Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 7, pp. 2073-2082, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00250-9

Enantiomerically Pure Isoxazolines by Stereoselective 1,3-Dipolar Cycloaddition of Silyl Nitronates

Guido Galley, Peter G. Jones[a] and Michael Pätzel*

Humboldt-Universität Berlin, Institut für Chemie, Hessische Str. 1-2, D-10115 Berlin, Germany and
[a] Institut für Anorganische und Analytische Chemie, Technische Universität Braunschweig, Postfach 3329, D-38023 Braunschweig, Germany

Abstract: The cycloaddition reactions of *in situ* generated silyl nitronates **3** to chiral enone **1a** or enoate **1b** proceed with high stereoselectivity to give enantiomerically pure N-silyloxyisoxazolidines **4**, which can easily be transformed into Δ^2-isoxazolines **5**. Based on an X-ray analysis the major diastereomers were assigned as the *syn*-derivatives, thus differing from diastereofacial selectivity found with nitrile oxides. The base-catalyzed ring-opening reaction of isoxazoline **5a** affords the chiral β-hydroxy nitrile **6**, which was cyclized to the sugar-like tetrahydrofuran **7**.

Introduction

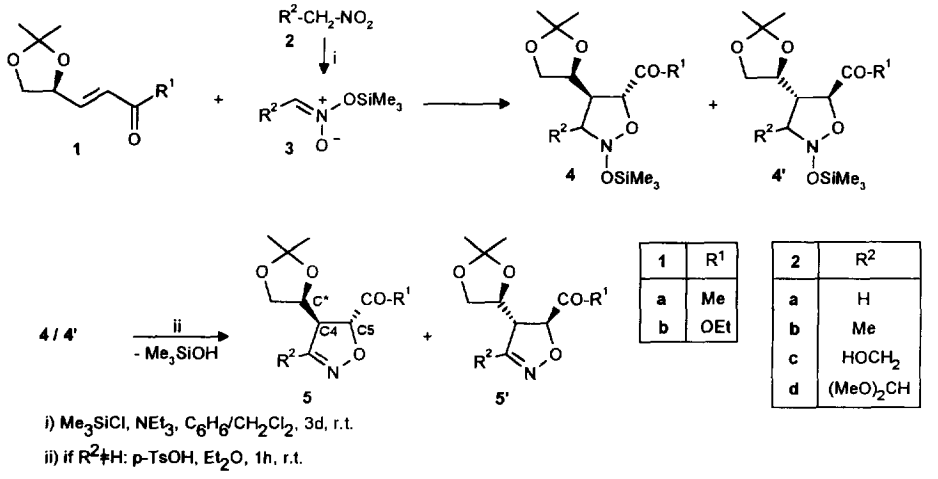
The stereochemical outcome of the 1,3-dipolar cycloaddition to γ-chiral α,β-unsaturated esters and ketones has been intensively investigated by several groups, [1,2,3] revealing that the facial selectivity of the cycloaddition depends especially on the nature of the dipole. Whereas diazo compounds [3b] and nitrilimines [3c] gave predominately *syn*-adducts, *anti*-configured products were found with azomethine ylides, [2a,3a] nitrones [2] and nitrile oxides. [1]

Silyl nitronates can be considered as synthetic equivalents of nitrile oxides. In their reaction with olefinic dipolarophiles the N-silyloxyisoxazolidines primarily formed are readily transformed into Δ^2-isoxazolines [4], which are widely known to be versatile building blocks for the formation of biofunctional molecules such as γ-amino alcohols and hydroxypyrrolidines. [5] However, silyl nitronates are much more rarely used than the related nitrile oxides and nitrones. To the best of our knowledge there are only two examples of intermolecular 1,3-dipolar cycloadditions of silyl nitronates to enantiomerically pure olefins. [6,7]

During the course of our investigations of diastereoselective cycloadditions to chiral enones [3] we now report the reaction of *in situ* prepared silyl nitronates **3** to 5(*S*)-E-5,6-O-isopropyliden-hex-3-en-2-one **1a** and the related enoate **1b**. Moreover, the use of nitro compounds as silyl nitronate precursors is extended to reactants bearing additional functional groups, resulting in a synthetically important functionalization of the 3-position of the final isoxazolines. [8]

Results and Discussion

Table 1 summarizes the experimental results of the cycloaddition reaction of various silyl nitronates **3** to the γ-chiral α,β-unsaturated carbonyl compounds **1**.



1	R^1
a	Me
b	OEt

2	R^2
a	H
b	Me
c	$HOCH_2$
d	$(MeO)_2CH$

Table 1. Silyl Nitronate Cycloaddition to Enone **1a** and Enoate **1b**

Entry	1	2	cycloadduct (yield) [a]	isoxazoline (yield) [c]	ratio of diastereomers [c] 4/4' and 5/5'
1	**a**	**a**	**4a/4'a** [b]	**5a/5'a** (60%)	92 : 8
2	**a**	**b**	**4b/4'b** (47%)	**5b/5'b** (95%)	83 : 17
3	**a**	**c**	**4c/4'c** (71%) [c]	**5c/5'c** (95%)	94 : 6
4	**a**	**d**	**4d/4'd** (75%)	**5d/5'd** (71%)	88 : 12
5	**b**	**a**	**4e/4'e** [b]	**5e/5'e** (55%)	91 : 9
6	**b**	**c**	**4f/4'f** (42%) [d]	**5f/5'f** (92%)	87 : 13

[a] unreacted olefin **1** could be recovered almost quantitatively by chromatography

[b] not isolated

[c] yield for reaction of **4/4'** to **5/5'** is given; except entries 1 and 5 for reaction of **3** to **5/5'**

[d] $R^2 = Me_3SiOCH_2$

[e] determined from NMR-spectra

It turned out that the cycloaddition was regiospecific and highly diastereoselective. Only two out of four possible (if $R^2 \neq H$) diastereomeric N-silyloxyisoxazolidines **4/4'** were formed according to NMR spectroscopy. Because of the generally low reactivity of 1,2-disubstituted olefins in 1,3-dipolar cycloadditions to silyl nitronates [9] the reactions of **1** proceeded slowly and only with modest to good yields. A mixture of benzene and dichloromethane proved to be the best solvent considering reaction times and yields. In all cases a threefold excess of nitro compound **2** was used. Column chromatography allowed the recovery of unreacted olefin **1** almost quantitatively and separation of the major diastereomer in each case.

