Novel Synthesis of 4,5-Unsubstituted 2,3-Dihydroisoxazoles from 5-Acetoxyisoxazolidines

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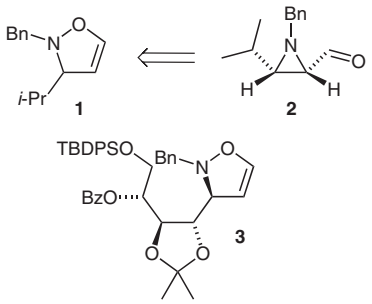
Received: 18.09.2012; Accepted after revision: 31.10.2012

Abstract: A new synthetic method for the preparation of 4,5-unsubstituted 2,3-dihydroisoxazoles from readily available 5-acetoxyisoxazolidines is presented. Elimination reactions are carried out in anhydrous *N*-methylpyrrolidin-2-one (NMP) with a catalytic amount of trimethylsilyl triflate in the presence of *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) and provide the 2,3-dihydroisoxazoles in very good yields. The nature of the silylating agent plays a very important role in elimination process. Anhydrous reaction conditions are required, while trimethylsilanol, the product of trimethylsilyl triflate and *N*,*O*-bis(trimethylsilyl)trifluoroacetamide hydrolysis, can initiate reactions leading to deacetylation, giving side products and thus decreasing the total yield of the elimination.

Key words: elimination, Lewis acids, cycloaddition, nitrones, 2,3-dihydroisoxazoles

4,5-Substituted 2,3-dihydroisoxazoles (4-isoxazolines) are interesting heterocycles used in various synthetic strategies as suitable building blocks.[1] On the other hand, 4,5-unsubstituted 2,3-dihydroisoxazoles **1** (Scheme 1) have mostly been observed as byproducts from 1,3-dipolar cycloadditions of nitrones with silyl enol ethers[2] and *p*-tolyl vinyl sulfoxides[3] or in the Swern oxidation of 5-hydroxyisoxazolidines.[4] Their chemical utilization is not well-documented except for the transformation to aziridines **2** (Scheme 1).[5] Recently, the *N*-benzyl-2,3-dihydroisoxazole **3** (Scheme 1) was isolated as an undesired byproduct in low yield in our laboratories during the Vorbrüggen nucleosidation of 5-acetoxyisoxazolidines, together with the corresponding isoxazolidinyl nucleosides.[6] To the best of our knowledge, this was the first time that a 4,5-unsubstituted 2,3-dihydroisoxazole was prepared directly from a 5-acetoxyisoxazolidine without isolating an intermediate. Based on these observations we focused our attention on the development of a new synthetic method for the synthesis of 4,5-unsubstituted 2,3-dihydroisoxazoles.

In accordance with our goal to study the transformation of 5-acetoxyisoxazolidines into 2,3-dihydroisoxazoles, we prepared some representative isoxazolidines **4**–**8** (Table 1) via regioselective 1,3-dipolar cycloaddition of nitrones with vinyl acetate as a mixture of two or four isomers depending upon the nitrone. The isoxazolidines **4**[7] and **5**[4] were isolated and subsequently used as a mixture of both



Scheme 1

3,5-*cis* and 3,5-*trans* isomers and the chiral isoxazolidines **6**[8] and **7**[9] as a mixture of four isomers 3,5-*cis*/3,5-*trans* together with the corresponding 1′,3-*syn*/1′,3-*anti* isomers. In the case of isoxazolidine **8**[9] we only isolated and used the major isomer 1′,3-*anti*-3,5-*trans*.

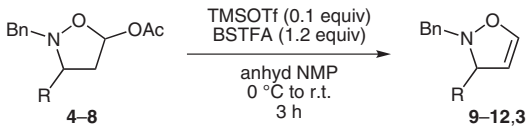
All elimination reactions were carried out in anhydrous NMP with a catalytic amount of trimethylsilyl triflate in the presence of *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) and provided 2,3-dihydroisoxazoles **3**, **9**–**12** in very good yields (Table 1).

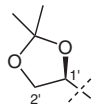
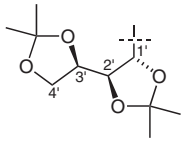
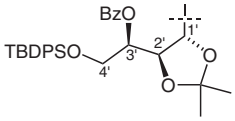
The progress of the reactions was easily followed by TLC (hexanes/ethyl acetate) and 2,3-dihydroisoxazoles **3**, **9**–**12** were identified as readily oxidized nonpolar components by permanganate detection at room temperature. After isolating the products by flash column chromatography on silica gel the structures were confirmed by ^{1}H NMR spectroscopic analysis. The existence of the C4–C5 double bond in **3**, **9**–**12** is confirmed by characteristic chemical shifts and multiplicity of the protons of H3, H4, and H5. In all cases we found three narrow apparent triplets with coupling constants in the range of 2–3 Hz.

