective amides. Consequently **13** gives **38**, **31** gives **39** and **34** gives **40**. The isoxazolidin-5-one - isoxazolidine rearrangement using compound **13** and *t*-butyl *N*-methylhydrazinoacetate **47** should lead directly to the negamycin precursor **48**. Numerous experiments failed, however, due to selfcondensation of the free base **46** and decomposition of the starting isoxazolidin-5-one **13**. If the reaction was carried out under 10 kbar pressure at 50°C the expected compound **47** was obtained in a low yield (10 %). Compound **49**, which is a derivative of isoxazolidine **48**, has been transformed into natural negamycin **11**[17].

In the case of epoxides **32** and **33** the isoxazolidin-5-one - isoxazolidine rearrangement returns to the initial D-*erythro* configuration (**44**) and D-*ribo* (**46**) respectively as the result of double inversion of C-2' carbon atom. Compound **30** treated with methanol - K_2CO_3, owing to competitive reactions: direct substitution at the C-2' carbon atom and the epoxide **33** formation affords a mixture of L-*lyxo* **41** and D-*ribo* **46** compounds. The stereochemical course of the isoxazolidin-5-one - isoxazolidine rearrangement was proved by NOE experiments of diastereomeric acetates **43** and **45**. Additional proof came from the NMR spectrum of negamycin lactone[15], which unequivocally testifies to *cis* configuration of acetamide and the terminal acetoxymethyl group.

In conclusion, we demonstrated a useful process leading to 3-amino sugars, in which configuration at the C-5 carbon atom of the sugar chain determines configuration of a newly formed chirality center at the C-3 carbon atom in such a way that subsequent inversion of configuration at C-5 is straightforward.



35: R^1= OBn, R^2= H, R_3= Sit-BuPh$_2$, R^4= OMe
36: R^1= OBn, R^2= H, R^3= Bn, R^4= OMe
37: R^1= H, R^2= OBn, R^3= Bn, R^4= OMe
38: R^1= R^2= H, R^3= Sit-BuPh$_2$, R^4= NHCH$_2$Ph
39: R^1= OBn, R^2= H, R^3= Bn, R^4= NHCH$_2$Ph
40: R^1= H, R^2= OBn, R^3= Bn, R^4= NHCH$_2$Ph
41: R^1= OBn, R^2= R^3= H, R^4= OMe
42: R^1= R^2= R^3= H, R^4= OMe
43: R^1= R^2= H, R^3= Ac, R^4= OMe



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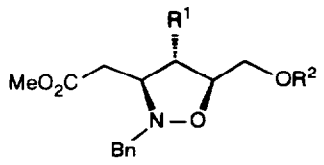
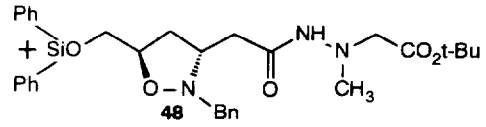
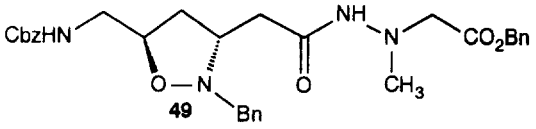


44: R^1= R^2= H
45: R^1= H, R^2= Ac
46: R^1= OBn, R^2= H



48



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Experimental

^{1}H NMR spectra were recorded with Bruker AM 500 and Varian Gemini 200 spectrometers. IR spectra were obtained on a FT-IR-1600 Perkin-Elmer spectrophotometer. Optical rotations were measured with a JACSO Dip-360 digital polarimeter. Melting points are uncorrected. Column chromatography was performed on Merck silica gel 230-400 mesh.

Lactone **3** was obtained according to the known procedure.[18,19] Lactone **12** was obtained from **3** by hydrolysis[19] followed by standard silylation with *t*-butyldiphenylsilyl chloride.[15] Lactones **16** and **17** were obtained from ethyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside by standard sequences which consisted in silylation-benzylation or double benzylation, followed by anomeric oxidation,[18] and will be published elsewhere. Compound **18** was obtained from ethyl 2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside according to the procedure used for **17**.

Addition of *O*-benzylhydroxylamine to lactone 3. The experiment performed in an NMR test-tube. A solution of the lactone **3** (0.017 g, 0.1 mmol) in methanol-d$_4$ (~0.2 ml) was placed in an NMR test-tube and *O*-benzylhydroxylamine (0.013 g, 0.1 mmol) in methanol-d$_4$ (~0.3 ml) was added. The spectrum recorded after 24 h showed the presence of the erythro lactone **4** as the only product, ^{1}H NMR: 1.81 (ddd, 1H, *J* 4.7, 11.5,

14.5 Hz, H-4), 1.94 (ddt, 1H, *J* 1.4, 3.3, 3.7, 14.5 Hz, H-4'), 2.06 (s, 3H, Ac), 2.51 (ddd, 1H, *J* 1.4, 4.5, 17.4 Hz, H-2), 2.68 (dd, 1H, *J* 5.8, 17.4 Hz, H-2'), 3.53 (quintet, 1H, ΣJ 18.7 Hz, H-3), 4.08 (dd, 1H, *J* 5.8, 12.1 Hz, H-6), 4.14 (dd, 1H, *J* 3.3, 12.1 Hz, H-6'), 4.64 (m, 1H, H-5), 4.65, 4.69 (2d, 2H, *J* 11.7 Hz, OBn). Subsequently the mixture was kept for 10 days at 50°C. The spectrum recorded after that time showed the presence of the threo lactone **5** contaminated with decomposition products, ^{1}H NMR: 1.5-1.7 (m, 2H, H-4, 4'), 2.05 (s, 3H, Ac), 2.51 (dd, 1H, *J* 5.6, 15.6 Hz, H-2), 2.63 (dd, 1H, *J* 6.9, 15.6 Hz, H-2'), 3.52 (m, 1H, ΣJ 25.8 Hz, H-3), 3.86-4.02 (m, 3H, H-5,6,6'), 4.66, 4.69 (2d, 2H, *J* 11.4 Hz, OBn).