When nitromethane **2a** was used as dipole precursor, the elimination of trimethylsilanol occurred spontaneously and the isoxazolines **5/5'** were isolated from the reaction mixture (entries 1 and 5). In other cases the elimination step is achieved by treating an ethereal solution of the crude **4** with p-toluenesulfonic acid.

Our experiments demonstrate that nitroethanol **2c** also can be used directly for silyl nitronate formation (entries 3 and 6). Under *Mukaiyama* conditions, an O-protection of nitroethanol is necessary to prevent the easy dehydration to nitroethylene.[5c] In the reaction sequence described here the hydroxyl function is temporarily protected by excess silylating agent, resulting in the disilylated cycloadducts **4c** and **4f**. The following acid- catalyzed elimination step simultaneously afforded the deprotection of the 3-hydroxymethyl function.

All compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy. Proton-decoupling experiments supported the assignment of the signals. Thus an identical regiochemical outcome of the cycloaddition of all silyl nitronates **3** used could be ensured forming isoxazolidines and isoxazolines with the acceptor group CO-R^1 in 5-position.

The absolute configuration of the isoxazolines **5** was determined with the help of a single crystal X-ray analysis of the major isomer **5a**. It revealed a *syn*-orientation of the hydrogen atoms at C* of the dioxolane moiety and at the newly formed stereocenter C4 (C4/C2 in Fig. 1). Furthermore, the arrangement of the substituents at C4 and C5 appeared to be *anti* (C2/C3 in Fig. 1), which is typical for a concerted cycloaddition process using an *E*-configured dipolarophile.

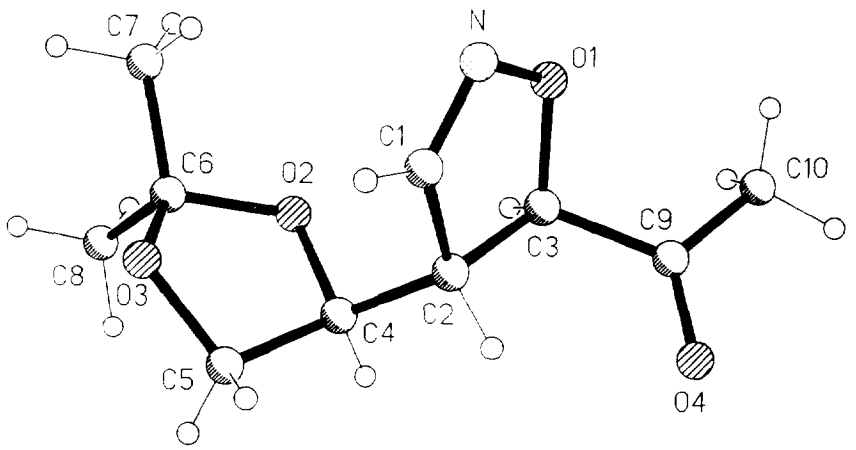
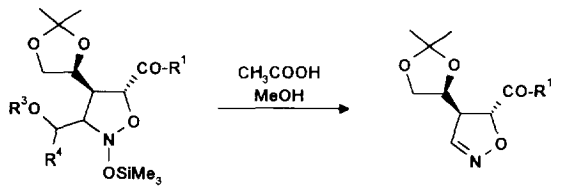


Fig. 1: X-ray structural analysis of isoxazoline **5a**

An interesting fragmentation reaction was observed when the 3-substituted N-siloxyisoxazolidines **4c**, **d**, **f** were treated with acetic acid in methanol. The products obtained proved to be identical with those arising from the cycloaddition of the C-unsubstituted silyl nitronate **3a**. By means of this *Grob*-like fragmentation further evidence for the structural assignment of **5** is given. For the enoate **3b** the examination of the NMR spectra supported an identical stereochemistry.



4c: R^1=Me, R^3=Me_3Si, R^4=H
4d: R^1=Me, R^3=Me, R^4=MeO
4f: R^1=OEt, R^3=Me_3Si, R^4=H

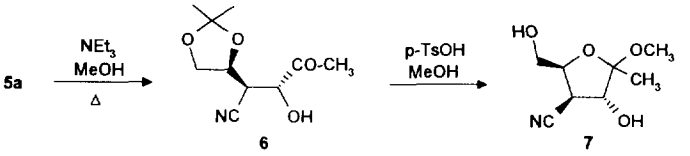
5a: R=Me
5a: R=Me
5b: R=OEt

Compared with the cycloaddition of nitrile oxides [1, 2a] the regiochemical outcome of the silyl nitronate cycloaddition is usually reversed. AM1-calculations revealed that the observed regioselectivity can be explained by the opposite magnitudes of the terminal HOMO coefficients of the dipoles.