The use of trimethylsilyl triflate/2,6-lutidine in the elimination reactions of methyl furanosides has been already published by the Leumann group,[10] but without mechanistic rationale. A mechanism for the elimination reaction is proposed according to the well-known Vorbrüggen nucleosidation[11] (Scheme 2). The oxocarbenium ion **13** created by trimethylsilyl triflate undergoes elimination to the 4,5-unsubstituted 2,3-dihydroisoxazoles **3**, **9**–**12** in the absence of nucleophiles. Trifluoromethanesulfonic acid is then rapidly silylated by *N*,*O*-bis(trimethylsilyl)trifluoroacetamide producing trimethylsilyl triflate and monosilylated trifluoroacetamide **14**, which is totally unreactive as a nucleophile because of the strong electron-withdraw-

SYNTHESIS 2012, 44, 3783–3788
Advanced online publication: 27.11.2012
DOI: 10.1055/s-0032-1317682; Art ID: SS-2012-T0731-OP

Table 1 Elimination Reactions of 5-Acetoxyisoxazolidines **4**–**8** to 2,3-Dihydroisoxazoles **9**–**12**, **3**



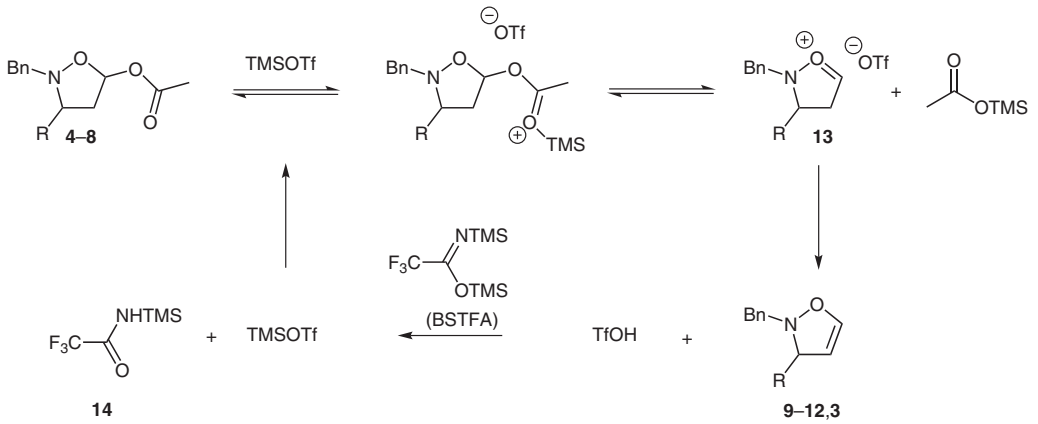
Entry	Isoxazolidine	R	2,3-Dihydroisoxazole	Total yield (%)
1	**4**	CO_2Et	**9**	55[a]
2	**4**		**9**	76[b]
3	**5**	Ph	**10**	53[a]
4	**5**		**10**	75[b]
5	**6**		**11a**,**b**[c]	70[a] (29:71)[d]
6	**7**		**12a**,**b**[c]	73[a] (15:85)[d]
7	**8**		**3**	73[a]

[a] 1 M concentration.
[b] 0.2 M concentration.
[c] Mixture of two isomers **a** (1′,3-*syn*) and **b** (1′,3-*anti*).
[d] Ratios were determined by ^{1}H NMR analysis of the crude reaction mixture.

ing group effect of the trifluoromethyl group. Thus, only a catalytic amount of trimethylsilyl triflate (0.1 equiv) and a slight excess of *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (1.2 equiv) is required, which is in agreement with experimental observations.

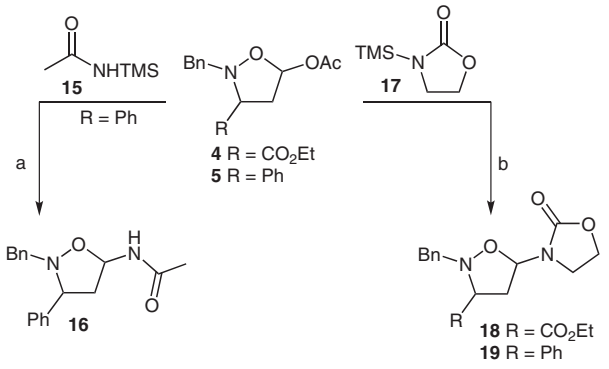
Other Lewis acids such as boron trifluoride–diethyl ether complex and tin(IV) chloride, which are commonly used in the Vorbrüggen nucleosidation and are also able to form the oxocarbenium ion did not cause any elimination. Solvents used in the Vorbrüggen nucleosidations namely acetonitrile or 1,2-dichloroethane as well as tetrahydrofuran, *N*,*N*-dimethylformamide, and *N*-methylpyrrolidin-2-one were also tested. While acetonitrile and 1,2-dichloroethane were found to be unsuitable (no or low conversion of the initial 5-acetoxyisoxazolidine, greater level of impurities in the reaction mixture), in the case of *N*,*N*-dimethylformamide and *N*-methylpyrrolidin-2-one we observed significant formation of 2,3-dihydroisoxazoles **3**, **9**–**12**. Moreover, the reaction in *N*-methylpyrrolidin-2-one was cleaner than in *N*,*N*-dimethylformamide. The use of less concentrated solutions led to higher yields with the same reaction time (Table 1, entries 1–4).