Addition of *N*-benzylhydroxylamine to lactones **3**, **12**, **16-18** was performed according to the procedure described earlier.[6]

(3S, 1'S, 2'R) 2-Benzyl-3-(1'-benzyloxy-2'-hydroxy-3'-*t*-butyldiphenylsiloxy)propyl-isoxazolidin-5-one (20) obtained from **16**; $[\alpha]_D$ -48.8° (c 1.2, CH_2Cl_2); IR (film): 3504, 1783 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.06 (s, 9H, t-Bu), 2.64 (dd, 1H, *J* 8.6, 17.5 Hz, H-4a), 2.94 (dd, 1H, *J* 7.0, 17.5 Hz, H-4b), 3.44-3.82 (m, 4H, H-1', 2', 3'a, 3'b), 3.94 (ddd, 1H, *J* 1.7, 7.0, 8.6 Hz, H-3), 4.18, 4.22 (2d, 2H, *J* 14.0 Hz, NBn), 4.37, 4.81 (2d, 2H, *J* 10.8 Hz, OBn). Anal. Calcd for $C_{36}H_{41}NO_5Si$: C, 72.57; H, 6.94; N, 2.35. Found: C, 72.34; H, 7.04; N, 2.33. Acetate **(3S, 1'S, 2'R) 2-Benzyl-3-(2'-acetoxy-1'-benzyloxy-3'-*t*-butyldiphenylsiloxy)propyl-isoxazolidin-5-one (25)**; $[\alpha]_D$ -73.9° (*c* 1.4, CH_2Cl_2); IR (film): 1787, 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.05 (s, 9H, t-Bu), 1.93 (s, 3H, Ac), 2.62 (dd, 1H, *J* 8.5, 17.7 Hz, H-4a), 2.98 (dd, 1H, *J* 6.9, 17.7 Hz, H-4b), 3.55 (ddd, 1H, *J* 2.3, 6.9, 8.5 Hz, H-3), 3.70 (dd, 1H, *J* 3.7, 11.3 Hz, H-3'a), 3.85 (dd, 1H, *J* 4.9, 11.3 Hz, H-3'b), 3.91 (dd, 1H, *J* 2.3, 6.8 Hz, H-1'), 4.16 (s, 2H, NBn), 4.64, 4.81 (2d, 2H, *J* 10.8 Hz, OBn), 4.92 (ddd, 1H, *J* 3.7, 4.9, 6.8 Hz, H-2'). Anal. Calcd for $C_{38}H_{43}NO_6Si$: C, 71.55; H, 6.79; N, 2.19. Found: C, 71.3; H, 6.8; N, 2.3.

(3S, 1'S, 2'R) 2-Benzyl-(1',3'-dibenzyloxy-2'-hydroxy)propyl-isoxazolidin-5-one (21) obtained from **17**; $[\alpha]_D$ -22.3° (*c* 1.3, CH_2Cl_2); IR (KBr): 3380, 1779 cm^{-1}; ^{1}H NMR ($CDCl_3$): 2.65 (dd, 1H, *J* 8.6, 17.5 Hz, H-4a), 2.94 (dd, 1H, *J* 6.8, 17.5 Hz, H-4b), 3.43-3.66 (m, 4H, H-1', 2', 3'a, 3'b), 3.94 (ddd, 1H, *J* 1.7, 6.8, 8.6 Hz, H-3), 4.16, 4.22 (2d, 2H, *J* 13.8 Hz, NBn), 4.43, 4.49 (2d, 2H, *J* 11.7 Hz, OBn), 4.46, 4.83 (2d, 2H, *J* 10.9 Hz, OBn). Anal. Calcd for $C_{27}H_{29}NO_5$: C, 72.46; H, 6.53; N, 3.13. Found: C, 72.1; H, 6.3; N, 3.0.

(3S, 1'R, 2'R) 2-Benzyl-3-(1',3'-dibenzyloxy-2'hydroxy)propyl-isoxazolidin-5-one (22) obtained from **18**; $[\alpha]_D$ -65° (*c* 2.3, CH_2Cl_2); IR (film): 3422, 1780 cm^{-1}; ^{1}H NMR ($CDCl_3$): 2.60 (dd, 1H, *J* 6.6, 17.8 Hz, H-4a), 2.65 (dd, 1H, *J* 8.1, 17.8 Hz, H-4b), 3.28 (dd, 1H, *J* 6.4, 9.3 Hz, H-3'a), 3.41 (dd, 1H, *J* 6.1, 9.3 Hz, H-3'b), 3.60

(dd, 1H, *J* 2.3, 6.8 Hz, H-1'), 3.66 (dt, 1H, 6.6, 6.8, 8.1 Hz, H-5), 3.84 (dt, 1H, *J* 2.3, 6.0 Hz, H-2'), 4.12, 4.24 (2d, 2H, *J* 13.8 Hz NBn), 4.45 (s, 2H, OBn), 4.56, 4.68 Hz, OBn). Anal. Calcd for $C_{27}H_{29}NO_5$: C, 72.46; H, 6.53; N, 3.13. Found: C, 72.2; H, 6.2; N, 3.3.