On the basis of the structural assignments of the major diastereomers of **4** and **5**, the preferred stereochemical mode of attack at the diastereotopic faces of the dipolarophile could be determined. As proposed earlier [3b, c] the observed *syn*-attack can be rationalized on the basis of the "antiperiplanar effect". [10]

From the fact that only two diastereomeric N-silyloxyisoxazolidines, viz. **4** and **4'**, are formed, and that their diastereomeric ratio equals the ratio of **5** : **5'**, a stereospecific creation of the chiral center C3 can be concluded. Since C3 is planarized in the course of isoxazoline formation no attempt was made to assign its configuration. However, from the similarity to cycloaddition reactions of diazo compounds to **1** an *anti*-relationship at C3 and C4 in the primary cycloadducts **4** can be assumed. This fact was confirmed by NOE experiments.

As mentioned above, isoxazolines are versatile synthons for further transformations. It was demonstrated by Torssell that Δ^2-isoxazolines with an H-atom at C3 can be opened to nitriles. [4a] Under basic conditions isoxazoline **5a** yielded the chiral β-hydroxynitrile **6**. Acid-catalyzed deprotection of the diol function afforded the cyanosugar compound **7** in a stereoselective manner. Its NMR spectrum is in agreement with the furanoside structure; the existence of a possible 6-membered ring could be excluded from examining the coupling constants. Related cyano sugars have some importance as synthetic intermediates for C-glycosyl compounds and branched chain sugars. [11]



Further utilization of the enantiomerically pure N-silyloxyisoxazolidines **4** and Δ^2-isoxazolines **5** as chiral building blocks for the synthesis of biologically active compounds is still being explored.

In conclusion our results demonstrate a further example of the predominance of *syn*-adducts in 1,3-dipolar cycloaddition to γ-oxygenated enones and esters. In particular, the reversed stereochemical outcome compared with the results obtained with nitrile oxides is remarkably. A theoretical analysis of the effects of regiochemical orientation, heteroatoms and charge distribution on the preferred transition state is currently under investigation.

Acknowledgment

Our work was inspired by a post-doctoral visit of M. P. in the group of Prof. V. Jäger, Universität Stuttgart. The friendly support and encouragement by Prof. Jäger at this time is thankfully acknowledged. We thank Prof. J. Liebscher, Humboldt-Universität Berlin, for the continuous promotion of our work and helpful discussions. G. Galley thanks the Fonds der Chemischen Industrie and the Humboldt-Universität Berlin for grants.

Experimental Section

The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ (compound **7** in D_2O) on a Bruker AC-300 spectrometer at 300 MHz and 75 MHz, respectively. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad singlet. Elemental analyses were performed in a Leco CHNS-932 apparatus. Optical rotations were measured on a Perkin Elmer 241 polarimeter using a 2 ml cell (c = 1.0; CH_2Cl_2).

The diastereomeric ratios were determined from the intensities of three characteristic signals in the ^{13}C NMR spectra of the mixtures. In the case of diastereomeric mixtures, the analytical data of the major isomer and partly of the minor isomer were reported. Enone **1a** was prepared according to the literature procedure [12], enoate **1b** was purchased from Merck Co. AM1 calculations were performed on an IRIX Indigo machine using Insight II package (BIOSYM®).

General Procedure for the Silyl Nitronate Cycloaddition.

To 1 mmol of α,β-unsaturated carbonyl compound **1** in benzene/CH_2Cl_2 (4 ml, 1:1, v/v) 2 mmol of nitro compound **2**, triethylamine (4 mmol, 408 mg) and chlorotrimethylsilane (4 mmol, 432 mg) were added at 0°C. The mixture was stirred at this temperature for 2 h and at room temperature for 3 days. The suspension was diluted with ether and washed with saturated NH_4Cl solution. After reextracting the aqueous solution with ether the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. To estimate the diastereomeric ratios the residue was analyzed using NMR techniques. In case of nitromethane **2a** as starting material only traces of N-silyloxyisoxazolidine **4a** or **4e** were detected and the residual mixture was separated by column chromatography over silica gel (eluent: hexane/ethyl acetate, 7:3, v/v) to yield the Δ^2-isoxazolines **5a** or **5e** and unreacted olefin **1**. In other cases hexane/ethyl acetate (8:2, v/v) was used to separate the N-silyloxyisoxazolidines **4/4'** from unreacted olefin. To obtain analytical samples of **4a** and **4e** the aqueous workup was omitted and the mixture was directly separated by column chromatography.

Transformation of 3-Substituted N-Silyloxyisoxazolidines **4b,c,d,f** *to* Δ^2*-Isoxazolines* **5b,c,d,f**.

To a stirred solution of N-silyloxyisoxazolidines **4/4'** (0.25 mmol) in ether (5 ml) was added p-toluenesulfonic acid (50 mg). After 1 h at room temperature, the reaction mixture was diluted with ether and washed with saturated $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was separated by column chromatography.

Acid Catalyzed Fragmentation Reaction of 3-Substituted N-Silyloxyisoxazolidines **4b,c,d** *to* **5a** *and* **4f** *to* **5e**.

To a stirred solution of N-silyloxyisoxazolidine **4** (0.25 mmol) in methanol (4 ml) were added 4 drops of acetic acid. After 3 h at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 and extracted with saturated $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and concentrated by rotary evaporation. The residue was separated by column chromatography to yield the Δ^2-isoxazolines **5a** or **5e** almost quantitatively.

