Evaluation of Protecting Groups for 3-Hydroxyisoxazoles − Short Access to 3-Alkoxyisoxazole-5-carbaldehydes and 3-Hydroxyisoxazole-5-carbaldehyde, the Putative Toxic Metabolite of Muscimol ☆[1]

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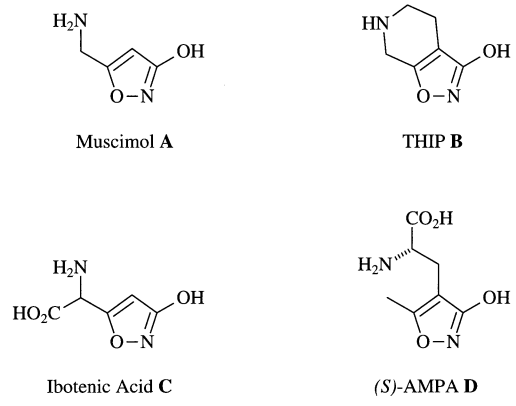
The regioselectivity of the 3-hydroxyisoxazole-5-ester **1** is studied with respect to *O*- versus *N*-alkylation. 3-*O*-Alkyl products **2** are highly favoured with benzyl, benzhydryl, and allyl bromide (≥ 91:9), in contrast to known uses of 5-alkyl-3-hydroxyisoxazoles or when methylation with diazomethane (or methyl iodide) is effected. Methoxymethylation leads to the *N*-substituted isoxazolinone **3e** only. On reduction with DIBAH, the esters **2** afford 3-*O*-protected 3-hydroxyisoxazole-5-carbaldehydes **4** (75−98%). For removal of the benzyl protecting groups, three variations (HBr/HOAc, H_2/Pd/$BaSO_4$, NBS/AIBN) were found useful with 5-ester, 5-formyl, and 5-hydroxymethyl derivatives. The free 3-hydroxy-5-carbaldehyde **9**, the putative toxic metabolite of the GABA agonist muscimol, is prepared accordingly. The *O*-protected 3-hydroxyisoxazole-5-carbaldehydes **4** constitute versatile intermediates in various routes to analogues of CNS-active amino acids and can now be obtained in a highly efficient manner.

Muscimol **A**[2] (5-aminomethyl-3-hydroxyisoxazole), the psycho-active, toxic constituent of the mushrooms *Amanita muscaria* and *A. pantherina*, is known to be a potent agonist of the $GABA_A$ receptor (GABA = γ-aminobutyric acid).[3] Since the discovery of its remarkable CNS activity, much attention has been focussed on the synthesis of related 3-hydroxyisoxazoles (Figure 1).[4−20] The most common examples are 4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridin-3-ol (THIP; **B**),[2][9a] a bicyclic and less toxic analogue of muscimol, and the glutamic acid analogues ibotenic acid (**C**),[3b][14] and (*S*)-2-amino-3-(3-hydroxy-4-isoxazolyl)propionic acid [(*S*)-AMPA; **D**][2][3b][5b]. THIP (**B**) has been subjected to clinical trials with epileptic patients, but no significantly positive effects were detected.[8b] The above compounds may be regarded as conformationally restricted bioisosteres[15] of neurotransmitters such as γ-aminobutyric acid (GABA),[3a] glutamic acid, or *N*-methyl-D-aspartic acid (NMDA).[3b] Although the 3-hydroxyisoxazole moiety thus represents an important group, only a few general approaches for their synthesis are presently known.[16]

We now give a full account of the synthesis of *O*-protected 3-hydroxyisoxazole-5-carbaldehydes **4**.[1d][1e] If efficient deprotections were feasible, such intermediates might serve as versatile building blocks for short syntheses of new 3-hydroxyisoxazoles, with the aldehyde function allowing for various modifications of the side-chain in position 5. We chose the commercially available 3-hydroxyisoxazole-5-ester **1**[17] as a starting and test material, in order to transform it into various 5-carbaldehydes **4** after OH protection and subsequent reduction of the intermediate esters **2** (see Scheme 1).

Figure 1. Examples of naturally occurring or synthetic 3-hydroxyisoxazoles of pharmaceutical interest



So far, *O*-protection has mostly been effected by methylation of 3-hydroxyisoxazole anions with methyl iodide or diazomethane.[4][11][16][18][21] However, this gives rise to mixtures of the two regioisomeric *O*- and *N*-alkylated products (vide infra), which have to be separated by chromatography. Rather limited studies exist concerning the dependence of the *O*/*N*-regioisomer formation on the substitution pattern of the 3-hydroxyisoxazole and on the type of reagent.[11b][19a][21] For example, methylation of 3-hydroxy-4,5-dimethylisoxazole with methyl iodide/potassium carbonate led to the *N*-methylisoxazolidinone only, while a ratio of 58:42 of *O*/*N*-methyl derivatives was produced on reaction with diazomethane.[11b][21] Similar results were found with 5-(diethoxymethyl)-3-hydroxyisoxazole.[19a] Notably, benzylation here[19a] and with 3-hydroxy-5-methylisoxazole

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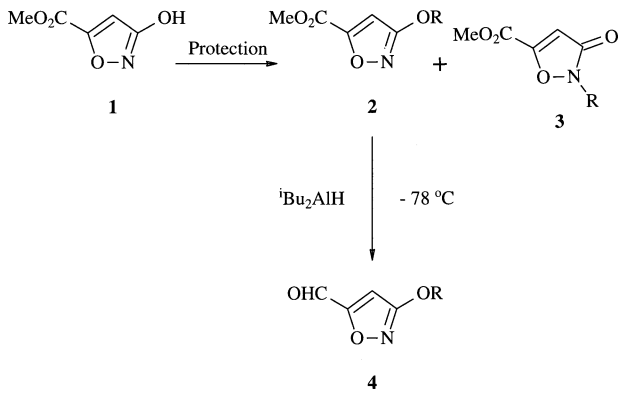
Scheme 1. Preparation of protected 3-hydroxyisoxazole-5-esters **2** and -carbaldehydes **4**



2, 3	a	b	c	d	e
R	Me	Bn	Bzh	All	MOM

4	a	b	c	d
R	Me	Bn	Bzh	All

(tachigarene)[10a] led to mixtures with regioisomeric ratios of 62:38 and 56:44, respectively, for *O*-/*N*-benzyl products. Another disadvantage of using methoxy derivatives is that rather harsh conditions are required for the final *O*-demethylation (e. g. reflux in 48% HBr[7a]). There are few examples of the use of the benzyl (Bn),[10a][19] *p*-methoxybenzyl (PMB),[8a] methoxymethyl (MOM),[5] phenylsulfonyl,[20] or benzoyl[21] groups in this series.

We have examined the suitability of various protecting groups for 3-hydroxyisoxazoles, in order to find out whether they could selectively be introduced at the oxygen atom and removed under mild reaction conditions. As shown below, only 3-*O*-alkyl compounds (isoxazolol derivatives) are subject to clean reduction of the 5-ester function to the formyl group. The *O*/*N*-alkyl ratios observed when the 3-hydroxyester **1** was submitted to several such transformations are summarized in Table 1.

