Isoxazolinium Salts in Asymmetric Synthesis. 1. Stereoselective Reduction Induced by a 3'-Alkoxy Stereocentre. A New Approach to Polyfunctionalized β-Amino Acids* [1, 2]

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Dedicated to Professor Ulrich Schmidt on the occasion of his 80th birthday

A new approach to optically active *N*-methylamino acids is presented, relying on stereoselective reduction of *N*-methylisoxazolinium salts with a dioxyethyl side-chain. The diastereoselectivity of the reduction step is studied systematically, in comparison with that of respective isoxazolines. A two-step transformation of isoxazolinium salts – with $NaBH_3(OAc)$ and subsequent catalytic hydrogenation as well as a one-pot reduction by catalytic hydrogenation led to high (95:5 and 87:13) diastereomeric ratios of protected *erythro*-*N*-methylaminopentanetriols. The hydroxyethyl side-chain is elaborated by oxidation to afford the β-*N*-methylamino acid **37**, exemplifying the potential of this strategy.

Key words: Isoxazolinium Salts, Methylamino Alcohols, Diastereoselective Reduction, Homoserine, β-Amino Acids

Introduction

The development of concise approaches for access to amino/imino polyols and acids continues to stimulate efforts of synthetically oriented chemists. Concerning amino acids, the synthesis of structures with multiple other functions and/or branched units at the α- or β-position has attracted wide-spread interest, due to extraordinary properties and challenging problems to be overcome [3 – 7]. In many of these studies additions to the C=N bond of imines or imine derivatives, both linear and cyclic, have been used, mostly involving chiral substrates or chiral *N*-bound auxiliaries [8].

Our own work in this field has been concerned with various routes to amino/imino polyols and acids, notably with the use of isoxazoline intermediates [9, 10], with imines derived from optically active aldehydes [11, 12], or additions to nitrones [13, 14] (from oxime cyclizations [13]) which may undergo Cope-House cyclization with suitable olefinic side-chains present [14]. Other strategies followed involved diastereoselective nitroaldol additions [15] and ring-opening of epoxypentenols obtained by asymmetric Sharpless epoxidation of divinylcarbinol [16].

The isoxazoline route has occasionally been drawn upon for the synthesis of hydroxy amino or imino acids [9, 10, 17 – 20]. Reductions with often high and predictable diastereoselectivity of isoxazolines occur by means of lithium aluminium hydride [9], but this cannot be applied to the case of isoxazoline-3-esters or -carboxylic acids [17d, 20]. On the other hand, catalytic hydrogenation of such esters has proceeded with little or no selectivity [9, 17b – d, 19, 20]. In order to avoid the accompanying ester reduction, carboxy group acid equivalents have been used [9], such as the oxazolinyl group [17a], *p*-anisyl [17c], 2,5-dimethoxyphenyl [17c], and 2-furyl [17c, 18], with the latter giving most satisfactory results [9a – c, 17c, 21]. Diol units protected as acetals are particularly suited to that purpose, first because of their inertness towards $LiAlH_4$ (and other strong nucleophiles and bases), and second, because thereby one may introduce optical

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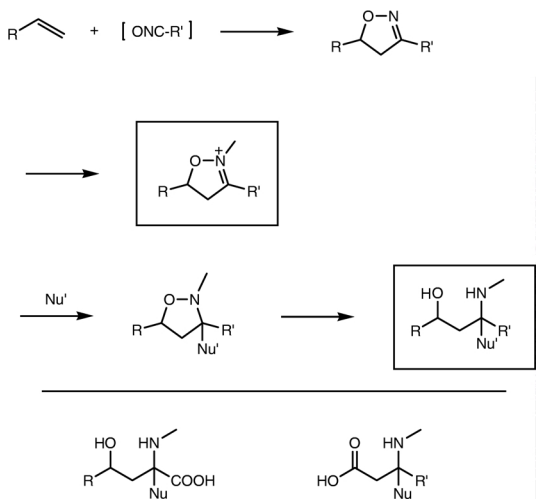
activity and induce asymmetric induction in addition steps [11, 17d – e, 18, 20, 22, 23].

Unfortunately, the C=N bond of isoxazolines is rather unreactive towards attack of nucleophiles other than hydride from $LiAlH_4$. With strongly basic nucleophiles such as phenyllithium, mixtures of products are obtained [24], and with hindered strong base such as lithium diisopropylamide deprotonation occurs [9, 10e – f, 17b, 17f, 24]. Activation of isoxazolines towards addition of strongly basic *C*-nucleophiles is possible, however, according to the seminal findings of Uno, Terakawa, and Suzuki, by means of boron trifluoride etherate [25]. Alkyl, aryl, hetaryl, and allyllithium or respective Grignard compounds react well and with high stereoselectivity; the limit was seen with phenylethinyllithium, *t*-butyllithium, phenylmagnesium bromide and lithium dimethylcuprate which failed to react [25a].

Another mode to activate isoxazolines towards addition of even weak nucleophiles should consist in *N*-alkylation, to produce *N*-alkylisoxazolinium salts, a class of compounds actually known since 1955 [26]. Few examples of nucleophilic additions to these – presumably highly reactive – *N*-oxyiminum salts have been reported [27 – 30], for example with sodium borohydride [27], methyl- and phenylmagnesium bromide [27], aqueous base or methoxide [29], and diphenyl phosphite [30]. Systematic studies on the potential utility of isoxazolinium salts in asymmetric synthesis are lacking though.