4(*S*), 5(*R*)-5-Acetyl-4-[4(*S*)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-2-trimethylsilyloxy-isoxazolidine 4a:
colourless oil; ^{1}H NMR (δ/ppm, J/Hz): 4.43 (td, 1H, 5.8/9.6, CH-O), 4.31 (d, 1H, 6.2, H5), 4.01 (dd, 1H, 5.8/8.7, CH_2O), 3.75 (dd, 1H, 5.8/8.7, CH_2O), 3.53 (dd, 1H, 1.8/12.4, H3), 3.32 (dd, 1H, 9.2/12.4, H3), 2.56 (qd, 1H, 9.2/1.8, H4), 2.15 (s, 3H, CH_3CO), 1.34 and 1.30 (s, 3H, CH_3C), 0.14 (s, 9H, Me_3Si); ^{13}C NMR (δ/ppm): 206.7 (C=O), 109.1 (OCO), 84.9 (C5), 78.6 (CH-O), 68.1 (CH_2O), 65.0 (C3), 48.6 (C4), 26.5 ($\underline{CH_3}CO$), 27.0, 25.6 ($\underline{CH_3}C$), -0.7 (Me_3Si).

4(*S*), 5(*R*)-5-Acetyl-4-[4(*S*)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-4,5-dihydroisoxazole 5a:
white crystals, mp. 70°C; ^{1}H NMR (δ/ppm, J/Hz): 7.13 (d, 1H, 1.7, H3), 4.51 (d, 1H, 6.3, H5), 4.13 (q, 1H, 6.3, CH-O), 4.03 (dd, 1H, 6.3/8.8, CH_2O), 3.75 (dd, 1H, 5.0/8.8, CH_2O), 3.56 (dt, 1H, 1.8/6.3, H4), 2.24 (s, 3H, CH_3CO), 1.39 and 1.28 (s, 3H, CH_3C); ^{13}C NMR (δ/ppm): 206.9 (C=O), 146.7 (C3), 110.2 (OCO), 84.4 (C5), 75.2 (CH-O), 67.1 (CH_2O), 56.0 (C4), 26.5 ($\underline{CH_3}CO$), 26.6, 24.9 ($\underline{CH_3}C$); $[\alpha]_{546}^{20} = -373$; Anal. Calcd. for $C_{10}H_{15}NO_4$ (213.23) C: 56.33%, H: 7.09%, N: 6.57%, Found: C: 56.30%, H: 6.96%, N: 6.65%.

Crystal Structure Analysis of **5a**

Crystal data: $C_{10}H_{15}NO_4$, $M_r = 213.23$, orthorhombic, $P2_12_12_1$, $a = 543.7$ (3), $b = 991.7$ (4), $c = 2020.0$ (8) pm, $V = 1.0892$ nm^3, $Z = 4$, $D_x = 1.300$ Mg m^{-3}, λ (Mo Kα) = 0.71073 Å, μ = 0.1 mm^{-1}, $F(000) = 456$, $T = -100$°C. Data collection and reduction: Colorless lath 0.8 x 0.35 x 0.1 mm, Siemens P4 diffractometer; 1466 unique intensities, $2\Theta_{max}$ 55°. Strukture solution and refinement: Direct methods, then refinement on F^2 using the programm SHELXL-93. Hydrogen atoms as rigid methyls or with riding model. Final $wR(F^2)$ for all reflections 0.140, conventional $R(F)$ 0.056, for 139 parameters and 136 restraints; $S = 0.85$, max. $\Delta/\delta = 0.001$, max. $\Delta\rho = 216$ e nm^3. Full details of the structure determination have been deposited at the Fachinformationszentrum Karlsruhe, Gesellschaft für Wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen 2, Germany. Any request for material should quote a full literature citation and the reference number CSD 405027.

4(*R*), 5(*S*)-5-Acetyl-4-[4(*S*)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-4,5-dihydroisoxazole 5'a (minor diastereomer): ^{13}C NMR (δ/ppm): 206.9 (C=O), 146.2 (C3), 109.9 (OCO), 83.7 (C5), 73.5 (CH-O), 66.8 (CH_2O), 55.2 (C4), 26.5 ($\underline{CH_3}CO$), 26.6 and 24.7 ($\underline{CH_3}C$).

4(*S*), 5(*R*)-5-Acetyl-4-[4(*S*)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-3-methyl-2-trimethylsilyloxy-isoxazolidine 4b: colourless oil; ^{1}H NMR (δ/ppm, J/Hz): 4.45 (td, 1H, 5.8/9.6, CH-O), 4.41 (d, 1H, 6.8, H5), 4.02 (dd, 1H, 5.8/8.7, CH_2O), 3.81 (dd, 1H, 5.8/8.7, CH_2O), 3.74 (qd, 1H, 7.1/2.2, H3), 2.26 (s, 3H, CH_3CO), 2.20 (td, 1H, 6.8/2.2, H4), 1.40 and 1.36 (s, 3H, CH_3C), 1.15 (d, 3H, 7.1, 3-CH_3), 0.18 (s, 9H, Me_3Si); ^{13}C NMR (δ/ppm): 207.0 (C=O), 108.9 (OCO), 85.3 (C5), 78.6 (CH-O), 72.8 (C3), 68.0 (CH_2O), 55.3 (C4), 26.5 ($\underline{CH_3}CO$), 27.0 and 25.6 ($\underline{CH_3}C$), 20.2 (3-CH_3), -0.6 (Me_3Si); $[\alpha]_{589}^{20}$ = -106.3; Anal. Calcd. for $C_{14}H_{27}NO_5Si$ (317.46) C: 52.97%, H: 8.57%, N: 4.41%, Found: C: 52.92%, H: 8.87%, N: 4.24%.