During our search for the best reaction conditions, we found that the nature of the silylating agent plays a very important role in the process of the elimination. *N*,*O*-Bis(trimethylsilyl)acetamide (BSA), which was originally used for silylation of nucleoside bases, is also able to react with the oxocarbenium ion.[12] We examined *N*,*O*-bis(trimethylsilyl)acetamide in *N*-methylpyrrolidin-2-one, and we observed the incorporation of the acetylamino group into the C5 position of the isoxazolidinyl ring along with 2,3-dihydroisoxazole formation. To demonstrate the possible negative effect of *N*,*O*-bis(trimethylsilyl)acetamide on the reaction course, we carried out the reaction of the isoxazolidine **5** with monosilylated acetamide **15** in 1,2-dichloroethane as a nonbasic solvent and we identified acetylamino derivative **16** in the reaction mixture (Scheme 3). Compound **16** was not observed when the reaction was carried out with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide alone, but in the presence of monosilylated acetamide **15** subsequently a more nucleophilic *N*,*O*-bis(trimethylsilyl)acetamide was produced in situ, which is a crucial reagent for the incorporation of the acetylamino group. Analysis of the original reaction mixture by NMR spectroscopy indicated the incorporation of the acetylamino group into the C5 position of the isoxazolidi-



Scheme 2

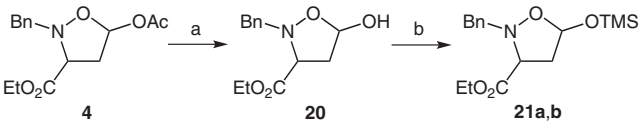
nyl ring.[13] 2,3-Dihydroisoxazole **10** was not observed owing to the absence of basic *N*-methylpyrrolidin-2-one which induces the elimination. Moreover, another silylating agent, 3-(trimethylsilyl)oxazolidin-2-one (**17**), which could reform trimethylsilyl triflate from triflic acid,[14] in its reaction with isoxazolidines **4** and **5** produced the corresponding isoxazolidinyl oxazolidinones **18** and **19** (Scheme 3) as a mixture of 3,5-*cis* and 3,5-*trans* isomers, which have been previously prepared by nitrone 1,3-dipolar cycloaddition with N-vinylated oxazolidin-2-one.[15] All of these obtained results indicate *N*,*O*-bis(trimethylsilyl)trifluoroacetamide to be the best silylating agent for our new method.



Scheme 3 *Reagents and conditions:* (a) TMSOTf (0.1 equiv), BSTFA (1.5 equiv), DCE (1 M), r.t., 24 h; (b) TMSOTf (0.1 equiv), DCE (1 M), r.t., 24 h, **18** 75%, ratio 3,5-*cis*/3,5-*trans*, 25:75, **19** 82%, ratio 3,5-*cis*/3,5-*trans*, 33:67, ratios were determined by ^{1}H NMR analysis of the crude reaction mixture.

Next we focused our attention on the preparative performance under anhydrous conditions since the both key reagents trimethylsilyl triflate and *N*,*O*-bis(trimethylsilyl)trifluoroacetamide are highly water-sensitive and can rapidly hydrolyze to form trimethylsilanol. On the basis of our observations, we suppose that the presence of trimethylsilanol along with trimethylsilyl triflate can initiate the reactions leading to deacetylation and producing 5-hydroxyisoxazolidines. The hydroxy group is subsequently silylated by excess *N*,*O*-bis(trimethylsilyl)trifluoroacetamide. The 5-(silyloxy)isoxazolidines are unreactive byproducts and decrease the total yield of the elimination. This was confirmed by reaction of 5-acetoxyisoxazolidine **4** (ratio 3,5-*cis*/3,5-*trans*, 20:80) with trimethylsilanol (2.5 equiv) and trimethylsilyl triflate (0.2 equiv) followed by the silylation of 5-hydroxyisoxazolidine **20** with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (Scheme 4). The final 5-(trimethylsilyloxy)isoxazolidine **21** was isolated in 55% yield over two steps as a mixture of 3,5-*cis* **21a** and 3,5-*trans* **21b** isomers with a ratio of **21a**/**21b** 30:70.

The isomers **21a** and **21b** were separated by the column chromatography on silica gel and their *cis*/*trans* relative configuration was assigned based on NOE experiments. During the separation process, the unstable trimethylsiloxy group was partially hydrolyzed. The undesired isoxazolidines **20** and **21a**,**b** were also detected in the crude reaction mixture when *N*-methylpyrrolidin-2-one was not stored over molecular sieves and, thus, probably contained traces of water.