With the ready availability of isoxazolines, built from alkenes and nitrile oxides, and with the rich chemistry and manifold transformations to acyclic structures in mind, isoxazolinium salts appear as promising candidates for extending this strategy: with nucleophilic additions stereoselective access to *N*-methylisoxazolidines might be found, and subsequent N-O reduction should provide syntheses of branched γ-amino alcohols. Further elaboration of the termini with R and R' would be open, leading to a great variety of polyfunctional, heavily substituted target structures such as branched amino sugars or amino acids (α-, β-, γ- *etc.*). The strategy for uses of isoxazolinium salts in asymmetric amino acid synthesis is summarized in Scheme 1.

The following report is the first part of our studies outlining stereoselective transformations of isoxazolinium salts [2]; it deals with the stereoselectivity of C=N reductions both of isoxazolines and *N*-methylisoxazolinium salts with (di)oxyethyl side-



Scheme 1.

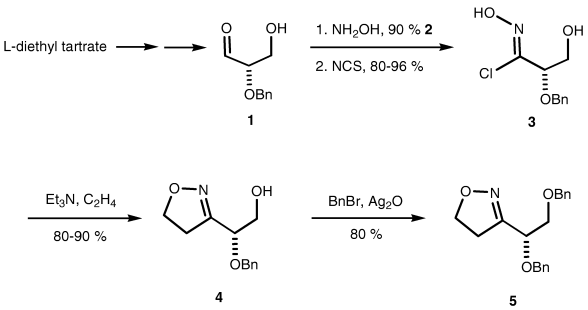
chains and induction from the 1'-stereocentre. It also discloses a new access to β-amino acids by oxidation of the (former) 5-position, as specified by a synthesis of (protected) D-*erythro*-4,5-dihydroxy-3-methylaminopentanoic acid **37**.

Results and Discussion

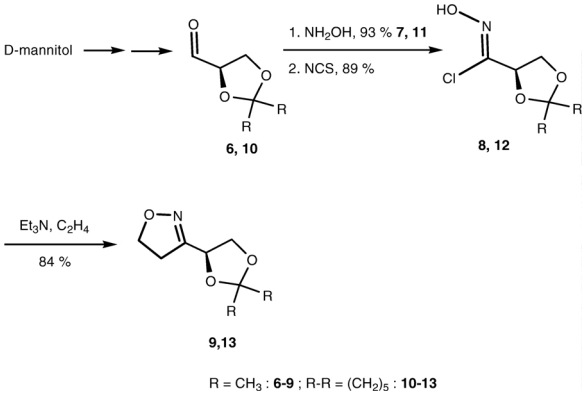
Preparation of isoxazolines and N-methylisoxazolinium tetrafluoroborates

The isoxazolines were prepared by 1,3-dipolar cycloaddition of respective olefins and nitrile oxides obtained in situ from oximes via hydroximoyl chlorides, using standard procedures, see Scheme 2, 3.

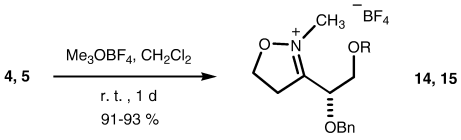
The nitrile oxide derived from 2-*O*-benzyl-L-glyceraldehyde **1** [31] *via* the hydroximoyl chloride **3** [17c – e, 20] smoothly underwent cycloaddition with ethylene, forming the isoxazoline **4** in 88 – 90% yield. The free hydroxy group was benzylated to provide a model substrate **5** with protected *O*-functions in



Scheme 2.



Scheme 3.



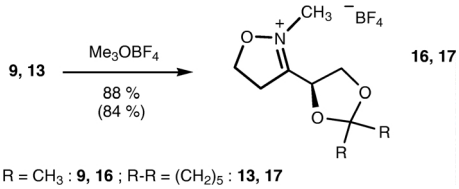
Scheme 4.

an acyclic side-chain (Scheme 2). Derivatives with acetal-protected side-chains **9** and **13** were obtained starting from the respective acetone or cyclohexanone bis(acetals) of D-mannitol, *via* the aldehydes **6** and **10**, the oximes **7** and **11**, and the chlorooximes **8** and **12** (Scheme 3).

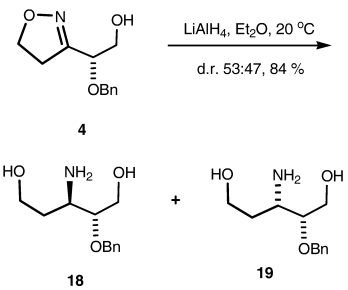
N-Methylation of the isoxazolines **4**, **5**, **9** and **13** was effected with trimethyloxonium tetrafluoroborate in dichloromethane at room temperature following work of Cerri *et al.* [27a] (Schemes 4, 5). The isoxazolinium salts **14**-**17** were obtained in high yield in analytically pure form; in some cases stable, crystalline products were isolated. Remarkably, functional groups such as acetal moieties or even a free hydroxy group proved compatible with these reaction conditions.

Reduction of isoxazolines with 3-dioxyethyl side-chains

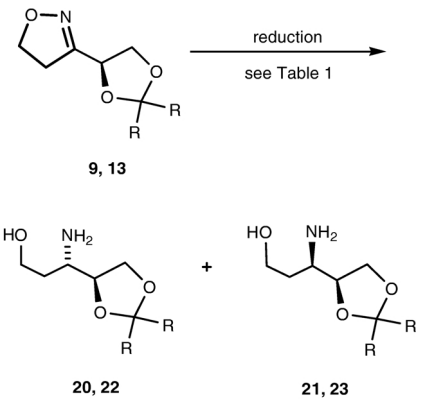
Employing lithium aluminium hydride, the reduction of isoxazolines with 5- and/or 4-substituents proceeds with often excellent stereoselectivity [9, 17, 32]. Catalytic hydrogenations usually are rather unselective [9, 17, 19, 32], unless special combinations of 3- and 5-substituents are present [9, 17d, e, 20]. Asymmetric induction from stereocentres in the 3-side-chain of isoxazolines had not been screened, so representative model compounds **4**, **9** and **13** were chosen for reductions with different reagents. First, $LiAlH_4$ reduction of the



Scheme 5.