Table 1. Ratios of *O*-/*N*-alkyl products **2** and **3** from 3-hydroxyisoxazole **1**

Entry	R	Reagent, Method	**2**/**3**[a]	Yield [%][b]
1	Me	CH_2N_2, A	73:27	57 (**2a**) 21 (**3a**)
2	Bn	$PhCH_2Br$, B	94:6	93 (**2b**) 5 (**3b**)
3	Bzh	Ph_2CHBr, B	> 95:5	94 (**2c**) – (**3c**)
4	All	$H_2C{=}CHCH_2Br$, B	91:9	80 (**2d**) 8 (**3d**)
5	MOM	$(MeO)_2CH_2$, C	< 5:95	– (**2e**) 97 (**3e**)
6[21]	Me	MeI	58:42	57 (**2a**) 41 (**3a**)

[a] Ratios determined from the crude reaction product by ^{13}C NMR. – [b] Yield of isolated, analytically pure products; reaction conditions: A: Et_2O, 0°C; B: K_2CO_3, acetone, reflux; C: P_4O_{10}, $CHCl_3$, room temp.

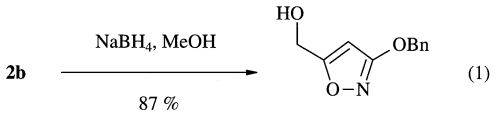
While the isomer ratio of methylation with diazomethane (entry 1) is within the usual range, the *O*-benzyl, *O*-benzhydryl, and *O*-allyl products were formed with unexpectedly high regioselectivity (entries 2–4). Although small in terms of energy (a change from 73:27 to 94:6 corresponds to a difference of only 1 kcal/mol in free activation enthalpies, $\Delta\Delta G^{\neq}_{298}$), this effect of the 5-methoxycarbonyl substituent is of great practical significance.

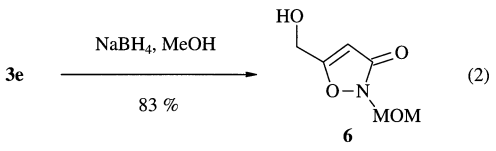
The highest *O*/*N*-product ratio was obtained in the case of the benzhydryl group (entry 3), a typical S_N1-type alkylating agent. The allyl and benzyl reagents proved slightly less regioselective (entries 2 and 4). However, the use of the somewhat less effective benzyl group (entry 2) eventually turned out to be preferable, since the benzhydryl group showed a tendency to migrate in some of the subsequent reactions studied.[1a] An example of a protecting group, which could be introduced selectively at the nitrogen atom, is the methoxymethyl moiety (entry 5); however, here the DIBAH reduction to the respective aldehyde failed and intractable mixtures were formed (vide infra).[1] On the other hand, the 3-*O*-alkyl-hydroxyisoxazoles **2a–d** could readily be reduced to the corresponding aldehydes **4a–d** by means of diisobutylaluminium hydride (DIBAH) (see Table 2). With the free 3-hydroxyisoxazole ester **1**, this had only led to mixtures and low yields.[1c]

Table 2. DIBAH reduction of *O*-alkylated 3-hydroxyisoxazole-5-esters **2**

Entry	R	Starting material	Product	Yield [%]
1	Me	**2a**	**4a**	93
2	Bn	**2b**	**4b**	98
3	Bzh	**2c**	**4c**	90
4	All	**2d**	**4d**	75

The merits of the above two-step sequence to produce 3-*O*-protected isoxazole-5-carbaldehydes **4** are evident on comparison with earlier approaches: For example, the aldehyde **4a** had been obtained in 5 steps in 4% yield from 2-(2-nitrovinyl)furan[2a][11b][18b][19b] or from 3,3-diethoxypropyne in 5 steps in 21% yield,[19a] as a key intermediate in syntheses of, inter alia, muscimol,[2a][18b] ibotenic acid,[19a] and homoibotenic acid.[11b] With sodium tetrahydridoborate[19c], clean reduction of the ester group to the primary alcohol occurred in **2b** to give **5** and in the isoxazolinone **3e** to give **6** (eqs. 1, 2).





With viable methods for protection of the OH function of the isoxazole ester **1** and efficient reductions at hand, appropriate methods for deprotection were studied (see Table 3). Three variations were found to be successful for the benzyl ethers: (i) Acid-catalyzed cleavage of the ester **2b**

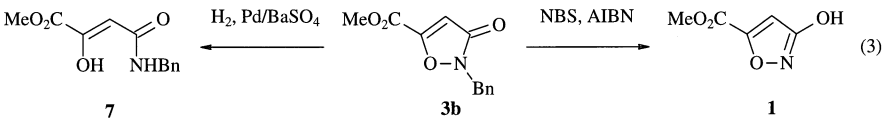
with 33% HBr/HOAc at room temperature: This gave back the free hydroxyisoxazole ester **1** in good yield (entry 1), under conditions similar to those applied earlier for deprotection of 3-methoxyisoxazoles[4][11][16][18] or 3-benzyloxyisoxazoles.[19b] (ii) Catalytic hydrogenation (entry 2): Although sporadic examples using Pd on C are known in the literature,[9a] hydrogenolysis of the *O*-benzyl bond of isoxazolol derivatives proved troublesome at first. However, the use of Rosenmund's catalyst (Pd on $BaSO_4$) in most cases gave none of the acyclic by-products and the free hydroxyisoxazole **1** was again isolated in good yield (entry 2). (iii) Alternatively, deprotection of the *O*-alkyl esters **2b** with NBS, according to Anson et al,[22] could also be achieved in high yield (entry 3).

Table 3. Deprotection of *O*- and *N*-benzyl-3-hydroxyisoxazole derivatives[a]

Entry	Starting material	Method	Product	Yield [%]
1	**2b**	A	**1**	88
2	**2b**	B	**1**	84
3	**2b**	C	**1**	98
4	**3b**	B	**7**	91
5	**3b**	C	**1**	96
6	**4b**	B	**8**	98
7	**5**	B	**8**	98
8	**4b**	A	**9**	61

[a] Method A: 33% HBr/HOAc, room temp., 1 d; Method B: H_2, $Pd/BaSO_4$, MeOH; Method C: NBS, AIBN, CCl_4, ΔT, then H_2O.

With the isoxazolinone ester **3b**, catalytic hydrogenation (method B) led to ring cleavage and gave the acetoacetamide **7**; however, deprotection with NBS occurred smoothly (entries 4, 5 and eq. 3).



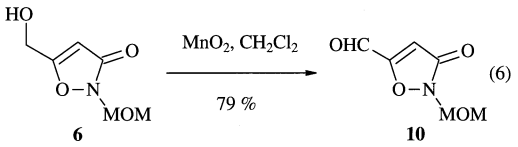
7 3b 1

A further objective of this work dealt with the preparation of the 3-hydroxyisoxazole-5-carbaldehyde **9**. DIBAH reduction of the ester **1** had failed (vide supra). Catalytic hydrogenation of the supposedly suitable precursor **4b**, however, caused removal of the *O*-benzyl group along with reduction of the aldehyde function. Thus, the free 5-hydroxymethylisoxazole **8** was obtained in nearly quantitative yield, similar to the result with the 3-benzyloxy alcohol **5** (entries 6, 7 and eq. 4).

Finally, the free 3-hydroxyisoxazole-5-carbaldehyde (**9**) was prepared from the benzyloxy aldehyde **4b**, using 33% HBr/HOAc, in 61% yield (eq. 5). This aldehyde had first been prepared by Nakamura et al.[18a][19a] starting from 3,3-diethoxypropyne, in 50% yield over 5 steps. It is presumed to be the first major metabolite of muscimol and supposedly causes the pronounced toxicity of this compound.[2] It is further known, that muscimol is degraded rapidly in vivo, probably by transamination catalyzed by GABA aminotransferase; while this should afford the aldehyde **9**, actual metabolites of muscimol have not yet been identified[2] and the toxicity of **9** remains to be studied.