(3S, 1'S, 2'S) 2-Benzyl-3-(1'-benzyloxy-3'-*t*-butyldiphenylsiloxy-2'-p-nitrobenzoyloxy)propyl-isoxazolidin-5-one (23). Alcohol **20** (0.30 g, 0.5 mmol) was dissolved in dry THF (5 ml) and with triphenylphosphine (0.65 g, 2.5 mmol), p-nitrobenzoic acid (0.42 g, 2.5 mmol) and diethyl azodicarboxylate (0.4 g, 0.4 ml, 2.5 mmol). The mixture was stirred overnight at room temperature. Subsequently, the precipitate was filtered off, the filtrate was evaporated, and the product was isolated by chromatography to afford **23** (0.29 g, 77%); $[\alpha]_D$ -35.5° (*c* 1.2, CH_2Cl_2) ; IR (film): 1786, 1728 cm^{-1} ;^1H NMR (C_6D_6): 1.08 (s, 3H, *t*-Bu), 2.22 (dd, 1H, *J* 8.5, 17.6 Hz, H-4a), 2.83 (dd, 1H, *J* 5.4, 17.6 Hz, H-4b), 3.33 (m, 1H, *J* 4.1, 5.4, 8.5 Hz, H-3), 3.65-3.95 (m, 5H, H-1', 3'a, 3'b, NBn), 4.43, 4.65 (2d, 2H, *J* 10.9 Hz, OBn), 5.43 (m, 1H, H-2'); MS (HR, LSIMS) m/z, (M+Na) Calcd for $C_{43}H_{44}N_2O_8SiNa$: 767.27643. Found: 767.27622.

(3S, 1'S, 2'S) 2-Benzyl-3-(2'-acetoxy-1'-benzyloxy-3'-*t*-butyl-diphenylsiloxy)propyl-isoxazolidin-5-one (26). p-Nitrobenzoate **23** (0.06 g, 0.008 mmol) was dissolved in abs. MeOH (3 ml) and treated with anhydrous K_2CO_3. The mixture was stirred at room temperature for 1 h. Subsequently, the solvent was evaporated and the residue was purified by chromatography to afford **24**. Standard acetylation of **24** with acetic anhydride-pyridine mixture gave **26**; $[\alpha]_D$ -59.5° (*c* 1.3, CH_2Cl_2); IR (film): 1785, 1743 cm^{-1}; ^1H NMR ($CDCl_3$): 1.05 (s, 9H, *t*-Bu), 1.91 (s, 3H, Ac), 2.54 (dd, 1H, *J* 8.5, 17.7 Hz, H-4a), 2.98 (dd, 1H, *J* 6.6, 17.7 Hz, H-4b), 3.61 (ddd, 1H, *J* 3.2, 6.6, 8.5 Hz, H-3), 3.70 (m, 2H, H-3'a, 3'b), 3.90 (dd, 1H, *J* 3.2, 4.1 Hz, H-1'), 4.16 (s, 2H, NBn), 4.61, 4.79 (2d, 2H, *J* 11.1 Hz, OBn), 4.98 (dt, 1H, *J* 4.1, 5.8, 5.8 Hz, H-2'). Anal. Calcd for $C_{38}H_{43}NO_6Si$: C, 71.55; H, 6.79; N, 2.19. Found: C, 71.5; H, 6.6; N, 2.1.

Mesylation of compounds 20, 21, and 22. 2'-Hydroxy-isoxazolidin-5-one (**20, 21** or **22**; 1 mmol) was dissolved in CH_2Cl_2 (15 ml), treated with pyridine (0.2 ml), and mesyl chloride (0.08 ml). The mixture was left for 4 h at room temperature. Subsequently it was poured into ice-water and extracted with CH_2Cl_2. The extract was washed with brine, dried, and evaporated. Chromatographical purification afforded the respective mesyl derivative (**29**, **31**, or **34**) in about 70% yield.

(3S, 1'S, 2'R) 2-Benzyl-3-(1'-benzyloxy-3'-*t*-butyldiphenylsiloxy-2'-methanesulfonyloxy)propyl-isoxazo-lidin-5-one (29) obtained from **20**; $[\alpha]_D$ -60.4° (*c* 1.1, CH_2Cl_2); IR (film): 1786 cm^{-1}; ^1H NMR ($CDCl_3$): 1.06 (s,

9H, *t*-Bu), 2.66 (dd, 1H, *J* 8.4, 17.9 Hz, H-4a); 2.85 (dd, 1H, *J* 5.7, 17.9 Hz, H-4b), 2.83 (s, 3H, OMs), 3.73-3.92 (m, 4H, H-3, 1', 3'a, 3'b), 4.16 (s, 2H, NBn), 4.59, 4.79 (2d, 2H, *J* 10.7 Hz, OBn), 4.60 (m, 1H, H-2'). Anal. Calcd for $C_{37}H_{43}NO_7SSi$: C, 65.94; H, 6.43; N, 2.07. Found: C, 65.8; H, 6.3; N, 2.1.