Scheme 6.



Scheme 7.

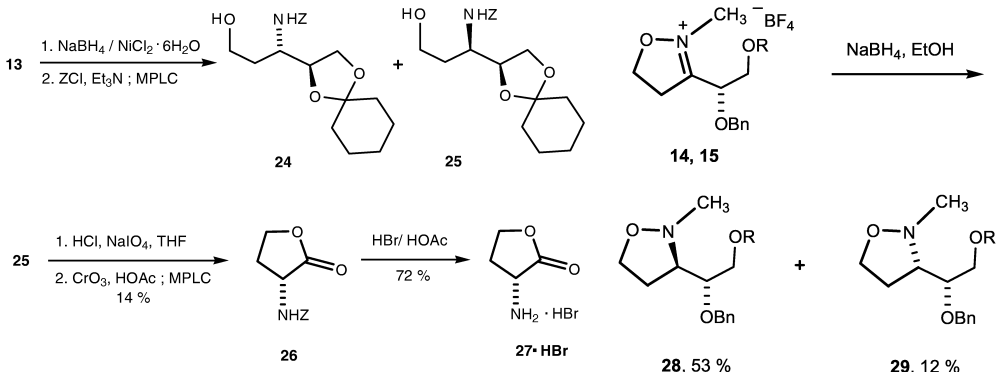
Table 1. Diastereoselective reduction of isoxazolines **9** and **13**.

Entry	Isoxazoline	Reducing Agent	Solvent	Temp. (°C)	d. r. **20/21** or **22/23** (*erythro*/*threo*)	Yield (%)[a]
1	**9**	$LiAlH_4$	Et_2O		45:55	(98)
2	**13**	$LiAlH_4$	Et_2O	25	44:56	(81)
3	**13**	iBu_2AlH	hexane	0	20:80	(51)
4	**13**	$NaBH_4$, $NiCl_2 \cdot 6H_2O$	MeOH	−30	35:65	(97)
5	**13**	H_2, Pd/C	MeOH	25	45:55	(100)
6	**13**	H_2, Rh/Al_2O_3	MeOH	25	20:80	(97)

[a] Spectroscopically pure; not purified further.

isoxazoline **4** with a 2'-OH group was performed, hoping for a chelate effect. This proceeded in good yield (as usual), but in a non-selective way (d. r. of amino alcohols: **18**:**19** = 53:47), see Scheme 6.

In order to avoid the presumed levelling effect of such OH groups, substrates **9** and **13** with ace-



Scheme 8.

tal side-chains were used and various reagents tried, see Scheme 7 and Table 1. Again, with $LiAlH_4$ non-selective reaction was seen (entries 1, 2 in Table 1). Since the cyclohexylidene acetal proved more stable during work-up, the isoxazoline **13** was preferred for most further studies. As seen from the selection of results collected in Table 1, excellent yields of amino alcohols **22**/**23** were obtained from reduction with "nickel boride" ($NaBH_4/NiCl_2 \cdot 6H_2O$) and catalytic hydrogenations. The highest diastereomeric ratios of 80:20 were achieved both with diisobutylaluminium hydride (entry 3) and the rhodium-catalyzed reaction (entry 6).

In order to assign the configuration to these diastereomeric amino alcohols, a mixture of **22**/**23** (d. r. 35:65) was transformed to the *N*-Z derivatives **24**/**25**, which were separated by MPLC. The major isomer **25** was converted into homoserinolactone **27** by acetal hydrolysis, oxidative diol cleavage and *N*-deprotection (see Scheme 8). Comparison of the specific rotation of this with literature data [43] established the configuration of the aminomethylidene centre as (R). The reductions of **13** therefore had furnished the *threo* isomer as the preponderant one. In hydrogenations of isoxazolines usually N-O cleavage occurs first, the new stereocentre is formed with C=N reduction of the intermediate β-hydroxyimine [9, 10d, 17, 20, 32], an acyclic species less amenable to steric induction.

Reduction of isoxazolinium salts; stereochemical course

In contrast to the case of isoxazolines, isoxazolinium salts **14**–**17** smoothly underwent reduction on treatment with sodium borohydride in ethanol, to afford the corresponding isoxazolidines. The substrates **14** and **15**, with an acyclic 3-side-chain, treated this way led to diastereomeric mixtures **28**/**29** and **30**/**31**, respectively, with similar ratios (76:24 from **14**, 73:27 from **15**); the free hydroxy group in **14** thus had little or no effect (Scheme 9).

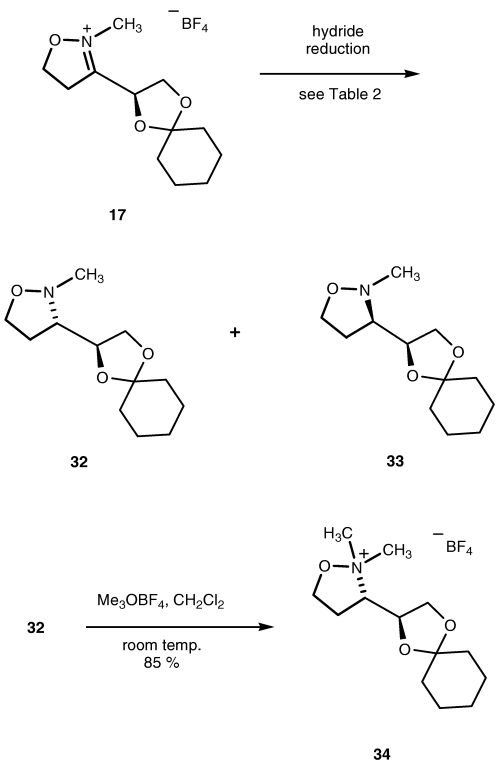
R = H : **14, 28, 29** ; R = Bn : **15, 30, 31**

Scheme 9.