Scheme 4 *Reagents and conditions:* (a) TMSOH (2.5 equiv), TMSOTf (0.2 equiv), MeCN, 40 °C, 6 h, 80%, 2 isomers with ratio 60:40; (b) BSTFA (4 equiv), DCE, r.t., 2 h, 69%, ratios were determined by ^{1}H NMR analysis of the crude reaction mixture.

In conclusion, a new synthetic method for the preparation of 4,5-unsubstituted 2,3-dihydroisoxazoles **3**, **9**–**12** from readily available 5-acetoxyisoxazolidines **4**–**8** is presented. Elimination reactions are carried out in anhydrous *N*-methylpyrrolidin-2-one with a catalytic amount of trimethylsilyl triflate in the presence of *N*,*O*-bis(trimethylsilyl)trifluoroacetamide and provide the 2,3-dihydroisoxazoles **3**, **9**–**12** in very good yields (70–76%). The nature of the silylating agent plays a very important role in the process of the elimination. Anhydrous reaction conditions are required, while trimethylsilanol, the product of trimethylsilyl triflate and *N*,*O*-bis(trimethylsilyl)trifluoroacetamide hydrolysis, can initiate reactions leading to deacetylation, giving side products and so decreasing the total yield of the elimination.

All melting points were measured on a Melting Point B-540 apparatus (Büchi) and are uncorrected. Elemental analyses were carried out on the analyzer Vario Macro Cube (Elementar). Optical rotations were measured on a Jasco P-2000 polarimeter (concentration *c* is given as g/100 mL). NMR spectra were recorded on a Varian VRX-300 spectrometer (^{1}H, 300 MHz and ^{13}C, 75.4 MHz) and Varian Inova-600 spectrometer (^{1}H, 600 MHz and ^{13}C, 150.8 MHz) in $CDCl_3$ using TMS as the internal standard. TLC analysis was carried out using TLC silica gel 60 F_{254} (Al sheets, Merck) and visualized by UV light or with permanganate soln followed by heating. Column chromatography was performed on Büchi system (Pump Manager C-615 and Fraction Collector C-660) using Normasil 60 silica gel (0.040–0.063 mm) (VWR). All solvents were dried and distilled according to conventional methods. NMP, DCE, and MeCN were stored over molecular sieves and handled under an inert atmosphere. All reagents were purchased from Aldrich, Acros Organics, Alfa-Aesar, Merck, and Mikrochem and were used without further purification.

2,3-Dihydroisoxazoles; General Procedure

The reaction flask was charged with 5-acetoxyisoxazolidine, sealed with a rubber septum and filled with argon. Anhyd NMP was added (0.2 M or 1 M) followed by BSTFA (1.2 equiv). The soln was cooled in an ice/water bath (2–5 °C) and TMSOTf (0.1 equiv) was added. The mixture was subsequently stirred at r.t. for 3 h in the dark. When the initial 5-acetoxyisoxazolidine had been consumed (TLC), the mixture was cooled in an ice/water bath, sat. aq $NaHCO_3$ and Et_2O were added, and the mixture was stirred for 5 min. The aqueous layer was removed, the organic layer was washed with H_2O (3 ×) and dried (Na_2SO_4), and the solvent was evaporated in vacuo (bath temperature < 35 °C). 2,3-Dihydroisoxazole was isolated by column chromatography (silica gel, hexanes–EtOAc, 90:10).

2-Benzyl-3-phenyl-2,3-dihydroisoxazole (10); Typical Procedure

The reaction flask was charged with 5-acetoxyisoxazolidine **5** (1.5 g, 5.0 mmol), sealed with a rubber septum, and filled with argon. Anhyd NMP (25 mL) was added followed by BSTFA (1.59 mL, 6.0 mmol). The soln was cooled in an ice/water bath (2–5 °C) and TMSOTf (0.09 mL, 0.5 mmol) was added. The mixture was subsequently stirred at r.t. for 3 h in the dark. When the initial 5-acetoxyisoxazolidine had been consumed (TLC, hexanes–EtOAc, 83:17), the mixture was cooled in an ice/water bath, sat. aq $NaHCO_3$ (30 mL) and Et_2O (50 mL) were added, and the mixture was stirred for 5 min. The precipitated solid was dissolved by addition of H_2O (50 mL). The aqueous layer was removed, the organic layer was washed with H_2O (3 × 30 mL) and dried (Na_2SO_4), and the solvent was evaporated in vacuo (bath temperature < 35 °C). 2,3-Dihydroisoxazole **10** was isolated by column chromatography (silica gel, hexanes–EtOAc, 90:10) as a colorless oil that became darker over time; yield: 0.89 g (3.75 mmol, 75%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.02 (d, *J* = 12.9 Hz, 1 H, NCH_2Ph), 4.30 (d, *J* = 12.9 Hz, 1 H, NCH_2Ph), 4.90–4.92 (m, 1 H, H3), 5.01 (dd, *J* = 2.3, 2.9 Hz, 1 H, H4), 6.56–6.58 (m, 1 H, H5), 7.20–7.40 (m, 10 H, Ph).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 63.3, 72.1, 100.1, 127.0, 127.5 (2 C), 128.3, 128.5, 129.3, 136.5 (2 C), 142.0.