4(*S*), 5(*R*)-5-Acetyl-4-[4(*S*)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-3-methyl-4,5-dihydroisoxazole 5b: colourless liquid; ^{1}H NMR (δ/ppm, J/Hz): 4.45 (d, 1H, 5.1, H5), 4.19 (q, 1H, 6.3, CH-O), 3.98 (dd, 1H, 6.4/8.7, CH_2O), 3.70 (dd, 1H, 5.8/8.7, CH_2O), 3.41 (dt, 1H, 0.6/5.3, H4), 2.23 (s, 3H, CH_3CO), 1.99 (s, 3H, 3-CH_3), 1.39, 1.28 (s, 3H, CH_3C); ^{13}C NMR (δ/ppm): 207.4 (C=O), 156.2 (C3), 110.1 (OCO), 85.5 (C5), 74.8 (CH-O), 66.7 (CH_2O), 56.7 (C4), 26.4 ($\underline{CH_3}CO$), 26.5 and 24.7 ($\underline{CH_3}C$), 12.7 (3-CH_3); $[\alpha]_{589}^{20}$ = -264; Anal. Calcd. for $C_{11}H_{17}NO_4$ (227.26) C: 58.14%, H: 7.54%, N: 6.16%, Found: C: 58.02%, H: 7.38%, N: 6.12%.

4(*R*), 5(*S*)-5-Acetyl-4-[4(*S*)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-3-methyl-4,5-dihydroisoxazole 5'b: (minor diastereomer): ^{13}C NMR (δ/ppm): 207.4 (C=O), 155.3 (C3), 109.6 (OCO), 84.5 (C5), 75.2 (CH-O), 66.8 (CH_2O), 56.5 (C4), 26.4 ($\underline{CH_3}CO$), 26.3 and 24.4 ($\underline{CH_3}C$), 12.6 (3-CH_3).

4(*S*), 5(*R*)-5-Acetyl-4-[4(*S*)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-2-trimethylsilyloxy-3-trimethylsilyloxy-methyl-isoxazolidine 4c: colourless oil; ^{1}H NMR (δ/ppm, J/Hz): 4.35 (d, 1H, 7.4, H5), 4.29-4.33 (m, 1H, CH-O), 3.93 (dd, 1H, 5.9/8.8, CH_2O), 3.77 (dd, 1H, 5.6/8.8, CH_2O), 3.64 (ddd, 1H, 2.5/5.3/7.5, H3), 3.34-3.48 (m, 2H, 3-CH_2O), 2.25 (dt, 1H, 2.2/7.2, H4), 2.12 (s, 3H, CH_3CO), 1.30 and 1.25 (s, 3H, CH_3C), 0.01-0.09 (m, 18H, Me_3Si); ^{13}C NMR (δ/ppm): 206.8 (C=O), 109.0 (OCO), 85.1 (C5), 77.5 and 77.0 (C3, CH-O), 67.9 (CH_2O), 63.2 (3-CH_2O), 49.7 (C4), 26.9 (CH_3CO), 26.9 and 25.5 ($\underline{CH_3}C$), -0.7 (Me_3Si); $[\alpha]_{546}^{20}$ = -64.6; Anal. Calcd. for $C_{17}H_{35}NO_6Si_2$ (405.64) C: 50.34%, H: 8.70%, N: 3.45%, Found: C: 49.60%, H: 8.55%, N: 3.75%.

4(*S*), 5(*R*)-5-Acetyl-4-[4(*S*)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-3-hydroxymethyl-4,5-dihydroisoxazole 5c: colourless liquid; ^{1}H NMR (δ/ppm, J/Hz): 4.44 (d, 1H, 6.2, H5), 4.38 (d, 2H, 7.1, 3-CH_2O), 4.20 (dt, 1H, 8.6/6.1, CH-O), 4.05 (dd, 1H, 6.1/8.8, CH_2O), 3.79 (dd, 1H, 6.0/8.8, CH_2O), 3.52 (dd, 1H, 6.1/8.6, H4), 2.88 (b, 1H, OH), 2.24 (s, 3H, CH_3CO), 1.42 and 1.31 (s, 3H, CH_3C); ^{13}C NMR (δ/ppm): 207.0 (C=O), 158.9 (C3), 110.7 (OCO), 86.2 (C5), 75.4 (CH-O), 67.6 (CH_2O), 57.5 (3-CH_2O), 55.5 (C4), 26.4 ($\underline{CH_3}CO$), 26.5 and 25.2 ($\underline{CH_3}C$); $[\alpha]_{546}^{20}$ = -78.4; Anal. Calcd. for $C_{11}H_{17}NO_5$ (243.26) C: 54.31%, H: 7.04%, N: 5.76%, Found: C: 53.87%, H: 6.62%, N: 5.78%.

4(*R*), 5(*S*)-5-Acetyl-4-[4(*S*)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-3-hydroxymethyl-4,5-dihydroisoxazole 5'c: (minor diastereomer): ^{13}C NMR (δ/ppm): 207.1 (C=O), 158.3 (C3), 110.1 (OCO), 85.3 (C5), 74.4 (CH-O), 66.6 (CH_2O), 57.3 (3-CH_2O), 54.3 (C4), 26.4 ($\underline{CH_3}CO$), 26.4 and 25.1 ($\underline{CH_3}C$).

4(*S*), 5(*R*)-5-Acetyl-4-[4(*S*)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-3-dimethoxymethyl-2-trimethylsilyloxy-isoxazolidine 4d: colourless oil; ^{1}H NMR (δ/ppm, J/Hz): 4.25 (d, 1H, 5.5, 3-CH), 4.27 (d, 1H, 6.8, H5), 3.99-4.02 (m, 1H, CH-O), 3.85 (dd, 1H, 6.1/8.6, CH_2O), 3.77 (dd, 1H, 5.5/8.6, CH_2O), 3.56 (dd, 1H, 2.3/5.5, H3), 3.22, 3.19 (s, 3H, CH_3O), 2.53 (dt, 1H, 2.3/6.7, H4), 2.02 (s, 3H, CH_3CO), 1.23 and 1.15 (s, 3H, CH_3C), 0.01 (s, 9H, Me_3Si); ^{13}C NMR (δ/ppm): 206.7 (C=O), 109.2 (OCO), 103.9 (3-CH), 85.5 (C5), 78.2, 77.4 (C3, CH-O), 67.7 (CH_2O), 54.9 and 54.7 (CH_3O), 48.8 (C4), 26.8 (CH_3CO), 26.5 and 25.4 ($\underline{CH_3}C$), -0.7 (Me_3Si); $[\alpha]_{546}^{20}$ = -150.4; Anal. Calcd. for $C_{16}H_{31}NO_7Si$ (377.51) C: 50.91%, H: 8.28%, N: 3.71%, Found: C: 50.96%, H: 8.37%, N: 4.16%.