(3S, 1'S, 2'R) 2-Benzyl-3-(1',3'-dibenzyloxy-2'-methanesulfonyloxy)propyl-isoxazolidin-5-one (31) obtained from **21**; $[\alpha]_D$ -50.3° (*c* 1.0, CH_2Cl_2); IR (film): 1785 cm^{-1}; ^1H NMR ($CDCl_3$): 2.68 (dd, 1H, *J* 8.2, 17.9 Hz, H-4a), 2.84 (dd, 1H, *J* 5.2, 17.9 Hz, H-4b), 2.95 (s, 3H, OMs), 3.50-3.66 (m, 2H, H-3'a,3'b), 3.72-3.86 (m, 2H, H-3, 1'), 4.12, 4.18 (2d, 2H, *J* 13.5 Hz, NBn), 4.44 (s, 2H, OBn), 4.61, 4.76 (2d, 2H, *J* 10.9 Hz, OBn), 4.76 (m, 1H, H-2'). Anal. Calcd for $C_{28}H_{32}NO_7S$: C, 63.85; H, 6.12; N, 2.66. Found: C, 63.8; H, 5.9; N, 2.6.

(3S, 1'R, 2'R) 2-Benzyl-3-(1',3'-dibenzyloxy-2'-methanesulfonyloxy)propyl-isoxazolidin-5-one (34) obtained from **22**; $[\alpha]_D$ -49.2 (*c* 1.4, CH_2Cl_2); IR (KBr): 1781 cm^{-1}; ^1H NMR ($CDCl_3$): 2.24 (dd, 1H, *J* 4.2, 17.7 Hz, H-4a), 2.77 (dd, 1H, *J* 8.4, 17.7 Hz, H-4b), 3.36 (dd, 1H, *J* 6.1, 11.1 Hz, H-3'a), 3.57-3.76 (m, 3H, H-3, 1', 3'b), 4.13 (s, 2H, NBn), 4.36, 4.47 (2d, 2H, *J* 11.8 Hz, OBn), 4.70 (s, 2H, OBn), 4.84 (m, 1H, H-2'). Anal. Calcd for $C_{28}H_{31}NO_7S$: C, 63.99; H, 5.95; N, 2.67. Found: C, 63.9; H, 5.7; N, 2.4.

(3S, 2'R) 2-Benzyl-3-(2',3'-epoxy)propyl-isoxazolidin-5-one (32) and (3S, 5R) 2-Benzyl-5-hydroxymethyl-3-metoxycarbonylmethyl-isoxazolidine (42). Compound **27** (0.215 g, 0.67 mmol) was dissolved in CH_2Cl_2 (20 ml) and slowly treated with sodium methoxide in methanol (0.036 g, 0.67 mmol in 2 ml of methanol). Subsequently, the solution was filtered through Celite and evaporated. Chromatographical separation on silica gel afforded two fractions in proportion 1:2. Compound **32** (0.045 g, 22%); $[\alpha]_D$ -129.8° (*c* 1, CH_2Cl_2); IR (KBr): 1775 cm^{-1}; ^1H NMR ($CDCl_3$): 1.51 (m, 1H, *J* 7.3, 7.6, 14.2 Hz, H-1'a), 2.09 (ddd, 1H, *J* 3.6, 6.4, 14.2 Hz, H-1'b), 2.51 (dd, 1H, *J* 2.7, 4.9 Hz, H-3'a), 2.62 (dd, 1H, *J* 7.9, 17.4 Hz, H-4a), 2.81 (dd, 1H, *J* 4.0, 4.9 Hz, H-3'b), 2.90 (dd, 1H, *J* 7.5, 17.4 Hz, H-4b), 2.99 (m, 1H, H-2'), 3.63 (m, 1H, H-3), 4.15, 4.23 (2d, 2H, *J* 13.8 Hz, NBn). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.6; H, 6.8; N, 5.7. Compound **42** (0.089 g, 43%); $[\alpha]_D$ +65.7° (*c* 1.2, CH_2Cl_2); IR (film): 3413, 1737 cm^{-1}; ^{1}NMR ($CDCl_3$): 2.08 (ddd, 1H, *J* 5.5, 7.9, 12.4 Hz, H-4a), 2.41 (dt, 1H, *J* 7.6, 7.6, 12.4 Hz, H-4b), 2.46 (dd, 1H, *J* 8.1, 15.5 Hz, $CH_AH_BCO_2Me$), 2.59 (dd, 1H, *J* 5.6, 15.5 Hz, $CH_AH_BCO_2Me$), 3.40 (m, 1H, H-3), 3.55 (dd, 1H, *J* 5.0, 12.0 Hz, CH_AH_BOH), 3.66 (s, 3H, CO_2CH_3), 3.73 (dd, 1H, *J* 3.1, 12.0 Hz, CH_AH_BOH), 3.92, 3.98 (2d, 2H, *J* 13.6 Hz, NBn), 4.18 (m, 1H, H-5). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.0; H, 7.5; N, 5.2. Acetate **43**; $[\alpha]_D$ +62.0° (*c* 1.1, CH_2Cl_2); IR (film): 1739 cm^{-1}; ^1H NMR ($CDCl_3$): 2.08 (s, 3H, OAc), 2.16 (ddd, 1H, *J* 5.5, 7.8, 12.6 Hz, H-4, 2.32 (dt, 1H, *J* 7.5, 7.5, 12.6 Hz, H-4'), 2.43 (dd, 1H, *J* 8.5, 15.7 Hz,

$CH_AH_BCO_2Me$), 2.55 (dd, 1H, *J* 5.4, 15.7 Hz, $CH_AH_BCO_2Me$), 3.40 (m, 1H, H-3), 3.65 (s, 3H, OCH_3), 3.94, 3.99 (2d, 2H, *J* 13.5 Hz, NBn), 4.11 (dd, 1H, *J* 5.9, 11.7 Hz, CH_AH_BOAc), 4.21 (dd, 1H, *J* 3.9, 11.7, CH_AH_BOAc), 4.29 (m, 1H, H-5). Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.2; H, 7.0; N, 4.5.