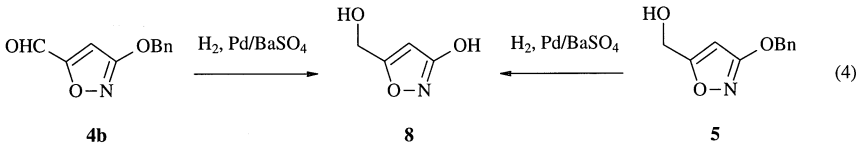
The protected aldehydes **4**, notably the benzyl derivative **4b**, have proven useful for syntheses of, inter alia, vinylenemuscimol[1d][1e] and 3-hydroxyisoxazolyl-substituted β-lactams,[23] to be detailed elsewhere.

As mentioned above, only the 3-alkoxyisoxazole-5-esters underwent clean reduction to afford the appropriate aldehydes. In order to complement the above scheme, an approach towards *N*-alkylated isoxazolinone-5-carbaldehydes was also sought: Indeed, oxidation of the alcohol **6** with manganese dioxide[24] gave rise to the aldehyde **10** (eq. 6), another potential intermediate in the synthesis of 3-hydroxyisoxazoles of pharmacological interest.

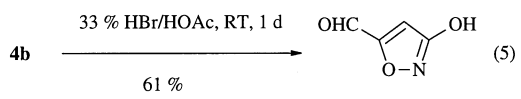


6 10

In conclusion, we have devised a short route towards protected 3-hydroxyisoxazole-5-carbaldehydes **4** and **10**, versatile key intermediates in the synthesis of known or new 3-hydroxyisoxazoles of pharmacological interest. These aldehydes are readily available in gram quantities in two steps (up to 91% overall yield), starting from the commercially available isoxazole ester **1**, by regioselective *O*-alkylation and subsequent DIBAH reduction. Further studies based on this work are in progress.



4b 8 5



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Experimental Section

Solvents and reagents were purified and dried according to standard procedures. − TLC analyses were done on Si60 F_{254}-coated aluminium sheets (E. Merck) using ethyl acetate/petroleum ether (b.p. 30−75°C) mixtures; detection by UV at 254 nm or phosphomolybdic acid (10% in EtOH). Silica gel 0.040−0.063 mm (E. Merck) was used for flash chromatography, with eluents as above. − Melting points were determined with a Tottoli apparatus, Fisher Jones 4017 or a heat bar (Kofler system) and are uncorrected. − B.p. refer to bath temperatures of kugelrohr distillations. − IR spectra were recorded with a Perkin-Elmer 4120 or Bruker IFS 28 spectrometer. − NMR spectra were obtained with Bruker AC 200 and 250 spectrometers (^{1}H: 200.1, 250.1 MHz; ^{13}C: 50.3, 62.9 MHz), with TMS as internal standard; evaluation of ^{1}H-NMR spectra according to first-order interpretation; multiplicity of ^{13}C-NMR signals from DEPT spectra. − Mass spectra were recorded with a Finnigan MAT 95 spectrometer.

Introduction of Protecting Groups

Methyl 3-(Methoxy)isoxazole-5-carboxylate (**2a**) *and Methyl 2-Methyl-3-oxoisoxazoline-5-carboxylate* (**3a**): At −5°C, a suspension of 5.20 g (36.4 mmol) of the ester **1**[17] in 40 ml of diethyl ether was treated with 130 ml of a ca. 0.4 M ethereal diazomethane solution. The reaction mixture was stirred for 18 h at −5°C and filtered to remove starting material (270 mg, 5%). Excess diazomethane was destroyed by addition of acetic acid (10 ml). The solution was washed with sat. aqueous $NaHCO_3$ (3 × 30 ml), dried with $MgSO_4$, and concentrated to afford 4.5 g (79%) of a yellow solid. The two regioisomers **2a**, **3a** (ratio 73:27 by ^{1}H NMR) were separated by flash chromatography (ethyl acetate/petroleum ether, 1:1) to yield 3.25 g (57%) of analytically pure *O*-methyl ester **2a** and 1.20 g (21%) of analytically pure *N*-methyl ester **3a,** both as colourless crystals. − **2a**: M.p. 71−72°C (ref.[21][25] 72−73°C). − IR (KBr): $\tilde{\nu}$ = 1745 cm^{-1} (C=O), 1605, 1410, 1310, 800. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.96 (s, 3 H, $COOCH_3$), 4.03 (s, 3 H, OCH_3), 6.55 (s, 1 H, 4-H). − ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 52.7 (q, $COOCH_3$), 57.4 (q, OCH_3), 100.6 (d, C-4), 157.0 (s, C-5), 160.4 (s, $COOCH_3$), 172.0 (s, C-3). − $C_6H_7NO_4$ (157.0): calcd. C 45.86, H 4.46, N 8.92; found C 46.04, H 4.56, N 8.81. − **3a**: M.p. 123−124°C (ref.[21] 120−121°C). − IR (KBr): $\tilde{\nu}$ = 1725 cm^{-1} (C=O), 1665 (NC=O), 1380, 1305, 910. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.60 (s, 3 H, $COOCH_3$), 3.95 (s, 3 H, OCH_3), 6.40 (s, 1 H, 4-H). − ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 32.4 (q, $COOCH_3$), 53.1 (q, OCH_3), 106.1 (d, C-4), 156.4 (s, C-5), 156.6 (s, C-3), 164.5 (s, $COOCH_3$). − $C_6H_7NO_4$ (157.0): calcd. C 45.86, H 4.46, N 8.92; found C 45.40, H 4.42, N 8.63.

Methyl 3-(Benzyloxy)isoxazole-5-carboxylate (**2b**) *and Methyl 2-Benzyl-3-oxoisoxazoline-5-carboxylate* (**3b**): A suspension of 3.50 g (24.5 mmol) of ester **1** and 6.9 g (50 mmol) of K_2CO_3 in 60 ml of acetone was heated to 70°C for 1 h. After addition of 6.3 g (37 mmol) of benzyl bromide over a period of 30 min, stirring was continued for 3 h at 70°C and for an additional 18 h at room temp. The mixture was filtered and concentrated in vacuo to afford 8.0 g of a pale-yellow oil (**2b**, **3b** and some benzyl bromide). The mixture was filtered through silica gel (column 10 cm × 3 cm) with petroleum ether/ethyl acetate (95:5) and the products were eluted with ethyl acetate, to give 5.32 g of a yellowish solid after the removal of volatiles, containing **2b**/**3b** = 91:9 (GC analysis). Separation of the two regioisomers by flash chromatography on silica gel (column 25 cm × 3 cm, ethyl acetate/petroleum ether, 6:4) afforded 5.25 g (93%) of *O*-benzylisoxazole **2b** and 310 mg (5%) of *N*-benzyl derivative **3b**, both as colourless crystals, in analytically pure form. − **2b**: M.p. 43°C. − IR (KBr): $\tilde{\nu}$ = 1735 cm^{-1} (C=O), 1500, 1460, 1360. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.90 (s, 3 H, CH_3), 5.29 (s, 2 H, OCH_2), 6.55 (s, 1 H, 4-H); 7.25−7.40 (m, 5 H, C_6H_5). − ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 52.6 (q, CH_3), 72.0 (t, OCH_2), 100.7 (d, C-4); 128.2, 128.3, 128.5 (3 d, *o*-, *m*-, *p*-C_6H_5), 135.2 (s, *i*-C_6H_5), 156.9 (s, C-5), 160.3 (COOMe), 171.8 (s, C-3). − $C_{12}H_{11}NO_4$ (233.2): calcd. C 61.80, H 4.71, N 6.01; found C 61.90, H 4.68, N 5.90. − **3b**: M.p. 99°C. − IR (KBr): $\tilde{\nu}$ = 1725 cm^{-1} (C=O), 1670 (NC=O), 1255. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.90 (s, 3 H, CH_3), 5.13 (s, 2 H, NCH_2), 6.40 (s, 1 H, 4-H), 7.34 (s, 5 H, C_6H_5). − ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 49.5 (q, CH_3), 53.0 (t, NCH_2), 106.2 (d, C-4); 128.0, 128.3, 128.6 (3 d, *o*-, *m*-, *p*-C_6H_5), 134.0 (s, *i*-C_6H_5), 156.5 (s, C-5), 160.0 (COOMe), 164.4 (s, C-3). − $C_{12}H_{11}NO_4$ (233.2): calcd. C 61.80, H 4.71, N 6.01; found C 61.88, H 4.83, N 5.79.