4(*S*), 5(*R*)-5-Acetyl-4-[4(*S*)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-3-dimethoxymethyl-4,5-dihydro-isoxazole 5d: colourless oil; ^{1}H NMR (δ/ppm, J/Hz): 4.93 (d, 1H, 6.7, 3-CH), 4.79 (d, 1H, 5.9, H5), 4.43-4.53 (m, 1H, CH-O), 4.02 (dd, 1H, 6.3/8.9, CH_2O), 3.90 (dd, 1H, 7.0/8.9, CH_2O), 3.53 (dd, 1H, 5.9/8.9, H4), 3.33 (s, 6H, CH_3O), 2.21 (s, 3H, CH_3CO), 1.39 and 1.27 (s, 3H, CH_3C); ^{13}C NMR (δ/ppm): 205.3 (C=O), 155.6 (C3), 109.9 (OCO), 99.9 (3-CH), 85.6 (C5), 73.3 (CH-O), 65.8 (CH_2O), 52.5 and 53.5 (CH_3O), 55.2 (C4), 26.2 ($\underline{CH_3}CO$), 26.3 and 24.4 ($\underline{CH_3}C$); $[\alpha]_{546}^{20}$ = -71.1; Anal. Calcd. for $C_{13}H_{21}NO_6$ (287.31) C: 54.35%, H: 7.37%, N: 4.84%, Found: C: 54.05%, H: 7.07%, N: 5.05%.

4(*R*), 5(*S*)-5-Acetyl-4-[4(*S*)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-3-dimethoxymethyl-4,5-dihydro-isoxazole 5'd: (minor diastereomer): ^{13}C NMR (δ/ppm): 205.3 (C=O), 155.4 (C3), 109.6 (OCO), 100.0 (3-CH), 84.5 (C5), 73.4 (CH-O), 67.2 (CH_2O), 52.7 and 53.6 (CH_3O), 55.1 (C4), 26.4 ($\underline{CH_3}CO$), 26.2 and 24.5 ($\underline{CH_3}C$).

Ethyl 4(*S*), 5(*R*)-4-[4(*S*)-2,2-Dimethyl-[1,3]-dioxolan-4-yl]-2-trimethylsilyloxy-isoxazolidine-5-carboxylate 4e: colourless oil; ^{1}H NMR (δ/ppm, J/Hz): 4.36 (td, 1H, 5.7/9.8, CH-O), 4.32 (d, 1H, 6.0, H5), 4.08 (q, 2H, 7.1, $CH_3\underline{CH_2}$), 3.94 (dd, 1H, 5.8/8.6, CH_2O), 3.65 (dd, 1H, 5.7/8.6, CH_2O), 3.40 (dd, 1H, 1.8/12.3, H3), 3.25 (dd, 1H, 9.0/12.3, H3), 2.56 (dtd, 1H, 1.8/6.0/8.9, H4), 1.23 and 1.19 (s, 3H, CH_3C), 1.13 (t, 3H, 7.1, $\underline{CH_3}CH_2$), 0.00 (s, 9H, Me_3Si); ^{13}C NMR (δ/ppm): 170.0 (COO), 109.1 (OCO), 78.5 (C5), 78.5 (CH-O), 68.3 (CH_2O), 64.7 (C3), 61.7 ($CH_3\underline{CH_2}$), 50.3 (C4), 27.0 and 25.5 ($\underline{CH_3}C$), 14.1 ($\underline{CH_3}CH_2$), -0.7 (Me_3Si); $[\alpha]_{546}^{20}$ = -221.

Ethyl 4(*S*), 5(*R*)-4-[4(*S*)-2,2-Dimethyl-[1,3]-dioxolan-4-yl]-4,5-dihydroisoxazole-5-carboxylate 5e: colourless oil; ^{1}H NMR (δ/ppm, J/Hz): 7.14 (d, 1H, 1.6, H3), 4.67 (d, 1H, 6.5, H5), 4.20 (q, 1H, 6.2, CH-O), 4.19 (q, 2H, 7.1, $CH_3\underline{CH_2}$), 4.07 (dd, 1H, 6.3/8.9, CH_2O), 3.78 (dd, 1H, 4.8/8.9, CH_2O), 3.65 (dt, 1H, 1.7/6.3, H4), 1.38 and 1.27 (s, 3H, CH_3C); 1.24 (t, 3H, 7.1, $\underline{CH_3}CH_2$); ^{13}C NMR (δ/ppm): 169.3 (COO), 145.9 (C3), 109.9 (OCO), 77.6 (C5), 74.6 (CH-O), 66.8 (CH_2O), 61.7 ($CH_3\underline{CH_2}$), 57.5 (C4), 26.1 and 24.6 ($\underline{CH_3}C$), 13.8

($\underline{CH_3}CH_2$); $[\alpha]_{546}^{20}$ = -355; Anal. Calcd. for $C_{11}H_{17}NO_5$ (243.26) C: 54.31%, H: 7.04%, N: 5.76%, Found: C: 53.96%, H: 6.57%, N: 6.01%.