(3S, 1'S, 2'S) **2-Benzyl-3-(1'-benzyloxy-2',3'-epoxy)propyl-isoxazolidin-5-one (33)**. Hydrogen fluoride - pyridine complex (0.5 ml) was added dropwise to a stirred solution of **29** (0.72 g, 1.06 mmole) in CH_2Cl_2 (5 ml). The reaction was left for 12 h. Subsequently the solvent was evaporated under vacuum, the oily residue was dissolved in CH_2Cl_2 (4 ml), the precipitate was filtered off and solvent evaporated. The residue was passed through silica gel to give crude **30** (0.35 g, 80%), ^{1}H NMR ($CDCl_3$): 2.7-2.9 (m, 2H, H-4,4'), 3.00 (s, 3H, Ms), 3.65-3.84 (m, 4H, H-3, 1',3'a,3'b), 4.14, 4.14, 4.29 (2d, 2H, *J* 13.2 Hz, NBn), m, 1H, H-2'), 4.67, 4.78 (2d, 2H, *J* 10.9 Hz, OBn).

Alcohol **30** (0.43 g, 1 mmole) was dissolved in C_6H_6 (10 ml) and upon stirring tetrabutylammonium hydroxide ($Bu_4NOH{\cdot}30H_2O$; 0.25 g, 0.3 mmole) was added. The progress of reaction was monitored by tlc. When about 30% of the substrate was converted into **33** the hydroxide was filtered, the solution was diluted with toluene, partially evaporated and passed through silica gel using hexane - ethyl acetate 3:1 $^v/_v$ mixture as an eluent to give **33** (0.033 g) and unreacted substrate (0.2 g). **33**: $[\alpha]_D$ -100.1° (*c* 0.4, CH_2Cl_2); IR (film): 1776 cm^{-1}; ^{1}H NMR ($CDCl_3$): 2.65 (dd, 1H, *J* 2.6, 4.9 Hz, H-3'a), 2.80 (m, 3H, H-4a, 4b, 3'b), 2.90 (ddd, 1H, *J* 2.6, 4.1, 6.4 Hz, H-2'), 3.19 (t, 1H, *J* 6.6 Hz, H-1'), 3.62 (ddd, 1H, *J* 5.4, 6.6, 8.0 Hz, H-3), 4.14, 4.25 (2d, 2H, *J* 13.2 Hz, NBn), 4.59, 4.82 (2d, 2H, *J* 11.6 Hz, OBn); MS (LSIMS) m/z: $M^{+\cdot}$: 339.

Formation of isoxazolidines 35, 36, and 37 from 2'-methanesulfonyloxy compounds 29, 31, and **34,** respectively. Compound **29, 31,** or **34** (1 mmol) was dissolved in dry methanol (25 ml) and slowly treated at room temperature with anhydrous K_2CO_3 (1 molar equiv.) until disappearance of the substrate. Subsequently the solution was filtered through Florisil, and evaporated to dryness. The crude product was purified by chromatography to afford **35, 36,** or **37** respectively (50-60%).

(3S, 4S, 5S) **2-Benzyl-4-benzyloxy-5-*t*-butyldiphenylsiloxymethyl-3-metoxycarbonylmethyl-isoxazolidine (35)** obtained from **29**; $[\alpha]_D$ +49.8° (*c* 0.9, CH_2Cl_2); IR (CCl_4): 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.04 (s, 9H, *t*-Bu), 2.42 (dd, 1H, *J* 8.1, 15.9 Hz, $CH_AH_BCO_2Me$), 2.48 (dd, 1H, *J* 6.0, 15.9 Hz, $CH_AH_BCO_2Me$), 3.60 (ddd, 1H, *J* 1.5, 6.0, 8.1 Hz, H-3), 3.63 (s, 3H, OCH_3), 3.89 (dd, 1H, *J* 5.3, 10.5 Hz, CH_AH_BO), 4.06, 4.15 (2d, 2H, *J* 13.0 Hz, NBn), 4.09 (dd, 1H, *J* 6.4, 10.5 Hz, CH_AH_BO), 4.18-4.24 (m, 2H, H-4,5), 4.56, 4.67 (2d, 2H, *J* 11.8

Hz, OBn). Anal. Calcd for $C_{37}H_{43}NO_5Si$: C, 72.88; H, 7.11; N, 2.30. Found: C, 72.7; H, 6.9; N, 2.3.

(3S, 4S, 5S) 2-Benzyl-4-benzyloxy-5-benzyloxymethyl-3-methoxycarbonylmethyl-isoxazolidine (36) obtained from **31**; $[\alpha]_D$ +79.1° (*c* 1.5, CH_2Cl_2); IR (film): 1737 cm^{-1}; ^1H NMR ($CDCl_3$): 2.40 (dd, 1H, *J* 8.2, 15.9 Hz, $CH_AH_BCO_2Me$), 2.46 (dd, 1H, *J* 5.8, 15.9 Hz, $CH_AH_BCO_2Me$), 3.59 (ddd, 1H, *J* 1.7, 5.8, 8.2 Hz, H-3), 3.62 (s, 3H, OCH_3), 3.73 (dd, 1H, *J* 5.8, 10.2 Hz, CH_AH_BO-), 3.93 (dd, 1H, *J* 5.8, 10.2 Hz, CH_AH_BO-), 4.10, 4.21 (2d, 2H, *J* 13.0 Hz, NBn), 4.22 (dd, 1H, *J* 1.7, 5.0 Hz, H-4), 4.25 (m, 1H, H-5), 4.52, 4.57 (2d, 2H, *J* 11.9 Hz, OBn), 4.55, 4.67 (2d, 2H, *J* 11.9 Hz, OBn). Anal. Calcd for $C_{28}H_3NO_5$: C, 72.86; H, 6.77; N, 3.03. Found: C, 72.7; H, 6.7; N, 3.2.