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.91; H, 6.14; N, 6.19.

(3*S*)-3-(3-*O*-Benzoyl-4-*O*-*tert*-butyldiphenylsilyl-1,2-*O*-isopropylidene-D-*xylo*-tetritol-1-yl)-2-benzyl-2,3-dihydroisoxazole (3)

Colorless oil, becomes darker over time; yield: 200 mg (73%); $[\alpha]_D^{20}$ –84.64 (*c* 0.86, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.96 [s, 9 H, $OSiC(CH_3)_3$], 1.39, 1.41 [2 s, 2 × 3 H, $C(CH_3)_2$], 3.84 (dd, *J* = 4.1, 7.6, 1 H, H1′), 3.87 (dd, *J* = 5.3, 10.6 Hz, 1 H, H4a′), 3.92 (d, *J* = 13.5 Hz, 1 H, NCH_2Ph), 3.95 (dd, *J* = 8.2, 10.6 Hz, 1 H, H4b′), 4.15 (d, *J* = 13.5 Hz, 1 H, NCH_2Ph), 4.18–4.20 (m, 1 H, H3), 4.29 (dd, *J* = 1.8, 7.6 Hz, 1 H, H2′), 4.94 (dd, *J* = 2.3, 2.9 Hz, 1 H, H4), 5.49 (ddd, *J* = 5.3, 8.2, 1.8 Hz, 1 H, H3′), 6.45–6.47 (m, 1 H, H5), 7.23–7.41 (m, 11 H, Ph), 7.44 (t, 2 H, Ph), 7.56 (t, 1 H, Ph), 7.62 (d, 2 H, Ph), 7.67 (d, 2 H, Ph), 8.09 (d, 2 H, Ph).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 19.1, 26.6, 27.1, 27.3, 63.4, 64.0, 70.0, 73.2, 76.1, 78.1, 95.6, 109.4, 127.5, 127.6 (2 C), 128.3 (2 C), 129.1, 129.6 (2 C), 129.8, 130.2, 133.0, 133.3, 133.4, 135.6 (2 C), 136.6, 143.5, 166.0.

Anal. Calcd for $C_{40}H_{45}NO_6Si$: C, 72.37; H, 6.83; N, 2.11. Found: C, 72.65; H, 7.09; N, 2.32.

Ethyl 2-Benzyl-2,3-dihydroisoxazole-3-carboxylate (9)

Colorless oil, becomes darker over time; yield: 610 mg (76%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.3 Hz, 3 H, OCH_2CH_3), 3.97 (d, *J* = 13.0 Hz, 1 H, NCH_2Ph), 4.16 (q, *J* = 7.3 Hz, 2 H, OCH_2CH_3), 4.29 (d, *J* = 13.0 Hz, 1 H, NCH_2Ph), 4.48 (dd, *J* = 2.4, 2.8 Hz, 1 H, H3), 4.94 (dd, *J* = 2.4, 2.8 Hz, 1 H, H4), 6.55–6.57 (m, 1 H, H5), 7.28–7.41 (m, 5 H, Ph).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 14.1, 61.3, 63.4, 70.1, 94.8, 127.8, 128.5, 129.3, 135.4, 143.8, 170.4.

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.99; H, 6.21; N, 6.27.

(3*R*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)]-2,3-dihydroisoxazole (11a)

Colorless solid; yield: 130 mg (18%); mp 47–48 °C; $[\alpha]_D^{20}$ +262.49 (*c* 1.01, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.30, 1.31 [2 s, 2 × 3 H, $C(CH_3)_2$], 3.71 (dd, *J* = 8.8, 11.2 Hz, 1 H, H2a′), 3.89 (d, *J* = 12.9 Hz, 1 H, NCH_2Ph), 3.98–4.01 (m, 2 H, H1′, H2b′), 4.06–4.07 (m, 1 H, H3), 4.19 (d, *J* = 12.9 Hz, 1 H, NCH_2Ph), 4.78 (dd, *J* = 2.3, 2.9 Hz, 1 H, H4), 6.54–6.56 (m, 1 H, H5), 7.26–7.39 (m, 5 H, Ph).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 25.1, 26.3, 63.3, 65.5, 70.7, 77.5, 94.9, 109.3, 127.6, 128.4, 129.5, 135.9, 143.9.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.08; H, 7.10; N, 5.09.