Ethyl 4(*R*), 5(*S*)-4-[4(*S*)-2,2-Dimethyl-[1,3]-dioxolan-4-yl]-4,5-dihydroisoxazole-5-carboxylate 5'e: (minor diastereomer): ^{13}C NMR (δ/ppm): 169.4 (COO), 144.8 (C3), 110.0 (OCO), 77.5 (C5), 74.9 (CH-O), 66.5 (CH_2O), 61.5 ($CH_3\underline{CH_2}$), 57.6 (C4), 26.1 and 24.5 ($\underline{CH_3}C$), 13.8 ($\underline{CH_3}CH_2$).

Ethyl 4(*S*), 5(*R*)-4-[4(*S*)-2,2-Dimethyl-[1,3]-dioxolan-4-yl]-2-trimethylsilyloxy-3-trimethylsilyloxymethyl-isoxazolidine-5-carboxylate 4f: colourless liquid; ^{1}H NMR (δ/ppm, J/Hz): 4.51-4.54 (m, 1H, CH-O), 4.34 (d, 1H, 5.3, H5), 4.11 (q, 2H, 7.1, $CH_3\underline{CH_2}$), 3.79 (dd, 1H, 5.1/10.0, CH_2O), 3.73 (dd, 1H, 5.6/9.6, CH_2O), 3.51-3.69 (m, 3H, H3, 3-CH_2O), 2.34 (dt, 1H, 1.9/7.0, H4), 1.30 and 1.23 (s, 3H, CH_3C), 1.18 (t, 3H, 7.1, $\underline{CH_3}$CH2), 0.00-0.05 (s, 18H, Me_3Si); ^{13}C NMR (δ/ppm): 169.9 (COO), 109.0 (OCO), 78.6, 78.2, 77.8 (C3, C5, CH-O), 68.0 (CH_2O), 64.4 (3-CH_2O), 62.9 ($CH_3\underline{CH_2}$), 52.0 (C4), 27.0 and 25.4 ($\underline{CH_3}C$), 14.1 ($\underline{CH_3}CH_2$), -0.7 (Me_3Si); $[\alpha]_{546}^{20}$ = -45.0; Anal. Calcd. for $C_{18}H_{37}NO_7Si_2$ (435.67) C: 49.62%, H: 8.56%, N: 3.21%, Found: C: 50.73%, H: 8.49%, N: 3.78%.

Ethyl 4(*S*), 5(*R*)-4-[4(*S*)-2,2-Dimethyl-[1,3]-dioxolan-4-yl]-3-hydroxymethyl-4,5-dihydroisoxazole-5-carboxylate 5f: colourless oil; ^{1}H NMR (δ/ppm, J/Hz): 4.69 (d, 1H, 6.1, H5), 4.48 (s, 2H, 3-CH_2O), 4.28 (q, 2H, 7.1, $CH_3\underline{CH_2}$), 4.15-4.27 (m, 1H, CH-O), 3.88 (dd, 1H, 5.6/8.8, CH_2O), 3.71 (dd, 1H, 6.2/8.3, CH_2O), 2.90-2.96 (m, 1H, H4), 2.48 (b, 1H, OH), 1.51 and 1.39 (s, 3H, CH_3C); 1.33 (t, 3H, 7.1, $\underline{CH_3}CH_2$); ^{13}C NMR (δ/ppm): 169.4 (COO), 158.2 (C3), 110.7 (OCO), 79.2 (C5), 75.2 (CH-O), 67.5 (CH_2O), 62.2 ($CH_3\underline{CH_2}$), 58.6 (3-CH_2O), 57.4 (C4), 26.5 and 25.0 ($\underline{CH_3}C$), 14.0 ($\underline{CH_3}CH_2$); $[\alpha]_{546}^{20}$ = -57.7; Anal. Calcd. for $C_{12}H_{19}NO_6$ (273.28) C: 52.74%, H: 7.01%, N: 5.12%, Found: C: 52.38%, H: 6.54%, N: 5.18%.

Ethyl 4(*R*), 5(*S*)-4-[4(*S*)-2,2-Dimethyl-[1,3]-dioxolan-4-yl]-3-hydroxymethyl-4,5-dihydroisoxazole-5-carboxylate 5'f: (minor diastereomer): ^{13}C NMR (δ/ppm): 169.4 (COO), 158.1 (C3), 110.8 (OCO), 79.1 (C5), 75.5 (CH-O), 67.3 (CH_2O), 62.2 ($CH_3\underline{CH_2}$), 58.3 (3-CH_2O), 57.1 (C4), 26.3 and 25.0 ($\underline{CH_3}C$), 14.0 ($\underline{CH_3}CH_2$).

2(*R*), 3(*R*)-2-[4(*S*)-2,2-Dimethyl-[1,3]-dioxolan-4-yl]-3-hydroxy-4-oxo-pentanenitril 6:
To a solution of **5a** (1 mmol, 213 mg) in methanol (10 ml) was added triethylamine (20 mg) and the mixture was refluxed for 2 hours. After concentrating under reduced pressure the residue was dissolved in CH_2Cl_2 and washed with saturated NH_4Cl solution. Column chromatogaphy with hexane/ethyl acetate (1:1, v/v) afforded 118 mg of **6** (55%). Pale yellow oil; $[\alpha]_{546}^{20}$ = -40.3; ^{1}H NMR (δ/ppm, J/Hz): 4.33 (td, 1H, 6.0/4.5, CH-O), 4.30 (d, 1H, 3.4, H3), 4.16 (b, 1H, OH), 4.11 (dd, 1H, 6.4/9.0, CH_2O), 3.90 (dd, 1H, 5.7/9.0, CH_2O), 3.20 (dd, 1H, 3.4/4.3, H2), 2.33 (s, 3H, H5), 1.44 and 1.29 (s, 3H, CH_3C); ^{13}C NMR (δ/ppm): 206.4 (CO), 116.5 (CN), 111.0 (OCO), 75.0, 72.5 (C3, CH-O), 67.2 (CH_2O), 39.2 (C2), 26.4 (C5), 26.2 and 25.1 ($\underline{CH_3}C$); Anal. Calcd. for $C_{10}H_{15}NO_4$ (213.23) C: 56.33%, H: 7.09%, N: 6.57%, Found: C: 56.60%, H: 7.04%, N: 6.45%.