(3S, 4R, 5S) 2-Benzyl-4-benzyloxy-5-benzyloxymethyl-3-metoxycarbonylmethyl-isoxazolidine (37) obtained from **34**; $[\alpha]_D$ +79.7° (*c* 0.4, CH_2Cl_2); IR (film): 1735 cm^{-1}; ^1H NMR ($CDCl_3$): 2.42 (bd, 1H, $CH_AH_BCO_2Me$); 2.90 (dd, 1H, *J* 9.1, 16.7 Hz, $CH_2H_BCO_2Me$), 3.36 (bm, 1H, H-3), 3.49 (d, 1H, CH_2OBn), 3.59 (s, 3H, OCH_3), 3.92, 4.01 (2bd, 2H, *J* 14.0, NBn), 4.14 (bs, 1H, H-5), 4.30 (dd, 1H, *J* 4.0, 6.3 Hz, H-4), 4.40, 4.52 (2d, 2H, *J* 11.9 Hz, OBn), 4.50, 4.55 (2d, 2H, *J* 12.0 Hz, OBn); Anal. Calcd for $C_{28}H_{31}NO_5$: C, 72.86; H, 6.77; N, 3.03. Found: C, 72.9; H, 6.9; N, 3.2.

(3S, 4S, 5S) 2-Benzyl-4-benzyloxy-5-hydroxymethyl-3-methoxycarbonylmethyl-isoxazolidine (41). Compound **30** treated with dry methanol and anhydrous K_2CO_3 according to the procedure described above gave a mixture of compounds **41** and **46** in a ratio of about 2:1 respectively. The mixture was separated by chromatography into pure components. **41**: $[\alpha]_D$ +35.3° (*c* 0.5, CH_2Cl_2); IR (film): 3430, 1735 cm^{-1}; ^1H NMR ($CDCl_3$): 2.42 (dd, 1H, *J* 7.9, 15.9 Hz, $CH_AH_BCO_2Me$), 2.53 (dd, 1H, *J* 5.8, 15.9 Hz, $CH_AH_BCO_2Me$), 3.63 (ddd, 1H, *J* 2.2, 5.8, 7.9 Hz, H-3), 3.66 (S, 3H, OCH_3), 3.91 (d, 2H, CH_2OH), 4.13 (q, 1H, H-5), 4.12, 4.22 (2d, 2H, *J* 13.3 Hz, NBn), 4.54, 4.73 (2d, 2H, *J* 11.7 Hz, OBn); Anal. Calcd for. $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.8; H, 6.7; N, 3.5.

The acetate of **41**: $[\alpha]_D$ +66.9° (*c* 1.1, CH_2Cl_2); IR (film): 1738 cm^{-1}; ^1H NMR ($CDCl_3$): 2.04 (s, 3H, Ac), 2.38 (dd, 1H, *J* 8.3, 16.0 Hz, $CH_AH_BCO_2Me$), 2.45 (dd, 1H, *J* 5.6, 16.0 Hz, $CH_AH_BCO_2Me$), 3.61 (ddd, 1H, *J* 1.5, 8.3 Hz, H-3), 3.63 (s, 3H, OCH_3), 4.13, 4.24 (2d, 2H, *J* 13.0 Hz, NBn), 4.21-4.35 (m, 3H, H-5, CH_2OAc), 4.50 (m, 1H, H-4), 4.53, 4.69 (2d, 2H, *J* 12.0 Hz, OBn). Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81, H, 6.58; N, 3.39. Found: C, 66.8; H, 6.7; N, 3.5.

Formation of amides 38, 39, and 40: Compound **13**, **31** or **34** (0.5 mmol) was dissolved in acetonitrile (2 ml)

and was treated with benzylamine (0.10 g). The mixture was left overnight and then neutralized with HCl in methanol (10 % solution). Solvents were evaporated under vacuum and the crude product was purified by chromatography to give **38**, **39**, or **40**, respectively, in 90% yield.

(3R, 5R) 2-Benzyl-3-(*N*-benzylcarbamoylmethyl)-5-*t*-butyldiphenylsiloxymethyl-isoxazolidine (38), obtained from **13**; $[\alpha]_D$ +17.1° (*c* 1.5, CH_2Cl_2); IR (film): 3295, 1649 cm^{-1}; ^1H NMR ($CDCl_3$): 1.06 (s, 3H, *t*-Bu), 2.07 (ddd, 1H, *J* 4.6, 7.7, 12.5 Hz, H-4a), 2.33 (dd, 1H, *J* 4.2, 15.4 Hz, CH_AH_BCO-), 2.53 (dd, 1H, *J* 7.5, 15.4 Hz, CH_AH_BCO-), 2.54 (dt, 1H, *J* 7.8, 7.8, 12.5 Hz, H-4b), 3.43 (m, 1H, H-3), 3.68 (dd, 1H, *J* 4.2, 11.1 Hz, CH_AH_BOSi), 3.76 (dd, 1H, *J* 4.1, 11.1 Hz, CH_AH_BOSi), 3.86, 3.95 (2d, 2H, *J* 13.2 Hz, NBn), 4.15 (m, 1H, H-5), 4.30 (dd, 1H, *J* 5.6, 14.7 Hz, $NHCH_AH_BPh$), 4.39 (dd, 1H, *J* 5.8, 14.7 Hz, $NHCH_AH_BPh$). Anal. Calcd for $C_{36}H_{42}N_2O_3Si$: C, 74.7; H, 7.3; N, 4.8. Found: C, 74.8; H, 7.3; 4.8.