(3*S*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)]-2,3-dihydroisoxazole (11b)

Colorless solid; yield: 385 mg (52%); mp 42–43 °C; $[\alpha]_D^{20}$ –265.73 (*c* 1.02, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.31, 1.38 [2 s, 2 × 3 H, $C(CH_3)_2$], 3.50–3.53 (m, 1 H, H2a′), 3.82 (d, *J* = 12.9 Hz, 1 H, NCH_2Ph), 3.89–3.91 (m, 1 H, H3), 3.92–3.97 (m, 2 H, H1′, H2b′), 4.15 (d, *J* = 12.9 Hz, 1 H, NCH_2Ph), 5.00 (dd, *J* = 2.3, 2.9 Hz, 1 H, H4), 6.51–6.53 (m, 1 H, H5), 7.25–7.38 (m, 5 H, Ph).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 25.3, 26.7, 63.3, 66.8, 70.6, 78.6, 97.1, 109.3, 127.8, 128.4, 129.5, 136.1, 143.2.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.76; H 7.06; N 5.12.

(3*S*)-2-Benzyl-3-(1,2:3,4-di-*O*-isopropylidene-D-*xylo*-tetritol-1-yl)-2,3-dihydroisoxazole (12b)

Colorless viscous oil, becomes darker over time; yield: 215 mg (50%); $[\alpha]_D^{20}$ –166.66 (*c* 1.03, $CHCl_3$). Additionally, a mixture of unseparated isomers **12a** and **12b** (100 mg, 23%) was also isolated.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.35, 1.37, 1.39, 1.40 [4 s, 4 × 3 H, $C(CH_3)_2$], 3.63 (dd, *J* = 4.1, 7.0 Hz, 1 H, H2′), 3.85 (d, *J* = 12.9 Hz, 1 H, NCH_2Ph), 3.85 (dd, *J* = 7.0, 6.5 Hz, 1 H, H1′), 3.88–3.94 (m, 2 H, H4′), 4.04 (td, *J* = 1.8, 2.3 Hz, 1 H, H3), 4.12 (dt, *J* = 7.0, 4.1 Hz, 1 H, H3′), 4.16 (d, *J* = 12.9 Hz, 1 H, NCH_2Ph), 5.00 (dd, *J* = 2.3, 2.9 Hz, 1 H, H4), 6.52–6.54 (m, 1 H, H5), 7.28–7.38 (m, 5 H, Ph).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 25.8, 26.3, 27.1, 27.5, 63.3, 66.0, 70.5, 76.3, 78.6, 79.6, 96.7, 109.5, 109.6, 127.8, 128.5, 129.6, 135.9, 143.4.

Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.23; H, 7.48; N, 3.63.

Ethyl 2-Benzyl-5-(2-oxooxazolidin-3-yl)isoxazolidine-3-carboxylate (18)

The reaction flask was charged with the 5-acetoxyisoxazolidine **4** (150 mg, 0.51 mmol), sealed with a rubber septum and filled with argon. Anhyd DCE was added (0.50 mL) followed by *N*-(trimethylsilyl)oxazolidin-2-one (**17**, 0.12 mL, 0.76 mmol). The soln was cooled in an ice/water bath (2–5 °C) and TMSOTf (10 μL, 0.05 mmol) was added. The mixture was subsequently stirred at r.t. for 24 h. When the initial 5-acetoxyisoxazolidine had been consumed (TLC, hexanes–EtOAc, 40:60), the mixture was cooled in an ice/water bath, sat. aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) were added, and the mixture was stirred for 5 min. The aqueous layer was removed and extracted with CH_2Cl_2 (5 mL). The combined organic layers were washed with H_2O and dried (Na_2SO_4), and the solvent was evaporated in vacuo. The products were separated by column chromatography (silica gel, hexanes–EtOAc, 40:60).

3,5-*cis*-18a

Colorless oil; yield: 33 mg (0.1 mmol, 20%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 2.57 (ddd, *J* = 4.1, 7.6, 13.8 Hz, 1 H, H4a), 2.87 (ddd, *J* = 8.2, 9.1, 13.8 Hz, 1 H, H4b), 3.55 (dd, *J* = 7.6, 9.1 Hz, 1 H, H3), 3.69–3.90 (m, 2 H, NCH_2CH_2O), 4.01 (d, *J* = 13.5 Hz, 1 H, NCH_2Ph), 4.09–4.16 (m, 2 H, OCH_2CH_3), 4.13 (d, *J* = 13.5 Hz, 1 H, NCH_2Ph), 4.22–4.35 (m, 2 H, NCH_2CH_2O), 5.92 (dd, *J* = 4.1, 8.2 Hz, 1 H, H5), 7.27–7.36 (m, 5 H, Ph).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.1, 36.3, 40.9, 61.6, 61.7, 62.4, 66.7, 81.6, 127.7, 128.3, 129.2, 135.9, 157.7, 169.9.

Anal. Calcd for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.74. Found: C, 60.25; H, 6.11; N, 8.59.