Methyl 3-(Benzhydryloxy)isoxazoline-5-carboxylate (**2c**): A suspension of 0.78 g (5.5 mmol) of ester **1** and 1.52 g (11.0 mmol) of K_2CO_3 in 15 ml of acetone was heated to 70°C for 1 h. After addition of 1.37 g (7.0 mmol) benzhydryl bromide over a period of 15 min, stirring was continued for 3 h at 70°C and for 12 h at room temp. The mixture was filtered and concentrated in vacuo to afford 1.98 g of a pale yellow oil (**2c**/**3c** > 95:5). The residue was purified by filtration through silica gel (column 15 cm × 3 cm) with petroleum ether/ethyl acetate (95:5; to remove excess benzhydryl bromide), then petroleum ether/ethyl acetate (80:20), which gave, after removal of the solvents, 1.60 g (94%) of analytically pure *O*-benzhydryl compound **2c** as colourless needles, m.p. 159°C. − IR (KBr): $\tilde{\nu}$ = 1730 cm^{-1} (C=O), 1655, 1265. − ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.82 (s, 3 H, CH_3), 6.34 (s, 1 H, $OCHPh_2$), 6.80 (s, 1 H, 4-H), 7.16−7.32 (m, 5 H, C_6H_5). − ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 53.6 (q, CH_3), 63.4 (d, $OCHPh_2$), 106.3 (d, C-4); 128.3, 128.4, 128.7 (3 d, *o*-, *m*-, *p*-C_6H_5); 137.0 (s, *i*-C_6H_5), 156.7 (s, C-5), 157.5 (COOMe), 166.0 (s, C-3). − $C_{18}H_{15}NO_4$ (309.3): calcd. C 69.90, H 4.89, N 4.53; found C 70.11, H 4.87, N 4.47.

Methyl 3-(Allyloxy)isoxazole-5-carboxylate (**2d**) *and Methyl 2-Allyl-3-oxoisoxazoline-5-carboxylate* (**3d**): A suspension of 286 mg (2.00 mmol) of the ester **1** and 552 mg (4.00 mmol) of K_2CO_3 in 10 ml of acetone was heated to 60−70°C for 1 h. After addition of 363 mg (24.0 mmol) of allyl bromide over a period of 20 min, stirring was continued for 3.5 h at 60−70°C (TLC control). The mixture was filtered through silica gel and concentrated in vacuo to afford 330 mg of a yellow oil (**2d**/**3d** = 91:9 from ^{1}H NMR). Separation of the two regioisomers by MPLC on silica gel (ethyl acetate/petroleum ether, 6:4) yielded 213 mg (80%) of analytically pure *O*-allyl ester **2d** as a colourless oil and 21 mg (8%) of analytically pure *N*-allyl ester **3d** as colourless crystals, m.p. 47°C. − On a larger scale (16 mmol of **1**), practically identical results were obtained. The pure regioisomers did not rearrange on heating to 140°C in xylene for 12 h. − **2d**: IR (KBr): $\tilde{\nu}$ = 1735 cm^{-1} (C=O), 1600, 1305, 1285, 1220, 1105, 995. − ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.28 (s, 3 H, $COOCH_3$), 4.54 (dt, $^3J_{1',2'}$ = 5.7, $^4J_{1',3'E}$ = $^4J_{1',3'Z}$ = 1.3 Hz, 2 H, 1′-H), 5.01 (dm, $^3J_{2',3E'}$ = 10.5 Hz, 1 H, 3′-H_E), 5.15 (dm, $^3J_{2',3Z'}$ = 17.2 Hz, 1 H, 3′-H_Z), 5.78 (ddt, $^3J_{1',2'}$ = 5.6, $^3J_{2',3E'}$ = 10.5, $^3J_{2',3Z'}$ = 17.2 Hz, 1 H, 2′-H), 6.34 (s, 1 H, 4-H). − ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 52.7 (q, OCH_3), 70.8 (t, C-1′), 100.7 (d, C-4), 119.2 (t, C-3′), 131.5 (d, C-2′), 157.0 (s, C-5), 160.1 (s, COOMe), 171.1 (s, C-3). − $C_8H_9NO_4$ (183.2): calcd.

C 52.51, H 4.91, N 7.64; found C 52.77, H 4.78, N 7.54. – **3d**: IR (KBr): $\tilde{\nu}$ = 1735 cm^{-1} (C=O), 1660 (NC=O), 1635, 1240. – ^1H NMR (C_6D_6, 200 MHz): δ = 2.92 (s, 3 H, $COOCH_3$), 3.90 (dt, $^3J_{1',2'}$ = 5.8, $^4J_{1',3'E}$ = $^4J_{1',3'Z}$ = 1.3 Hz, 2 H, 1′-H), 4.69 (dm, $^3J_{2',3'E}$ = 10.1 Hz, 1 H, 3′-H_E), 4.74 (dm, $^3J_{2',3'Z}$ = 17.1 Hz, 1 H, 3′-H_Z), 5.28 (ddt, $^3J_{1',2'}$ = 5.8, $^3J_{2',3E}$ = 10.1, $^3J_{2',3Z}$ = 17.1 Hz, 1 H, 2′-H), 5.87 (s, 1 H, 4-H). – ^{13}C NMR (C_6D_6, 50.3 MHz): δ = 48.3 (q, 1′-H), 52.1 (q, COO*C*H_3), 106.2 (d, C-4), 119.2 (t, C-3′), 128.3 (d, C-2′), 156.7 (s, C-5), 161.2 (s, COOMe), 168.5 (s, C-3). – $C_8H_9NO_4$ (183.2): calcd. C 52.51, H 4.91, N 7.64; found C 52.83, H 4.74, N 7.71.

Methyl 2-(Methoxymethyl)3-oxoisoxazoline-5-carboxylate (**3e**): A solution of 143 mg (1.00 mmol) of the ester **1** and 3.8 g (50 mmol) of 2,2-dimethoxypropane in 5 ml of $CHCl_3$ was treated with 3.0 g (10 mmol) of P_4O_{10}, as described for the case of aliphatic alcohols.[26] The resulting mixture was stirred for 22 h at room temp., poured onto 20 ml of saturated aqueous Na_2CO_3, separated, and cautiously extracted with $CHCl_3$ (2 × 20 ml). The combined organic layers were washed with 30 ml of saturated aqueous NaCl, dried with Na_2SO_4, and concentrated in vacuo to afford 248 mg of a pale-yellow oil. Filtration through silica gel (methyl *tert*-butyl ether/petroleum ether, 8:2) and subsequent kugelrohr distillation (0.1 mbar, 120–140°C) afforded 148 mg (79%) of analytically pure **3e** as a colourless oil. – IR (CCl_4): $\tilde{\nu}$ = 1745 cm^{-1} (C=O), 1697 (C=O), 1247, 1230, 1105, 1045. – ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.43 (s, 3 H, OCH_3), 3.98 (s, 1 H, $COOCH_3$), 5.25 (s, 2 H, NCH_2), 6.41 (1 H, 4-H). – ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 53.1 (q, COO*C*H_3), 57.2 (q, OCH_3), 74.9 (t, NCH_2), 105.5 (d, C-4), 156.5 (s, C-5), 157.8 (s, C-3), 165.0 (s, *C*OOCH$_3$). – $C_7H_9NO_5$ (187.0): calcd. C 44.92, H 4.81, N 7.49; found C 44.83, H 4.80, N 7.43.