(3S, 4S, 5S) 2-Benzyl-4-benzyloxy-5-benzyloxymethyl-3-(*N*-benzylcarbamoylmethyl)-isoxazolidine (39). $[\alpha]_D$ +58.1° (*c* 1.0, CH_2Cl_2); IR (KBr): 3463, 1642, 1628 cm^{-1}; ^{1} H NMR ($CDCl_3$): 2.22 (dd, 1H, *J* 4.9, 15.2 Hz, $CH_AH_BCO_2Me$), 2.36 (dd, 1H, *J* 7.4, 15.2 Hz, $CH_AH_BCO_2Me$), 3.54 (ddd, 1H, *J* 1.4, 4.9, 7.4 Hz, H-3), 3.72 (dd, 1H, *J* 5.7, 10.2 Hz, CHH_BO-), 3.89 (dd, 1H, *J* 5.1, 10.2 Hz, CH_AHO-), 4.03, 4.21 (2d, 2H, *J* 12.9 Hz, NBn), 4.20 (m, 2H, H-4, 5), 4.30, 4.34 (2dd, 2H, *J* 5.7, 14.7 Hz, $NHCH_2Ph$), 4.50, 4.55 (2d, 2H, *J* 12.0 Hz, OBn), 4.53, 4.64 (2d, 2H, *J* 11.8 Hz, OBn), 7.04 (bt, 1H, NH). Anal. Calcd for $C_{34}H_{36}N_2O_4$: C, 76.09; H, 6.76; N, 5.22. Found: C, 76.3; H, 6.6; N, 5.1.

(3S, 4R, 5S) 2-Benzyl-4-benzyloxy-5-benzyloxymethyl-3-(*N*-benzylcarbamoylmethyl)-isoxazolidine (40). $[\alpha]_D$ +51.9 (*c* 1.4, CH_2Cl_2); IR (film): 3318, 1646 cm^{-1}; ^1H NMR ($CDCl_3$): 2.44 (bdd, 1H, $CH_AH_BCO_2Me$), 2.66 (dd, 1H, *J* 7.2, 15.2 Me, $CH_AH_BCO_2Me$), 3.39 (bm, 1H, H-3), 3.48 (dd, 1H, *J* 4.9, 10.5 Hz, CH_AH_BOBn), 3.50 (dd, 1H, *J* 4.6, 10.5 Hz, CH_AH_BOBn), 3.88, 4.01 (2d, 2H, *J* 13.9 Hz, NBn), 4.11 (bm, 1H, H-5), 4.28, 4.34 (2d, 2H, *J* 14.6 $NHCH_2Ph$), 4.29 (dd, 1H, *J* 4.4, 6.0 Hz, OBn). Anal. Calcd for $C_{34}H_{36}N_2O_4$: C, 76.09; H, 6.76; N, 5.22. Found: C, 76.0; H, 6.8; N, 5.3.

Formation of isoxazolidines 44 and 46 from 2',3'-epoxy compounds 32 and 33. Compound **32** or **33** (0.5 mmol) was dissolved in methanol (5 ml) and slowly treated with small portions of anhydrous potassium carbonate (0.5 mmol). After disappearance of the substrate, about 2 h, the mixture was passed through a Florisil column. Subsequently, the solvent was evaporated and the residue was purified by chromatography to afford **44** or **46**, respectively, in 65% yield.

(3R, 5S) 2-Benzyl-5-hydroxymethyl-3-methoxycarbonylmethyl-isoxazolidine (44): $[\alpha]_D$ +101.2° (*c* 0.8, CH_2Cl_2); IR (film): 3315, 1739 cm^{-1}; ^1H NMR ($CDCl_3$): 1.93 (dt, 1H, *J* 5.8, 6.0, 12.6 Hz, H-4a), 2.50 (dd, 1H, *J* 7.8 Hz, $CH_AH_BCO_2Me$), 2.62 (dd, 1H, *J* 6.2, 15.8 Hz, $CH_AH_BCO_2Me$), 2.67 (dt, 1H, *J* 8.3, 8.5, 12.6 Hz, H-4b), 3.47 (m, 1H, *J* 5.8, 6.2, 7.8, 8.3 Hz, H-3), 3.58 (m, 1H, CH_AH_BOH), 3.65 (s, 3H, OCH_3), 3.75 (bd, 1H, CH_AH_BOH), 3.93 (s, 2H, NBn), 4.34 (m, 1H, *J* 2.8, 4.8, 6.0, 8.5 Hz, H-5). Anal. Calcd for. $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.2; H, 7.3; N, 5.3. The acetate of **45** $[\alpha]_D$ +41.1° (*c* 0.8; CH_2Cl_2); IR (film): 1739 cm^{-1}; ^1H NMR ($CDCl_3$): 1.81 (ddd, 1H, *J* 4.7, 6.3, 12.9 Hz, H-4a), 2.06 (s, 3H, Ac), 2.47 (dd, 1H, *J* 8.0, 15.8 Hz, $CH_AH_BCO_2Me$), 2.63 (dd, 1H, *J* 6.2, 15.8 Hz, $CH_AH_BCO_2Me$), 2.71 (dd, 1H, *J* 8.0, 8.6, 8.6, 12.9 Hz, H-4b), 3.52 (tdd, 1H, *J* 4.7, 6.2, 8,0 Hz, H-3), 3.63 (s, 3H, OCH_3), 3.89, 4.00 (2d, 2H, *J* 13.4 Hz, NBn), 4.17 (d, 2H, CH_2OAc), 4.48 (tdd), 1H, 4.7, 4.8, 6.3, 8.6 Hz, H-5). Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; C, 62.53; H, 6.89; N, 4.56. Found: C, 62.4; H, 6.7; N, 4.4.