The cyclohexylidene acetal **17** gave somewhat better results (d. r. **32**:**33** = 81:19) under these conditions and was chosen for a more detailed study with a variety of hydride-delivering reagents, see Scheme 10 and Table 2.

As seen from these results, many reagents are suited to this purpose, concerning yield of isoxazolidines **32**/**33**. Except for the case of diisobutylaluminium hydride (entry 6), the *erythro* isomer **32** was the preponderant one throughout, with highest selectivity found for sodium triacetoxyborohydride – rapid reaction even at −78 °C, with a diastereomeric ratio of 95:5.

A remaining problem was how to unambiguously assign the relative configuration to these isoxazolidine pairs. This was not possible from ^{1}H or ^{13}C NMR data; the differences were too small both with ^{1}H and ^{13}C NMR shifts ($\Delta\delta$ 0 – 0.41 and 0 – 1.9, respectively) as well as with coupling constants $J_{3,1'}$ ($\Delta J \leq 1$ Hz). Fortunately, the N-methylisoxazolidine **32** (major isomer) on alkylation with trimethyloxonium tetrafluoroborate gave a crystalline ammonium salt **34**, from which the relative configuration – *erythro* – could be established by X-ray crystal structure analysis [33], see Scheme 10. The course of dominant hydride addition then is presumed to be *anti* to the oxygen substituent at C-1', just as seen with the conformation present in the crystal (Fig. 1), in perfect agreement with the Felkin-Anh-Houk model of such transition states of carbonyl additions [34].



Scheme 10.

Table 2. Reduction of the isoxazolinium salt **17** with hydrides.

Entry	Reagent	Solvent	Temp. (°C)	Reaction time	d. r.[a] **32/33**	Yield[b,c] (%)
1	$NaBH_4$	EtOH	20	1 d	81:19	84
2	$NaBH_4$	EtOH	−30	7 h	84:16	65
3	catecholborane	THF	−78	*ca.* 1 min	90:10	(79)
4	$LiBHEt_3$	THF	−78	*ca.* 1 min	76:24	84
5	$LiBH(iBu)_3$	THF	−78	*ca.* 1 min	82:18	(73)
6	$(iBu)_2AlH$	THF	−78	*ca.* 1 min	37:63	83
7	$LiAlH(OtBu)_3$	THF	−78	*ca.* 1 min	65:35	78
8	$NaAlH_2(OR)_2$ (Red-Al)	THF	−78	15 min	61:39	84
9	$NaBH(OAc)_3$	THF	0	*ca.* 1 min	93: 7	81
10	$NaBH(OAc)_3$	THF	−78	*ca.* 1 min	95: 5	86

[a] From ^{13}C NMR of crude product or after chromatography; [b] yield relates to analytically pure material, otherwise put in brackets; [c] further reagents tested: $Zn(BH_4)_2$ gave low recovery of products (24%) with good d. r. (90:10); $LiBH_4$, $NaBH(OMe)_3$ led to decomposition.

Further transformation of these isoxazolidines to the corresponding *N*-methylamino alcohols was studied next, see Scheme 11.

As expected, hydrogenation with palladium on carbon readily afforded the respective diastereomers **35** and **36** which, of course, tempted to look at direct conversion of isoxazolinium salt to amino alcohols

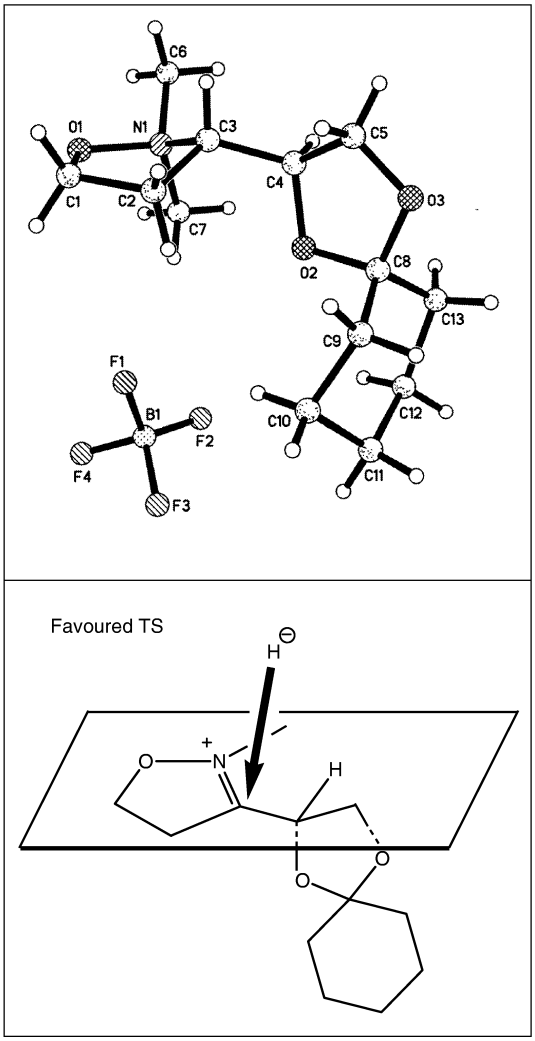
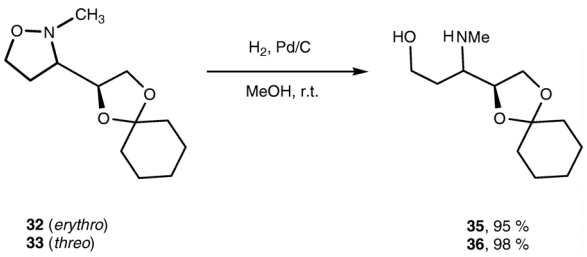
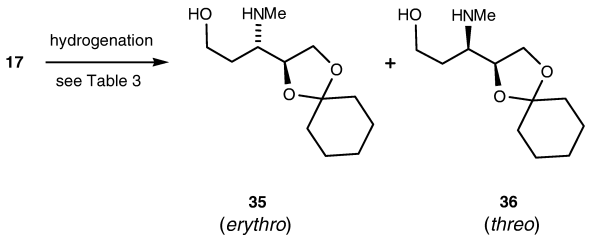


Fig. 1. Conformation of **34** in the crystal and presumed stereochemical course of predominant hydride addition to the precursor **17**.