Reductions

3-Methoxyisoxazole-5-carbaldehyde (**4a**). – *Typical Procedure:* A 25-ml flask, purged with N_2, was charged with a solution of 850 mg (5.40 mmol) of **2a** in 10 ml of anhydrous CH_2Cl_2. At –78°C, 6.5 ml (6.5 mmol) of DIBAH (1 M solution in hexane) was added dropwise by means of a syringe. Stirring was continued for 1 h at –78°C. After hydrolysis with 1 ml of saturated aqueous NH_4Cl and 5 ml of 2 N HCl, the two layers were separated and the aqueous solutes was extracted with CH_2Cl_2 (5 × 5 ml). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to afford 746 mg of a pale-yellow oil. The crude product was purified by kugelrohr distillation (115°C, 20 mbar; ref.[19a] b.p. 100–105°C, 19 Torr) to yield 635 mg (93%) of analytically pure aldehyde **4a** as a colourless oil. – IR (CCl_4): $\tilde{\nu}$ = 1710 cm^{-1} (C=O), 1415, 1380, 1100, 1030. – ^1H NMR ($CDCl_3$, 200 MHz): δ = 4.04 (s, 3 H, OCH_3), 6.67 (s, 1 H, 4-H), 9.84 (s, 1 H, CHO). – ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 57.8 (q, OCH_3), 100.4 (d, C-4), 166.0 (s, C-5), 172.4 (s, C-3), 178.9 (d, CHO). – C_5H_5NO (127.0): calcd. C 47.24, H 3.94, N 11.02; found C 47.02, H 4.03, N 11.17.

3-(Benzyloxy)isoxazole-5-carbaldehyde (**4b**): According to the Typical Procedure given for **4a**; 933 mg (4.0 mmol) of ester **2b**, 4.8 ml (4.8 mmol) of DIBAH (1 M solution in hexane) in 15 ml of anhydrous CH_2Cl_2 were allowed to react for 1 h at –78°C. Hydrolysis with 0.5 ml of saturated aqueous NH_4Cl and 2 ml of 2 N HCl was followed by extraction with 5 × 10 ml CH_2Cl_2. Kugelrohr distillation (120–140°C, 0.05 mbar) afforded 780 mg (98%) of analytically pure aldehyde **4b** as a colourless oil that crystallized on standing (ref.[19a]: b.p. 114–116°C/1 Torr, m.p. 42.5–43.5°C). – IR (CCl_4): $\tilde{\nu}$ = 1730 cm^{-1} (C=O), 1695, 1590, 1495, 1440, 1355, 1280, 1030, 745, 695. – ^1H NMR ($CDCl_3$, 200 MHz): δ = 5.30 (s, 2 H, OCH_2), 6.57 (s, 1 H, 4-H), 7.24–7.42 (m, 5 H, C_6H_5), 9.74 (s, 1 H, CHO). – ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 72.2 (t, OCH_2Ph), 100.0 (d, C-4); 128.0, 128.2, 128.6 (3 d, *o*-, *m*-, *p*-C_6H_5); 135.0 (s, *i*-C_6H_5), 165.8 (s, C-5), 171.4 (s, C-3), 178.4 (d, CHO). – $C_{11}H_9NO_3$ (203.2): calcd. C 65.02, H 4.46, N 6.89; found C 64.78, H 4.40, N 6.73.

3-(Benzhydryloxy)isoxazole-5-carbaldehyde (**4c**): According to the Typical Procedure given for **4a**, 1.01 g (3.30 mmol) of ester **2c**, 4.7 ml (4.7 mmol) of DIBAH (1 M solution in hexane) in 20 ml of anhydrous CH_2Cl_2 were allowed to react for 3 h at –78°C. Hydrolysis with 4.5 ml of MeOH and 10 ml of 1 N HCl was followed by extraction with 3 × 10 ml CH_2Cl_2. Evaporation of the solvents in vacuo afforded 830 mg (90%) of analytically pure aldehyde **4c**, colourless crystals, m.p. 84–85°C. – IR ($CDCl_3$): $\tilde{\nu}$ = 1715 cm^{-1} (C=O), 1490, 1455, 1035. – ^1H NMR ($CDCl_3$, 250 MHz): δ = 6.62 (s, 1 H, 4-H), 6.76 (s, 1 H, $CHPh_2$), 7.2–7.6 (m, 10 H, C_6H_5), 9.75 (s, 1 H, CHO). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 83.5 (d, $OCPh_2$), 100.1 (d, C-4); 126.5, 128.4, 128.6 (3 d, *o*-, *m*-, *p*-C_6H_5); 139.3 (s, *i*-C_6H_5), 165.8 (s, C-5), 170.8 (s, C-3), 178.6 (d, CHO). – $C_{17}H_{13}NO_3$ (279.3): calcd. C 73.11, H 4.69, N 5.02; found C 73.14, H 4.80, N 4.64.

3-Allyloxyisoxazole-5-carbaldehyde (**4d**): According to the Typical Procedure given for **4a**, 2.2 g (12.0 mmol) of ester **2d**, 15 ml (15.0 mmol) of DIBAH (1 M solution in hexane) in 30 ml of anhydrous CH_2Cl_2 were allowed to react for 75 min at –78°C. Hydrolysis with 1.5 ml of saturated aqueous NH_4Cl and 3 ml of 2 N HCl, extraction with 5 × 30 ml CH_2Cl_2, and Kugelrohr distillation (120–140°C, 0.01 mbar) afforded 1.37 g (75%) of analytically pure aldehyde **4d** as a colourless oil. – IR ($CDCl_3$): $\tilde{\nu}$ = 1700 cm^{-1} (C=O), 1590, 1495. – ^1H NMR ($CDCl_3$, 200 MHz): δ = 4.81 (dt, $^3J_{1',2'}$ = 5.7, $^4J_{1',3'E}$ = $^4J_{1',3'Z}$ = 1.5 Hz, 2 H, 1′-H), 5.35 (dt, $^3J_{1',3'E}$ = $^3J_{3'E,3'Z}$ = 1.5, $^3J_{2',3'E}$ = 10.4 Hz, 1 H, 3′-H_E), 5.45 (dt, $^3J_{1',3'Z}$ = $^3J_{3'E,3'Z}$ = 1.5, $^3J_{2',3'Z}$ = 17.2 Hz, 1 H, 3′-H_Z), 6.07 (ddt, $^3J_{1',2'}$ = 5.7, $^3J_{2',3'E}$ = 10.4, $^3J_{2',3'Z}$ = 17.2 Hz, 1 H, 2′-H), 6.66 (s, 1 H, 4-H), 9.84 (s, 1 H, CHO). – ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 70.2 (t, C-1′), 100.0 (d, C-4), 119.1 (t, C-3′), 131.2 (d, C-2′), 165.6 (s, C-5), 171.1 (s, C-3), 178.5 (d, CHO). – $C_7H_7NO_3$ (153.1): calcd. C 54.90, H 4.61, N 9.14; found C 54.86, H 4.87, N 9.13.