4-Hydroxy-2-hydroxymethyl-5-methoxy-5-methyl-tetrahydrofuran-3-carbonitrile 7:

To a solution of **6** (0.5 mmol, 106 mg) in methanol (5 ml) was added p-toluenesulfonic acid (20 mg) and the mixture was stirred overnight. After concentrating under reduced pressure the residue was purified by column chromatogaphy with hexane/ethyl acetate (1:1, v/v) to yield 61 mg of **7** (65%). White crystals; mp. 136°C, ^{1}H NMR in D_2O (δ/ppm, J/Hz): 3.99 (td, 1H, 10.7/5.3, H2), 3.76 (d, 1H, 10.8, H4), 3.72 (dd, 1H, 5.3/10.9, H3), 3.36 (t, 1H, 10.9, CH_2O), 3.29 (s, 2H, CH_3O), 3.28 (s, 1H, CH_3O), 3.10 (t, 1H, 10.8, CH_2O), 1.42 (s, 2H, 5-CH_3), 1.41 (s, 1H, 5-CH_3); ^{13}C NMR in D_2O (δ/ppm): 119.4 (CN), 97.6 (C5), 72.7, 66.8 (C2, C4), 62.9 (CH_2O), 48.3 (OCH_3), 41.6 (C4), 19.4 (5-CH_3); Anal. Calcd. for $C_8H_{13}NO_4$ (187.19) C: 51.33%, H: 7.00%, N: 7.48%, Found: C: 50.99%, H: 6.25%, N: 7.33%.

References and Notes

1. Jäger, V.; Müller, I.; Schohe, R.; Frey, M.; Ehrler, R. Häfele, B.; Schröter, D. *Lect. Heterocycl. Chem.* **1985**, *8*, 79.
2. (a) Annunziata, R.; Benaglia, M.; Cinquini, M.; Raimondi, L. *Tetrahedron* **1993**, *38*, 8629; (b) de March, P.; Figueredo, M.; Font, J.; Monsalvatje, M. *Rec. Trav. Chim. Pays-Bas* **1995**, *114*, 357.
3. (a) Galley, G.; Liebscher, J.; Pätzel, M. *J. Org. Chem.*, **1995**, *60*, 5005; (b) Galley, G.; Pätzel, M.; Jones, P. G. *Tetrahedron*, **1995**, *51*, 1631; (c) Grubert, L.; Galley, G.; Pätzel, M. *Tetrahedron: Asymmetry* **1996** in press.
4. (a) Torssell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH Weinheim, 1988; p. 119ff.; (b) Andersen, S. H.; Das, B. N.; Jorgensen, R. D.; Kjeldsen, G.; Knudsen, J. S.; Sharma, S. C.; Torssell, K. B. G. *Acta Chem. Scand.* **1982**, *B36*, 1 and preceeding papers; (c) Torssell, K. B. G.; Hazell, A. C.; Hazell, R. G. *Tetrahedron* **1985**, *41*, 5569.
5. (a) Müller, R.; Leibold, T.; Pätzel, M.; Jäger, V. Angew. Chem. **1994**, *106*, 1305; (b) Jäger, V.; Schröter, D. *Synthesis* **1990**, 556; (c) Jäger, V.; Schohe, R. *Tetrahedron* **1984**, *40*, 2199. (d) Jäger, V.; Grund, H.; Buß, V.; Schwab, W.; Müller, I.; Schohe, R.; Franz, R; Ehrler, R. *Bull. Soc. Chim. Belg.* **1983**, *92*, 1093.
6. (a) Kim, B. H.; Lee, J. Y.; Kim, K.; Whang, D. *Tetrahedron: Asymmetry* **1991**, *2*, 27. (b) Kim, B. H.; Lee, J. Y. *Tetrahedron: Asymmetry* **1991**, *2*, 1359.
7. Pitlik, J. *Synth. Comm.* **1994**, *24*, 243.
8. Kamimura, A.; Yoshihara, K.; Marumo, S.; Yamamoto, A.; Nishiguchi, T.; Kaheki, A.; Hori, K. *J. Org. Chem.* **1992**, 5403.
9. Torssell, K.B.G.; Zeuthen, O. *Acta Chem. Scand.* **1978**, *B 32*, 118.
10. (a) Caramella, P.; Ronda, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438. (b) Mulzer, J.; Altenbach, H.-J.; Braun, M.; Krohn, K.; Reissig, H.-U. *Organic Synthesis Highlights*, Verlag Chemie: Weinheim, 1991; pp. 3 and 243.
11. (a) Kazmi, S.; Ahmed, Z.; Khan, A.; Malik, A. *Synth. Comm.* **1988**, *18*, 151; (b) Kazmi, S.; Ahmed, Z.; Malik, A.; Afza, N.; Voelter, W. *Z. Naturf.* **1995**, 294.
12. Ronnenberg, H.; Borch, G.; Buchecker, R.; Arpin, N.; Liaaen-Jensen, S. *Phytochemistry* **1982**, *21*, 2087.

(*Received in UK* 2 *May* 1996)