Scheme 11.

(Scheme 12). Again, a variety of reagents and conditions was tested, with a selection of results gathered in Table 3.



Scheme 12.

Table 3. Amino alcohols **35** and **36** from isoxazolinium salts **17**.

Entry	Reagent(s) (°C)	Temp. **35**/**36**	d. r.[a] (%)	Yield[b]
1	H_2, Pd/C, MeOH	r. t.	80:20	73
2	H_2, Rh/C, MeOH	r. t.	87:13	68
3	H_2, Rh/Al_2O_3, MeOH	r. t.	88:12	(72)
4	$NiCl_2 \cdot 6H_2O/NaBH_4$, MeOH	−78	86:14	(81)
5	1. $NaBH(OAc)_3$, THF	−78	95: 5	
	2. H_2, Pd/C, MeOH		>95: 5	82

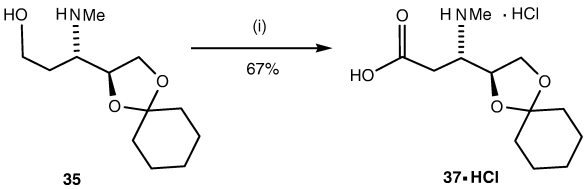
[a] From ^{13}C NMR of crude product; [b] yields refer to isolated, analytically pure material, otherwise put in brackets.

The conditions successful with isoxazolidines – Pd/C catalyst – worked likewise, but with unsatisfactory diastereoselectivity (entry 1 in Table 13). With rhodium catalysts the d. r. of the products **35**/**36** was improved somewhat from 80:20 to 88:12 (entries 2, 3). The "nickel boride" reagent [35] (entry 4) was similarly effective, and probably would be the best choice for large-scale preparative runs. The best method in terms of diastereoselectivity, however, was the two-step reduction with $NaBH(OAc)_3$ with subsequent catalytic hydrogenation (entry 5 in Table 3).

Completion of a new β-amino acid synthesis

One of the incentives of these studies, new approaches to (branched) amino acids, was put to practice with the conversion of the amino alcohol **35** to the corresponding amino acid **37**. After *N*-protection, the Zhao modification of the Jones oxidation [36] was applied and indeed gave spectroscopically pure resinous amino acid product **37**. Analytically pure material was obtained in the form of the hydrochloride **37**·HCl, a crystalline product which also permitted to carry out an X-ray structure determination [37].

In summary, isoxazolinium salts are readily available by 1,3-dipolar cycloaddition of alkenes and nitrile oxides *via* isoxazolines. In contrast to isoxazolines, they display high reactivity towards nucleophiles, as exemplified here with hydride reagents, and they accept these (hydride) in a highly stereoselective way induced by an alkoxy stereocentre in the 3-side-chain. Thus, a basis is laid for the vast field of additions of C-nucleophiles to these substrates, which hitherto have constituted a rather inconspicuous class of compounds. Results of such extensions and applications in synthesis will be forwarded.



Scheme 13. (i) 1. Z-Cl, Et_3N, CH_2Cl_2, 0 °C to r. t., 2 h, 92% of *N*-Z-**35**; 2. H_5IO_6/CrO_3, CH_3CN; 3. H_2 (1 bar), Pd/C, MeOH; 4. HCl (gas), crystallization, 53% from *N*-Z-**35**.

Experimental Section

For general experimental details see ref. [14]. Reagents $NaBH(OAc)_3$ (*ca.* 95%, Fluka); Me_3OBF_4 (Fluka, Aldrich); Pd/C (10%, Degussa); iBu_2AlH (1.0 M in THF, Aldrich); catecholborane (1.0 M in THF, Aldrich); $LiBH_4$ (Fluka); $LiBHEt_3$ (1.0 M in THF, Aldrich); $LiBH(iBu)_3$ (1.0 M in THF, Aldrich); $LiAlH(OtBu)_3$ (1.1 M in THF, Fluka); $NaAlH_2(OCH_2CH_2OMe)_2$ (3.5 M in toluene, Fluka); $NaBH(OMe)_3$ (Janssen); $NaBH(OAc)_3$ (*ca.* 95%, Fluka) were purchased and used without further purification.

CAUTION: Hydroximoyl chlorides are strong skin irritants!