3-Benzyloxy-5-(hydroxymethyl)isoxazole (**5**): At 0°C 35 mg (0.91 mmol) of sodium tetrahydridoborate was added to a solution of 163 mg (0.70 mmol) of ester **2b** in 5 ml of MeOH. The mixture was stirred for 22 h, hydrolyzed with 10 ml of MeOH and 20 ml of 1 N HCl and extracted with CH_2Cl_2 (3 × 20 ml). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. Filtration through silica gel (column 4 cm × 3 cm, ethyl acetate/petroleum ether, 3:7) and subsequent kugelrohr distillation (120°C, 0.001 mbar) yielded 124 mg (87%) of analytically pure alcohol **5** as a colourless oil. – IR ($CDCl_3$): $\tilde{\nu}$ = 1506 cm^{-1}, 1457, 1365 (s), 818, 784, 651 (s) – ^1H NMR ($CDCl_3$, 250 MHz): δ = 4.62 (s, 2 H, 5-C*H*$_2$OH), 5.23 (s, 2 H, OCH_2Ph), 5.89 (s, 1 H, 4-H); 7.31–7.53 (m, 5 H, C_6H_5). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 56.8 (t, CH_2OH), 71.6 (t, OCH_2Ph), 93.5 (d, C-4), 128.2, 128.5, 128.6 (3 d, *o*-, *m*-, *p*-C_6H_5), 135.6 (s, *i*-C_6H_5); 171.6, 172.3 (2 s, C-3, C-5). – $C_{11}H_{11}NO_3$ (205.2): calcd. C 64.38, H 5.40, N 6.83; C 64.04, H 5.56, N 6.78.

5-Hydroxymethyl-2-(methoxymethyl)isoxazoline-3-one (**6**): At 0°C, 526 mg (13.9 mmol) of sodium tetrahydridoborate was added to a solution of 260 mg (1.39 mmol) of ester **3e** in 10 ml of MeOH, and the reaction mixture was stirred at room temp. for 18 h. After hydrolysis with 2 ml of 2 M H_2SO_4, 5 g of strongly acidic ion exchange resin (Lewatit S 100 G1) was added. The mixture was filtered using 100 ml of methanol, then 5 g of weakly basic ion exchange resin (Lewatit MP 62) was added. After filtration and rins-

ing with 100 ml of methanol, the filtrate was concentrated in vacuo (45°C, 0.1 mbar) to afford 237 mg of a pale-yellow oil. Purification of this material by filtration through silica gel (20 g, column 8 cm × 3 cm, 400 ml of ethyl acetate) yielded 183 mg (83%) of analytically pure alcohol **6** as a colourless oil. − IR ($CDCl_3$): $\tilde{\nu}$ = 1679 cm^{-1} (NC=O), 1378, 1097, 922, 727 (s). − ^1H NMR ($CDCl_3$, 250 MHz): δ = 3.34 (s, 3 H, OCH_3), 3.88 (br., 1 H, OH), 4.47 (d, J = 5.0 Hz, 2 H, 5-CH_2OH), 5.08 (s, 2 H, NCH_2O), 5.69 (s, 1 H, 4-H). − ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 56.7 (q, OCH_3), 57.2 (t, CH_2OH), 75.2 (t, NCH_2O), 97.5 (d, C-4), 167.9 (s, C-3), 173.6 (s, C-5). − $C_6H_9NO_4$ (159.1): calcd. C 45.28, H 5.70, N 8.80; found C 44.96, H 5.64, N 8.58.

Deprotection

Methyl 3-Hydroxyisoxazole-5-carboxylate (**1**) *from 3-O-Benzylisoxazole* **2b**. − *Method A* (HBr/acetic acid): A solution of 221 mg (0.95 mmol) of the ester **2b** in 5 ml of 33% HBr in glacial acetic acid was stirred for 1 d at room temp. After evaporation of the solvents (40°C, 0.1 mbar), the remainder was dried in a desiccator (KOH) and recrystallized from $CHCl_3$ to afford 120 mg (88%) of the analytically pure ester **1** as colourless crystals, m.p. 164−165°C (ref.[17] 165°C), with spectroscopic data identical to those reported.[17] − $C_5H_5NO_4$ (143.1): calcd. C 41.97, H 3.52, N 9.79; found C 41.98, H 3.39, N 9.76.

Method B (Hydrogenation with $Pd/BaSO_4$). − *Typical Procedure:* A suspension of 55 mg $Pd/BaSO_4$ (5%) in 5 ml of MeOH was stirred under H_2 (1 bar) in a Schlenk tube until hydrogen consumption had stopped. A solution of 62 mg (0.25 mmol) of the ester **2b** was added and the reaction mixture was again stirred until hydrogen uptake had stopped. Solids were removed by means of a centrifuge, washed with methanol (3 × 10 ml), and the combined solutions were concentrated in vacuo. Recrystallization of the residue from $CHCl_3$ afforded 32 mg (84%) of spectroscopically and analytically pure ester **1** as colourless crystals, m.p. 164−165°C (ref.[17] 165°C).

Method C (NBS, AIBN): According to the procedure of Anson et al.[22], a solution of 106 mg (0.455 mmol) of the 3-*O*-benzylisoxazole **2b**, 88 mg (0.49 mmol) of NBS and 5 mg (0.3 μmol) of AIBN in 7 ml of CCl_4 was heated at reflux for 2 h. After evaporation of the solvents in vacuo, the residue was dissolved in 20 ml of ethyl acetate and washed with 10 ml of water. The aqueous layer was extracted with ethyl acetate (3 × 15 ml) and the combined organic layers were dried with Na_2SO_4. After evaporation of the solvents in vacuo the crude product (162 mg of a yellow oil) was purified by flash chromatography (silica gel, 25 g, column 10 cm × 3 cm, ethyl acetate/petroleum ether, 7:3) to yield 64 mg (98%) of the pure (vide supra) hydroxyisoxazole **1** as colourless crystals, m.p. 164−165°C (ref.[17] 165°C).

Hydrogenation of the N-Benzylisoxazolinone **3b**, *2-Hydroxy-2-butenedicarboxylic Acid 4-Benzylamide 1-Methyl Ester* (**7**): According to Method B, 69 mg (0.30 mmol) of isoxazolinone **3b**, 56 mg $Pd/BaSO_4$ and 10 ml of MeOH. Recrystallization of the crude product (67 mg) from CH_2Cl_2/petroleum ether yielded 63 mg (91%) of analytically pure benzylamide **7** as colourless crystals, m.p. 131−132°C. − IR (KBr): $\tilde{\nu}$ = 3335 cm^{-1}, 1725, 1635, 1545, 1290, 1240, 985, 765, 725, 682. − ^1H NMR ([D_6]acetone, 250 MHz): δ = 3.80 (s, 3 H, OCH_3), 4.51 (d, $^3J_{1',NH}$ = 6.0 Hz, 2 H, 1′-H), 6.12 (s, 1 H, 3-H), 7.26−7.37 (m, 5 H, C_6H_5), 8.1 (br., 1 H, NH), 13.8 (br., 1 H, 2-OH). − ^{13}C NMR ([D_6]acetone, 62.9 MHz): δ = 43.4 (t, NCH_2Ph), 52.8 (q, OCH_3), 98.9 (d, C-3); 128.1, 128.5, 129.4 (3 d, *o*-, *m*-, *p*-C_6H_5); 139.9 (s, *i*C_6H_5), 163.5 (s, C-1), 171.6 (s, C-4), 203.1 (s, C-2). − MS (CI, CH_4); *m*/*z* (%): 264 (10) [M^+ + C_2H_5], 236 (100) [M^+ + H], 176 (20) [M^+ − COOMe], 91 (20) [$C_7H_7^+$]. − $C_{12}H_{13}NO_4$ (235.2): calcd. C 61.27, H 5.57, H 5.95; found C 60.94, H 5.55, N 5.84.