3,5-*trans*-18b
Colorless oil; yield: 90 mg (0.3 mmol, 55%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 2.55 (ddd, *J* = 4.7, 7.6, 13.5 Hz, 1 H, H4a), 2.83 (ddd, *J* = 6.4, 8.2, 13.5 Hz, 1 H, H4b), 3.54 (dd, *J* = 7.6, 8.2 Hz, 2 H, NCH_2CH_2O), 3.74 (dd, *J* = 7.0, 7.6 Hz, 1 H, H3), 4.09 (d, *J* = 13.5 Hz, 1 H, NCH_2Ph), 4.16 (d, *J* = 13.5 Hz, 1 H, NCH_2Ph), 4.18 (q, *J* = 7.0 Hz, 2 H, OCH_2CH_3), 4.30 (dd, *J* = 7.0, 9.4 Hz, 2 H, NCH_2CH_2O), 5.84 (dd, *J* = 4.7, 8.2 Hz, 1 H, H5), 7.28–7.37 (m, 5 H, Ph).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.2, 35.4, 40.4, 60.3, 61.5, 62.0, 65.3, 82.1, 127.7, 128.3, 129.3, 135.8, 157.1, 169.3.

Anal. Calcd for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.74. Found: C, 59.75; H, 6.48; N, 8.47.

3-(2-Benzyl-3-phenylisoxazolidin-5-yl)oxazolidin-2-one (19)
The reaction flask was charged with the 5-acetoxyisoxazolidine **5** (200 mg, 0.67 mmol), sealed with a rubber septum, and filled with argon. Anhyd DCE was added (0.70 mL) followed by *N*-(trimethylsilyl)oxazolidin-2-one (**17**, 0.16 mL, 1.0 mmol). The soln was cooled in an ice/water bath (2–5 °C) and TMSOTf (13 μL, 0.07 mmol) was added. The mixture was subsequently stirred at r.t. for 24 h. When the initial 5-acetoxyisoxazolidine had been consumed (TLC, silica gel, hexanes–EtOAc, 60:40), the mixture was cooled in an ice/water bath, sat. aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) were added, and the mixture was stirred for 5 min. The aqueous layer was removed and extracted with CH_2Cl_2 (1 × 5 mL). The combined organic layers were washed with H_2O and dried (Na_2SO_4), and the solvent was evaporated in vacuo. The products were separated by column chromatography (silica gel, hexanes–EtOAc, 70:30).

3,5-*cis*-19a
Colorless solid; yield: 60 mg (0.18 mmol, 28%); mp 157–159 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (ddd, *J* = 4.8, 9.9, 13.6 Hz, 1 H, H4a), 2.99 (ddd, *J* = 7.7, 8.1, 13.6 Hz, 1 H, H4b), 3.66 (d, *J* = 14.3 Hz, 1 H, NCH_2Ph), 3.73 (td, *J* = 5.9, 8.4 Hz, 1 H, NCH_2CH_2O), 3.85 (dd, *J* = 7.7, 9.9 Hz, 1 H, H3), 3.88 (q, *J* = 8.4 Hz, 1 H, NCH_2CH_2O), 3.97 (d, *J* = 14.3 Hz, 1 H, NCH_2Ph), 4.23–4.36 (m, 2 H, NCH_2CH_2O), 5.92 (dd, *J* = 5.1, 8.4 Hz, 1 H, H5), 7.24–7.45 (m, 10 H, Ph).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 40.6, 43.0, 59.8, 62.2, 70.8, 81.3, 127.2, 127.4, 128.2, 128.3, 128.7, 129.0, 137.4, 138.0, 157.8.

Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.07; H, 6.18; N, 8.46.

3,5-*trans*-19b
Colorless solid; yield: 118 mg (0.36 mmol, 54%); mp 153–155 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ =2.53–2.69 (m, 2 H, H4a, H4b), 3.55–3.69 (m, 2 H, NCH_2CH_2O), 3.71 (d, *J* = 14.7 Hz, 1 H, NCH_2Ph), 3.84–3.95 (m, 1 H, H3), 4.01 (d, *J* = 14.7 Hz, 1 H, NCH_2Ph), 4.27–4.39 (m, 2 H, NCH_2CH_2O), 5.92 (dd, *J* = 4.0, 7.7 Hz, 1 H, H5), 7.23–7.43 (m, 10 H, Ph).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 40.0, 41.5, 58.9, 62.0, 68.6, 81.5, 127.3, 127.9, 128.1, 128.3, 128.8, 129.0, 136.6, 137.9, 157.2.

Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.10; H, 6.31; N, 8.34.

Ethyl 2-Benzyl-5-(trimethylsilyloxy)isoxazolidine-3-carboxylate (21)
The reaction flask was charged with the 5-acetoxyisoxazolidine **4** (300 mg, 1.0 mmol), sealed with a rubber septum, and filled with argon. Anhyd MeCN was added (2 mL) followed by TMSOH (0.28 mL, 2.5 mmol), and TMSOTf (0.04 mL, 0.2 mmol) was added. The mixture was subsequently stirred at 40 °C for 6 h. Afterwards, the mixture was cooled in an ice/water bath, sat. aq $NaHCO_3$ (5 mL) was added, and the mixture was stirred for 5 min. MeCN was partially removed by evaporation under reduced pressure. H_2O (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with H_2O and dried (Na_2SO_4), and the solvent was evaporated in vacuo. The mixture of two isomers **20** was isolated by column chromatography (silica gel, hexanes–EtOAc, 60:40).