*(1'R)-3-(1'-O-Benzyloxy-2'-hydroxyethyl)-4,5-dihydro-1,2-oxazole (**4**)*

*a) 2-O-Benzyl-L-glyceraldoxime (**2**) [20, 31]*

A solution of K_2CO_3 (19.5 g, 141 mmol) and $HONH_3Cl$ (8.55 g, 94.2 mmol) in water (150 ml) at 0 °C was added dropwise to a stirred solution of the aldehyde **1** [31] (8.65 g, *ca.* 47 mmol) in methanol (150 ml). The mixture warmed up overnight and was rota-evaporated (15 Torr); the cloudy solution was extracted with CH_2Cl_2 (4 × 80 ml), the organic solutes were dried ($MgSO_4$) and the solvent was removed *in vacuo* (10^{-3} Torr). The oxime **2** was obtained as a colorless analytically pure oil; yield 8.23 g (90% from 2-*O*-benzylthreitol [2d, 31]; *E*/*Z*-mixture 86:14 (from NMR), $[\alpha]_D^{20} = 57.9$ ($c = 1.04$, EtOH); $[\alpha]_D^{20} = -62.4$ ($c = 1.51$, EtOH). – IR (film): $\nu = 3300$ (b, OH), 2915, 2860, 1490, 1445, 1090, 930, 735, 695 cm^{-1}. – ^1H NMR (200.1 MHz, $CDCl_3$; *E*/*Z* mixture 75:25); major isomer (*E*): $\delta = 3.66$ (m, 3-H, 3'-H, OH), 4.05 (dM of ABM, $J_{3,2} = 4.6$ Hz, $J_{1,2} = 7.3$ Hz, 2-HM), 4.40, 4.57 (A,B of AB, $J = 11.6$ Hz, CH_2Ph), 7.28 (m, C_6H_5), 7.36 (d, $J_{2,1} = 7.3$ Hz, 1-H), 9.68 (bs, NOH). – Minor isomer (*Z*): $\delta = 4.40$, 4.56 (A,B of AB, $J = 11.5$ Hz, CH_2Ph), 4.77

(m, 2-H), 6.77 (d, $J_{2,1} = 6.0$ Hz, 1-H); other signals coinciding with those of the major isomer. – ^{13}C NMR (50.3 MHz, $CDCl_3$; *E/Z* mixture 75:25); major isomer (*E*): $\delta = 63.21$ (t, C-3), 71.16 (t, CH_2Ph), 76.74 (d, C-2), 127.92, 127.97, 128.37 (3d, C_6H_5), 137.06 (s, *i*-C_6H_5), 149.31 (d, C-1). – Minor isomer (*Z*): $\delta = 62.07$ (t, C-3), 72.09 (t, CH_2Ph), 73.49 (d, C-2), 127.92, 127.97, 128.37 (3d, C_6H_5), 137.06 (s, *i*-C_6H_5), 150.98 (d, C-1). – $C_{10}H_{13}NO_3$ (195.2): calcd. C 61.53, H 6.71, N 7.17; found C 61.79, H 7.09, N 7.10.

*b) 2-O-Benzyl-L-glycerohydroximoyl chloride (**3**)*

According to ref. [38] a solution of the oxime **2** (8.16 g, 41.8 mmol) in abs. DMF (150 ml) was treated with N-chlorosuccinimide (NCS; 6.14 g, 48.0 mmol). First at room temp. *ca.* one fourth of NCS was added and the reaction was started by blowing in 20 ml of gaseous HCl (taken from the vapour of a bottle with conc. hydrochloric acid). The rest of NCS was added portionwise within 20 min and the solution was stirred for another 1.5 h at room temp.; there was slight warming of the mixture which took a light-green color. For work-up, the mixture was put on ice water (400 ml), extracted with ether (4×100 ml) and partitioned against ice water (100 ml). After drying ($MgSO_4$) the solvent was removed on a rotary evaporator (15 Torr), leaving a colorless oil (9.84 g) which contained some DMF (*ca.* 3%) and ether (*ca.* 15%) according to ^{1}H NMR; this crude product was used for the next step. – Yield 8.08 g (corrected), 84%.

Analytically pure hydroximoyl chloride **3** was obtained, when extraction was performed with *tert*-butyl methyl ether (3×60 ml for a 12 mmol run) [17d, 20]; 91% from 2-*O*-benzyl-L-threitol (3 steps). $[\alpha]_D^{20} = -79.7$ ($c = 0.78$, MeOH). – IR (film): $\nu = 3300$ (b, OH), 1653, 1631, 1497, 1455, 1100, 1056, 1028, 984 cm^{-1}. – ^{1}H NMR (200.1 MHz, $CDCl_3$): $\delta = 2.57$ (s, 1 H, OH), 3.76 ("dd", $J_{2,3a} = 5.4$, $J_{3a,b} = 11.7$ Hz, 1 H, 3-H_a), 3.87 ("dd", $J_{2,3b} = 6.7$, $J_{3a,3b} = 11.7$ Hz, 1 H, 3-H_b), 4.30 ("dd", $J_{2,3a} = 5.4$, $J_{2,3b} = 6.7$ Hz, 1 H, 2-H), 4.42, 4.66 (A,B of AB, $J_{A,B} = 11.4$ Hz, 2 H, CH_2Ph), 7.30 – 7.40 (m, 5 H, C_6H_5). – ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 62.7$ (C-3), 71.6 (CH_2Ph), 79.8 (C-2), 128.0 (*p*-C), 128.2 (*o*-C), 128.4 (*m*-C), 136.7 (*i*-C), 139.2 (C-1). – $C_{10}H_{12}NO_3Cl$ (229.7): calcd. C 52.30, H 5.27, N 6.09; found C 51.91, H 5.37, N 5.92.

*c) Isoxazoline (**4**)*

At 0 °C ethylene was bubbled into a solution of the hydroximoyl chloride **3** (crude, 9.79 g, content *ca.* 82%, 35.0 mmol) in toluene (abs., 150 ml). While keeping a slow stream of ethylene in the vessel, a solution of triethylamine in toluene (38.5 ml of a 1.00 M solution, 38.5 mmol) was added dropwise within 43 h (Dosimat, *ca.* 0.015 ml/min). For work-up 1 N HCl (300 ml) was added, the organic layer was removed and the aqueous phase was extracted with ether (3×100 ml). The combined organic solutes were dried ($MgSO_4$) and evaporated (15 Torr), leaving a yellowish oil (6.97 g). This was filtered through silica (column 3 cm × 15 cm) by means of petrol ether/ethyl acetate (3:7), the solvents were removed (15 Torr), and the resulting yellow oil (6.61 g) was submitted to MPLC (column type C, eluent as above). After concentrating the solvents *in vacuo* (10^{-3} Torr), a colorless oil of the isoxazoline **4** (5.52 g, 75% from **3**, 63% from oxime **2**) was recovered which solidified overnight.