Methyl 3-Hydroxyisoxazole-5-carboxylate (**1**) *from N-Debenzylation of Isoxazolinone* **3b** *with NBS:* According to Method C, a solution of 83 mg (0.36 mmol) of *N*-benzylisoxazolinone **3b**, 69 mg (0.39 mmol) of NBS, and 5 mg (0.3 μmol) of AIBN in 5 ml of CCl_4 was heated under reflux for 2 h and worked up as described above. The crude product (110 mg, yellow oil) was purified by flash chromatography (silica gel, 20 g, column 8 cm × 3 cm, ethyl acetate/petroleum ether, 6:4) to give 48 mg (96%) of pure hydroxyisoxazole **1** (vide supra) as colourless crystals, m.p. 164−165°C (ref.[17] 165°C).

3-Hydroxy-5-(hydroxymethyl)isoxazole (**8**) *by Hydrogenation of the 3-O-Benzyloxyaldehyde* **4b**: According to Method B, 100 mg (0.49 mmol) of aldehyde **4b**, 30 mg $Pd/BaSO_4$, 10 ml of MeOH. Yield 55 mg (98%) of analytically pure hydroxyisoxazole **8** as colourless crystals, m.p. 78−79°C [**8** had been obtained in a 7-step sequence[27] as a yellow, impure syrup, with ^1H-NMR data (in D_2O) in accord with data given below]. − IR (KBr): $\tilde{\nu}$ = 3600−2600 cm^{-1}, 1620, 1520, 1330, 1055. − ^1H NMR (CD_3OD, 250 MHz): δ = 4.56 (s, 2 H, CH_2OH), 5.93 (s, 1 H, 4-H). − ^{13}C NMR (CD_3OD, 62.9 MHz): δ = 58.4 (t, CH_2OH), 95.8 (d, C-4), 173.7 (s, C-5), 176.2 (s, C-3). − MS (FAB pos, NBA); *m*/*z* (%): 116 (100) [M^+ + H], 55 (20) [$C_2H_2NO^+$ + H]. − $C_4H_5NO_3$ (115.1): calcd. C 41.75, H 4.38, N 12.17; found C 41.48, H 4.36, N 11.79.

3-Hydroxy-5-hydroxymethylisoxazole (**8**) *by Hydrogenation of the 3-O-Benzyloxyalcohol* **5**: According to Method B, 210 mg (1.02 mmol) of alcohol **5**, 90 mg $Pd/BaSO_4$ and 15 ml of MeOH. Yield 112 mg (98%) of analytically pure hydroxyisoxazole **8** as colourless crystals, m.p. 78−79°C; data as above.

3-Hydroxyisoxazole-5-carbaldehyde (**9**) *by Cleavage of the Benzyloxy Compound* **4b** *with HBr:* According to Method A, a solution of 203 mg (1.00 mmol) of the aldehyde **4b** in 3 ml of 33% HBr in glacial acetic acid was stirred for 24 h at room temp. (TLC control). After evaporation of the solvents in vacuo, the viscous, yellow residue was dried in a desiccator (KOH) and recrystallized from benzene to afford 70 mg (61%) of analytically pure aldehyde **9** as colourless crystals, m.p. 141°C (ref.[18a][19a] 141−142°C). − IR (KBr): $\tilde{\nu}$ = 3280−2840 cm^{-1} (OH), 1710 (C=O), 1495. − ^1H NMR ([D_6]DMSO, 200 MHz): δ = 6.85 (s, 1 H, 4-H), 9.74 (1 H, CHO). − ^{13}C NMR ([D_6]DMSO, 62.9 MHz): δ = 100.4 (d, C-4), 166.0 (s, C-5), 171.8 (s, C-3), 178.5 (d, CHO). − $C_4H_3NO_3$ (114.1): calcd. C 42.49, H 2.67, N 12.39; found C 42.62, H 2.78, N 12.04.

2-(Methoxymethyl)-3-oxoisoxazoline-5-carbaldehyde (**10**): Manganese dioxide (3.18 g) was added to a solution of 318 mg (2.00 mmol) of the alcohol **6** in 2 ml of CH_2Cl_2. The reaction mixture was stirred for 18 h, filtered through Celite, and concentrated in vacuo. Purification of the residue by kugelrohr distillation (110°C, 0.35 mbar) afforded 248 mg (79%) of analytically pure aldehyde **10** as a colourless oil. − IR ($CDCl_3$): $\tilde{\nu}$ = 1705 cm^{-1} (vs), 1670 (s), 1115, 925, 719 (s). − ^1H NMR ($CDCl_3$, 250 MHz): δ = 3.40 (s, 3 H, OCH_3), 5.21 (s, 2 H, NCH_2), 5.95 (s, 1 H, 4-H), 9.89 (s, 1 H, CHO). − ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 57.0 (q, OCH_3), 75.6 (t, NCH_2O), 100.2 (d, C-4), 168.1 (s, C-5), 173.7 (s, C-3), 179.3 (d, CHO). − $C_6H_7NO_4$ (157.1): calcd. C 45.87, H 4.49, N 8.91; found C 46.04, H 4.35, N 9.00.

☆ Dedicated to Professor *Waldemar Adam* on the occasion of his 60th birthday.

[1] Taken in part from: [1a] M. Schön, Dissertation, Stuttgart **1997**; − [1b] R. Riess, Dissertation, Würzburg, **1993**; − [1c] S. Laschat, Diplomarbeit, Würzburg, **1987**. Preliminary results reported in:

– [1d] M. Schön, S. Laschat, R. Riess, V. Jäger, *3-Hydroxyisoxazole-5-carbaldehydes – Versatile Key Intermediates in the Synthesis of New 3-Hydroxyisoxazoles*, 5th Blue Danube Symposium on Heterocyclic Chemistry, Castá-Papiernicka, Slovak Republic, 14.–17.6.1995, PO–56, Proceedings p. 127 and [1e] M. Schön, S. Laschat, R. Riess, V. Jäger, *New Approach to 3-Hydroxyisoxazole-5-carbaldehydes – Key Intermediates in the Synthesis of New 3-Hydroxyisoxazoles of Pharmacological Interest*, Article 059, "1st Electronic Conference on Heterocyclic Chemistry", H. S. Rzepa, J. P. Snyder, C. Leach (Eds.); The Royal Society of Chemistry, **1997**, ISBN 0-85404-894-4.

[2] [2a] L. Brehm, P. Krogsgaard-Larsen, K. Schaumburg, *Acta Chem. Scand., B* **1981**, *35*, 311–324. – [2b] F. V. De Feudis, *Rev. Pure Appl. Pharmacol. Sci.* **1982**, *3,* 319–379. – [2c] K. Bowden, A. C. Drysdale, *Tetrahedron Lett.* **1965**, 727–728.

[3] [3a] *GABA Neurotransmitters* (Eds.: P. Krogsgaard-Larsen, J. Scheel-Krüger, H. Kofod) Munksgaard, Copenhagen, **1990**. – [3b] P. Krogsgaard-Larsen, "Amino Acid Receptors", in *Comprehensive Medicinal Chemistry*, vol. 3 (Eds.: C. Hansch, P. G. Sammes, J. B. Taylor), Pergamon Press, Oxford, **1990**, 493–537. – [3c] P. Krogsgaard-Larsen, B. Frølund, F. S. Jørgensen, A. Schousboe, *J. Med. Chem.* **1994**, *37*, 2489–2505.