Unseparated 3,5-*cis* and 3,5-*trans* isomers of 20
Colorless oil; yield: 200 mg (0.8 mmol, 80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.0 Hz, 3 H), 1.22 (t, *J* = 7.0 Hz, 3 H), 2.39 (ddd, *J* = 1.2, 4.1, 13.5 Hz, 1 H), 2.53–2.64 (m, 2 H), 2.72 (ddd, *J* = 5.0, 8.2, 12.9 Hz, 1 H), 3.61 (dd, *J* = 4.1, 9.4 Hz, 1 H), 3.95 (dd, *J* = 7.6, 7.9 Hz, 1 H), 4.03 (d, *J* = 12.9 Hz, 1 H), 4.07–4.16 (m, 5 H), 4.25 (d, *J* = 12.9 Hz, 1 H), 4.38 (d, *J* = 12.9 Hz, 1 H), 5.51 (d, *J* = 4.1 Hz, 1 H), 5.63 (d, *J* = 4.7 Hz, 1 H), 7.28–7.42 (m, 10 H, Ph).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 14.0, 14.1, 40.4, 40.6, 61.4, 61.9, 62.5, 64.7, 65.3, 65.4, 96.7, 98.0, 127.5, 127.8, 128.3, 128.4, 129.2, 129.4, 135.8, 136.8, 170.7, 172.3.

The mixture of 3,5-*cis* and 3,5-*trans* isomers **20** (185 mg, 0.74 mmol) was dissolved in anhyd DCE (0.80 mL), the reaction flask was flushed with argon, and BSTFA (0.79 mL, 2.98 mmol) was added dropwise. The mixture was stirred at r.t. for 2 h. The solvent was evaporated to dryness in vacuo. The products were separated by column chromatography (silica gel, hexanes–EtOAc, 90:10).

3,5-*cis*-21a
Colorless oil; yield: 50 mg (0.15 mmol, 21%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.06 [s, 9 H, $OSi(CH_3)_3$], 1.26 (t, *J* = 6.9 Hz, 3 H, OCH_2CH_3), 2.53 (ddd, *J* = 2.0, 6.9, 13.0 Hz, 1 H, H4a), 2.62 (ddd, *J* = 5.7, 8.9, 13.0 Hz, 1 H, H4b), 3.50 (dd, *J* = 7.3, 8.9 Hz, 1 H, H3), 3.99 (d, *J* = 13.4 Hz, 1 H, NCH_2Ph), 4.11–4.20 (m, 3 H, NCH_2Ph, OCH_2CH_3), 5.52 (dd, *J* = 2.0, 5.7 Hz, 1 H), 7.26 (t, 1 H, Ph), 7.30 (t, 2 H, Ph), 7.40 (d, 2 H, Ph).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 0.1, 14.1, 42.5, 61.2, 62.0, 65.8, 95.7, 127.4, 128.1, 129.6, 136.4, 170.1.

Anal. Calcd for $C_{16}H_{25}NO_4Si$: C, 59.41; H, 7.79; N, 4.33. Found: C, 59.69; H, 7.56; N, 4.60.

3,5-*trans*-21b
Colorless oil; yield: 115 mg (0.36 mmol, 48%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.17 [s, 9 H, $OSi(CH_3)_3$], 1.19 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 2.49 (ddd, *J* = 1.2, 7.0, 12.3 Hz, 1 H, H4a), 2.70 (ddd, *J* = 4.7, 8.2, 12.3 Hz, 1 H, H4b), 3.91 (dd, *J* = 7.6, 8.2, 1 H, H3), 4.09 (q, *J* = 7.0 Hz, 2 H, OCH_2CH_3), 4.16 (d, *J* = 12.9 Hz, 1 H, NCH_2Ph), 4.37 (d, *J* = 12.9 Hz, 1 H, NCH_2Ph), 5.58 (d, *J* = 4.7 Hz, 1 H), 7.26 (t, 1 H, Ph), 7.31 (t, 2 H, Ph), 7.40 (d, 2 H, Ph).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 0.2, 14.1, 42.4, 61.2, 65.5, 65.6, 98.0, 127.4, 128.3, 129.2, 137.0, 171.0.

Anal. Calcd for $C_{16}H_{25}NO_4Si$: C, 59.41; H, 7.79; N, 4.33. Found: C, 59.65; H, 7.67; N, 4.55.

Acknowledgment

The authors are grateful to the Slovak Grant Agency (No. 1/0236/09 and No. 1/0115/10) and EU Structural Funds (ITMS 262 401 20001, 262 401 20025).

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