M. p. 33 °C; $[\alpha]_D^{20} = -116$ ($c = 1.15$, $CHCl_3$). – IR (KBr): $\nu = 3253$ (OH), 1452 (C=N), 1434, 1104, 1087, 1066, 1048, 1019, 854 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 2.39$ (sb, 1 H, OH), 2.91 – 3.05 (m, 2 H, 4-H), 3.76 – 3.83 (m, 2 H, 2'-H), 4.24 – 4.35 (m, 2 H, 5-H), 4.43 (dd, $J_{1',2'A} = 4.9$, $J_{1',2'B} = 5.8$ Hz, 1 H, 1'-H), 4.52, 4.60 (A, B von AB, $^2J_{AB} = 11.7$ Hz, 2 H, C$H_2C_6H_5$), 7.27 – 7.40 (m, 5 H, C_6H_5). – ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 34.4$ (t, C-4), 63.5 (t, C-2'), 68.6 (t, C-5), 71.6 (t, C$H_2C_6H_5$), 74.7 (d, C-1'), 128.1, 128.6 (2 d, *o*-, *m*-, *p*-C of C_6H_5 – only 2 of the expected 3 signals could be seen), 137.2 (s, *i*-C of C_6H_5), 157.8 (s, C-3). - $C_{12}H_{15}NO_3$ (221.3): calcd. C 65.14, H 6.83, N 6.33; found C 64.96, H 6.77, N 6.36.

*(1R')-3-(1',2'-Dibenzyloxyethyl)-4,5-dihydro-1,2-oxazole (**5**)*

Silver oxide (1.03 g, 4.44 mmol) was added in portions to a solution of the isoxazoline **4** (983 mg, 4.44 mmol) and benzyl bromide (1.15 g, 6.72 mmol) in ether (20 ml). After standing at room temp for 1 h., the suspension was heated to reflux. After 2 d TLC analysis still showed the presence of starting material, therefore more benzyl bromide (760 mg, 4.44 mmol) and Ag_2O (1.03 g, 4.44 mmol) were added. After 5 d the reaction was virtually complete (TLC), Ag salts were filtered off and the precipitate rinsed with abs. ether. After rota-evaporation (15 Torr) of the organic solution, an orange oil (2.21 g) was recovered and filtered through silica (column 3 cm × 14 cm; petrol ether/EtOAc 1:1) to afford 2.13 g of an orange oil. MPLC separation (column type C, petrol ether/EtOAc 85:15) as above gave a colorless, analytically pure oil of the isoxazoline (1.11 g, 80%), solidifying overnight.

M. p. 24 – 25 °C. – $[\alpha]_D^{20} = -51.8$ ($c = 0.97$, CH_2Cl_2). – IR (KBr): $\nu = 1454$ (C=N), 1101, 1083, 1066, 862 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 2.92 - 2.96$ (m, 2 H, 4-H); 3.69 (dd, $J_{1',2'A} = 5.5$, $^2J_{2'A,2'B} = 10.3$ Hz, 2'-H_A), 3.73 (dd, $J_{1',2'B} = 5.9$, $^2J_{2'A,2'B} = 10.3$ Hz, 2'-H_B) – sum 2 H; 4.23 – 4.33 (m, 2 H, 5-H), 4.51 – 4.61 (m, 5 H, 1'-H, 2 C$H_2C_6H_5$), 7.25 – 7.38 (m, 10 H, 2 C_6H_5). – ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 34.1$ (t, C-4), 68.6 (t, C-5), 70.6 (t, C-2'), 71.5 (t, C$H_2C_6H_5$), 73.1 (d, C-1'), 73.4 (t, C$H_2C_6H_5$), 127.75, 127.79, 127.9, 128.0, 128.42, 128.44 (6 d, *o*-, *m*-, *p*-C of 2 C_6H_5), 137.5, 137.7 (2 s, *i*-C of 2 C_6H_5), 157.9 (s,

C-3). – $C_{19}H_{21}NO_3$ (311.4): calcd. C 73.29, H 6.80, N 4.50; found. C 73.15, H 6.85, N 4.55.

General Procedure A, N-methylation of 2-isoxazolines to form N-methylisoxazolinium tetrafluoroborates

In analogy to Gandolfi's procedure [27a, c] 1.1 eq of trimethyloxonium tetrafluoroborate at room temp. was added to a stirred solution of the isoxazoline (0.5 to 15 mmol runs) in CH_2Cl_2 (5 – 30 ml). The mixture was stirred overnight, then rota-evaporated (room temp./15 Torr) to leave the crude salt. For details of isolation and characterization see individual compounds. – In many cases the crude product was used for reduction.

*(1'R)-3-(1'-Benzyloxy-2-hydroxyethyl)-2-methyl-4,5-dihydro-1,2-oxazolium tetrafluoroborate (***14***)*

General Procedure: Isoxazoline **4** (455 mg, 2.01 mmol), Me_3OBF_4 (327 mg, 2.21 mmol), CH_2Cl_2 (abs., 5 ml). The crude product, a colorless oil, was dissolved in EtOH and cooled to −30 °C which made a cloudy oil separate. After decanting carefully, the oil was concentrated (10^{-3} Torr) to give the salt **14** as an analytically pure, colorless oil; yield 602 mg (91%).