[4] T. N. Johansen, K. Frydenvang, B. Ebert, P. Krogsgaard-Larsen, U. Madsen, *J. Med. Chem.* **1994**, *37*, 3252–3262.

[5] [5a] N. Skjærbœk, B. Ebert, E. Falch, L. Brehm, P. Krogsgaard-Larsen, *J. Chem. Soc., Perkin Trans. 1* **1995**, 221–225. – [5b] M. Begtrup, F. A. Sløk, *Synthesis* **1993**, 861–863.

[6] [6a] U. Madsen, B. Bang-Andersen, L. Brehm, I. T. Christensen, B. Ebert, I. T. S. Kristoffersen, Y. Lang, P. Krogsgaard-Larsen, *J. Med. Chem.* **1996**, *39*, 1682–1691. – [6b] R. Amici, P. Pevarello, M. Colombo, M. Varasi, *Synthesis* **1996**, 1177–1179.

[7] [7a] U. Madsen, K. Frydenvang, B. Ebert, T. N. Johansen, L. Brehm, P. Krogsgaard-Larsen, *J. Med. Chem.* **1996**, *39*, 183–190. – [7b] B. Ebert, S. Lenz, L. Brehm, P. Bregnedal, J. J. Hansen, K.; Frederiksen, K. P. Bøgesø, P. Krogsgaard-Larsen, *J. Med. Chem.* **1994**, *37*, 878–884. – [7c] J. J. Hansen, J. Lauridsen, E. Nielsen, P. Krogsgaard-Larsen, *J. Med. Chem.* **1983**, *26*, 901–903.

[8] [8a] B. Frølund, U. Kristiansen, L. Brehm, A. B. Hansen, P. Krogsgaard-Larsen, E. Falch, *J. Med. Chem.* **1995**, *38*, 3287–3296. – [8b] H. Hjeds, I. T. Christensen, C. Cornett, B. Frølund, E. Falch, J. B. Pedersen, P. Krogsgaard-Larsen, *Acta Chem. Scand.* **1992**, *46*, 772–777.

[9] [9a] U. Madsen, E. H. F. Wong, *J. Med. Chem.* **1992**, *35*, 107–111. – [9b] L. Brehm, J. S. Johansen, P. Krogsgaard-Larsen, *J. Chem. Soc., Perkin Trans. 1* **1992**, 2059–2063. – [9c] P. Krogsgaard-Larsen, J. W. Ferkany, E. Ø. Nielsen, U. Madsen, B. Ebert, J. S. Johansen, N. H. Diemer, T. Bruhn, D. T. Beattie, D. R. Curtis, *J. Med. Chem.* **1991**, *34*, 123–130.

[10] [10a] U. Madsen, L. Brehm, P. Krogsgaard-Larsen, *J. Chem. Soc. Perkin Trans. 1* **1988**, 359–364. – [10b] J. Lauridsen, T. Honoré, P. Krogsgaard-Larsen, *J. Med. Chem.* **1985**, *28*, 668–672. – [10c] P. Krogsgaard-Larsen, L. Brehm, J. S. Johansen, P. Vinzents, J. Lauridsen, D. R. Curtis, *J. Med. Chem.* **1985**, *28*, 673–679. – [10d] P. Krogsgaard-Larsen, E. Ø. Nielsen, D. R. Curtis, *J. Med. Chem.* **1984**, *27*, 585–591.

[11] [11a] J. J. Hansen, B. Nielsen, P. Krogsgaard-Larsen, L. Brehm, E. Ø. Nielsen, D. R. Curtis, *J. Med. Chem.* **1989**, *32*, 2254–2260. – [11b] J. J. Hansen, P. Krogsgaard-Larsen, *J. Chem. Soc., Chem. Commun.* **1979**, 87–88; *J. Chem. Soc., Perkin Trans. 1* **1980**, 1826–1833.

[12] S. Mzengeza, R. A. Whitney, *J. Org. Chem.* **1988**, *53*, 4074–4081.

[13] [13a] P. Krogsgaard-Larsen, T. Honoré, J. J. Hansen, D. R. Curtis, D. Lodge, *Nature* **1980**, *284*, 64–66. – [13b] R. L. Johnsen, J. F. Koerner, *J. Med. Chem.* **1988**, *31*, 2057–2065.

[14] N. R. Farnsworth, *Science* **1968**, *162*, 1086.

[15] G. A. Patani, E. J. La Voie, *Chem. Rev.* **1996**, *96*, 3147–3176.

[16] For synthesis of 3-hydroxyisoxazoles in general see, e. g.: M. Sutharchanadevi, R. Murugan in *Comprehensive Heterocyclic Chemistry*, vol. 6 (Eds.: A. R. Katritzky, C. W. Rees), Pergamon Press, London, New York, **1996**, p. 221.

[17] [17a] C. Bennouna, F. Pétrus, J. Verducci, *Bull. Soc. Chim. Fr.* **1980**, 478–480. – [17b] V. Jäger, M. Frey, *Liebigs Ann. Chem.* **1982**, 817–820; M. Frey, V. Jäger, *Synthesis* **1985**, 1100–1104.

[18] [18a] Y. Kishida, T. Hiroako, J. Ide, A. Terada, N. Nakamura, *Chem. Pharm. Bull.* **1966**, *14*, 92. – [18b] P. Krogsgaard-Larsen, S. B. Christensen, *Acta Chem. Scand., B* **1974**, *28*, 636–640; idem, *ibid.* **1976**, *30*, 281.

[19] [19a] Y. Kishida, T. Hiracho, J. Ide, A. Terada, N. Nakamura, *Chem. Pharm. Bull.* **1967**, *15*, 1025–1031; N. Nakamura, *Chem. Pharm. Bull.* **1971**, *19*, 46–51. – [19b] A. R. Gagneux, F. Häfliger, R. Meier, C. M. Eugster, *Tetrahedron Lett.* **1965**, 2081–2084. – [19c] A. Barco, S. Benetti, G. P. Pollini, P. G. Baraldi, M. Guarner, *J. Chem. Research S* **1979**, 176–177.

[20] N. Nakamura, Y. Tajima, S. Sakai, *Heterocycles* **1982**, *17*, 235–245.

[21] G. Schlewer, P. Krogsgaard-Larsen, *Acta Chem. Scand., B* **1984**, *38*, 815–819.

[22] M. S. Anson, J. G. Montana, *Synlett* **1994**, 219–221.

[23] M. Schön, V. Jäger, in preparation.

[24] [24a] A. J. Fatiadi, *Synthesis* **1976**, 65–104; idem, *ibid.* 133–167. – [24b] N. J. P. Broom, J. S. Elder, P. C. T. Hannan, J. E. Pons, P. J. O'Hanlon, G. Walker, J. Wilson, P. Woodall, *J. Antibiot.* **1995**, *48*, 1336–1344.

[25] [25a] A. Melikian, G. Schlewer, J.-P. Chambon, C. G. Wermuth, *J. Med. Chem.* **1992**, *35*, 4092–4097. – [25b] K. Bowden, G. Crank, W. J. Ross, *J. Chem. Soc. C* **1968**, 172–185.

[26] K. Fuji, S. Nakano, E. Fujita, *Synthesis* **1975**, 276–277.

[27] H. Göth, A. R. Gagneux, C. H. Eugster, H. Schmid, *Helv. Chim Acta* **1967**, *50*, 137–142; J. R. Geigy A.-G., Belg. Pat. 665,-249 (Dec. 10, 1965); *Chem. Abstr.* **1966**, *65*, 2266e.

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