(3S, 4S, 5R) 2-Benzyl-4-benzyloxy-5-hydroxymethyl-3-methoxycarbonylmethyl-isoxazolidine (46); $[\alpha]_D$ +172.9° (*c* 1, CH_2Cl_2); IR (film): 3425, 1734 cm^{-1}; ^1H NMR ($CDCl_3$): 2.54 (dd, 1H, *J* 7.6, 15.9 Hz, $CH_AH_BCO_2Me$), 2.61 (dd, 1H, *J* 6.9, 15.9 Hz, $CH_AH_BCO_2Me$), 3.62 (s, 3H, OCH_3), 3.66 (m, 1H, CH_AH_BOH), 3.67 (ddd, 1H, *J* 1.9, 6.9, 7.6 Hz, H-3), 3.78 (bdd, 1H, CH_AH_BOH), 4.13, 4.24 (2d, 2H, *J* 13.1 Hz, NBn), 4.19 (dd, *J* 1.9, 3.7, H-4), 4.38 (q, 1H, H-5), 4.56, 4.67 (2d, 2H, *J* 11.8 Hz, OBn). Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.5; H, 6.5; N, 3.5. The acetate of **46**: $[\alpha]_D$ +92.0° (*c* 0.5, CH_2Cl_2); IR (film): 1741 cm^{-1}; ^1H NMR ($CDCl_3$): 2.06 (s, 3H, Ac), 2.53 (dd, 1H, *J* 8.3, 16.0 Hz, CH_AH_BMe), 2.64 (dd, 1H, *J* 6.7, 16.0 Hz, $CH_AH_BCO_2Me$), 3.62 (s, 3H, OCH_3), 3.72 (ddd, 1H, *J* 1.3, 6.7, 8.3 Hz, H-3), 4.10 (dd, 1H, *J* 1.3, 3.7 Hz, H-4), 4.18, 4.30 (2d, 2H, *J* 12.8 Hz, NBn), 4.21 (d, 2H, CH_2OAc), 4.57 (q, 1H, H-5), 4.54, 4.67 (2d, 2H, *J* 11.8 Hz, OBn); MS (LSIMS) m/z: (M+1): 414.

***t*-Butyl (3'R, 5'R) 2-[[2'-benzyl-5'-(*t*-butyldiphenylsiloxymethyl)-isoxazolidin-3'-yl]acetyl]-1-methylhydrazinoacetate (48)**. Compound **15** (0.10 g, 0.17 mmol) and *t*-butyl-1-methyl-hydrazinoacetate (**47**) (0.07 g, 0.43 mmol) were dissolved in acetonitrile (5 ml) and placed in a teflon ampoule in a high-pressure vessel. A pressure 10 kbar and 50°C were applied for 48 h. After decompression, solvent was evaporated and the residue was separated on a silica gel column to afford **48** (0.13 g, 12%) as a mixture of two conformational isomers derived from slow inversion process in the place of the hydrazine fragment; $[\alpha]_D$ 32.1 (*c* 0.5, CH_2Cl_2); IR (film): 3245, 1731, 1678 cm^{-1}; ^1H NMR ($CDCl_3$), major better resolved stereoisomer: 1.06 (s, 9H, Si-*t*-Bu), 1.47 (s, 9H, O-*t*-Bu), 2.07 (ddd, 1H, *J* 5.8, 7.2, 12.4 Hz, H-4a), 2.22 (dd, 1H, *J* 5.7, 14.7 Hz, CH_AH_BCO-), 2.37 (dd, 1H, *J* 6.6, 14.7 Hz, CH_AH_BCO-), 2.51 (dt, 1H, *J* 7.6, 7.6, 12.4 Hz, H-4b), 2.74 (s, 3H, NCH_3), 3.43 (b

quintet, 1H, H-3), 3.53, 3.57 (2d, 2H, *J* 17.6 Hz, NCH_2), 3.68 (dd, 1H, *J* 4.3, 11.0 Hz, CH_AH_BOSi), 3.75 (2d, 1H, 4.3, 11.0 Hz, CH_AHD_BOSi), 3.93 (2d, 2H, *J* 13.6 Hz, NBn), 4.19 (m, 1H, H-5); minor stereoisomer showing significant line broadening: 1.07 (s, 9H, *t*-Bu), 1.47 (s, 9H, *t*-Bu), 2.11 (ddd, 1H, *J* 5.2, 7.6, 12.6 Hz, H-4a), 2.58 (dt, 1H, H-4b), 2.68 (bd, 2H, CH_2CO-), 3.49 (bm, 1H, H-3), 3.71 (dd, 1H, *J* 4.3, 11.0 Hz, CH_AH_BOSi), 3.76 (dd, 1H, *J* 4.5, 11.0 Hz, CH_AH_BOSi), 3.95, 3.97 (2d, 2H, NBn), 4.22 (m, 1H, H-5). MS (EI, HR) m/z. Calcd for $C_{36}H_{49}N_3O_5Si$: 631.34415. Found: 631.3443.

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