$[\alpha]_D^{20} = -9.8$ ($c = 1.18$, MeOH). – IR (Film): $\nu =$ 3539 (OH), 1679 (C=N), 1068, 927, 755 cm^{-1}. – ^1H NMR (500.1 MHz, CD_3OD): $\delta = 3.93 - 3.99$ (m, 2 H, 4-H); 4.09 (t, $^5J_{4,1''} = 2.0$ Hz, NCH_3), 4.10 – 4.17 (m, 2'-H) – sum 5 H; 4.88 – 5.00 (m, 4 H, 5-H, CH_2C$_6$H$_5$), 5.10 – 5.12 (m, 1 H, 1'-H), 7.56 – 7.68 (m, 5 H, C_6H_5). – ^{13}C NMR (125.8 MHz, CD_3OD): $\delta = 39.4$ (t, C-4), 41.2 (q, NCH_3), 63.5 (t, C-2'), 72.3, 75.3 (2 t, C-5, CH_2C$_6$H$_5$), 77.6 (d, C-1'), 130.3, 130.4, 130.5 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 138.6 (s, *i*-C of C_6H_5), 170.3 (s, C-3). – $C_{13}H_{18}BF_4NO_3$ (323.1): calcd. C 48.33, H 5.62, N 4.34; found C 48.27, H 5.84, N 4.17.

*(1'R)-3-(1',2'-Dibenzyloxyethyl)-2-methyl-4,5-dihydro-1,2-oxazolium tetrafluoroborate (***15***)*

The General Procedure A was followed: Isoxazoline **5** (136 mg, 0.44 mmol), Me_3OBF_4 (71 mg, 0.48 mmol), CH_2Cl_2 (abs., 5 ml). The resulting crude product, a colorless oil, was treated as described for **14**; isoxazolinium salt **15** (168 mg, 93%), analytically pure, colorless oil.

$[\alpha]_D^{20} = 0.0$ ($c = 1.12$, CH_2Cl_2) (reproducible value; products prepared from **15** again showed optical activity, *vide infra*). – IR (Film): $\nu = 1681$ (C=N), 1605 (w), 1455, 1365, 1055, 927 cm^{-1}. – ^1H NMR (500.1 MHz, $CDCl_3$): $\delta =$ 3.57 − 3.63 (m, 2 H, 4-H), 3.67 (t, $^5J_{4,1''} = 2.0$ Hz, 3 H, NCH_3); 3.76 (dd, $J_{1',2'A} = 5.6$, $^2J_{2'A,2'B} = 10.5$ Hz, 2'-H_A), 3.80 (dd, $J_{1',2'B} = 4.4$, $^2J_{2'A,2'B} = 10.5$ Hz, 2'-H_B) – sum 2 H; 4.47, 4.49 (A, B of AB, $^2J_{A,B} = 11.9$ Hz, 2 H, CH_2C$_6$H$_5$); 4.60 (ddd, $J_{4A,5A}$, $J_{4B,5A}$, $^2J_{5A,5B} = 7.6$, 9.4, 10.9 Hz, 5-H_A), 4.63 – 4.67 (m, 5-H_B), 4.64, 4.70 (A, B of AB, $^2J_{A,B} = 11.5$ Hz, CH_2C$_6$H$_5$) – sum 4 H; 4.89 – 4.91 (m, 1 H, 1'-H), 7.24 – 7.36 (m, 10 H, 2 C_6H_5). Due to incomplete resolution not all couplings could be identified. – ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 38.1$ (t, C-4), 40.5 (q, NCH_3), 69.1 (t, C-2'), 70.6 (t, C-5), 74.0, 74.1 (2 t, 2 CH_2C$_6$H$_5$), 74.5 (d, C-1'), 128.5, 128.6, 128.9, 128.99, 129.03, 129.1 (6 d, *o*-, *m*-, *p*-C of 2 C_6H_5), 136.6, 137.4 (2 s, *i*-C of 2 C_6H_5), 168.2 (s, C-3). – $C_{20}H_{24}BF_4NO_3$ (413.2): calcd. C 58.13, H 5.85, N 3.39; found C 58.14, H 5.95, N 3.35.

*(1'S)-3-(1',2'-Isopropylidenedioxyethyl)-4,5-dihydro-1,2-oxazole (***9***)*

a) 2,3-*O*-Isopropylidene-D-glyceraldoxime (**7**): prepared according to the literature [39, 40].

b) 2,3-*O*-Isopropylidene-D-glycerohydroximoyl chloride (**8**): Obtained as described for **3**; oxime **7** (3.90 g, 26.9 mmol), NCS (3.95 g, 29.6 mmol), DMF, moist HCl vapour (20 ml). The crude product was a colorless solid, yield 4.41 g, 89% after correction for impurities (DMF 2.6%, ether 0.3%); spectroscopic data in agreement with those given in ref. [39]. The chlorooxime was used for the next step without further purification.

c) Isoxazoline **9**: Prepared as described for **4**; hydroximoyl chloride **8** (4.39 g, content 97%, 23.7 mmol), ether (300 ml), saturation with ethylene, triethylamine in ether (26.1 ml of 1 N solution, 26.1 mmol), addition rate 0.02 ml/min. After purification by MPLC, the isoxazoline **9** was isolated as a colorless, analytically pure oil; yield 3.38 g (83%; 74% from oxime **7**).

$[\alpha]_D^{20} = -5.8$ ($c = 2.56$, $CHCl_3$). – IR (Film): $\nu = 2989$, 1456 (m, C=N), 1373, 1259, 1216, 1153, 1062, 872 cm^{-1}. – ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.41$, 1.46 (2 s, each 3 H, $C(CH_3)_2$), 2.98 – 3.12 (2 dddd, $^2J_{4A,4B} = 10.2$, $J_{4A,5A} = J_{4B,5B} = 11.1$, $J_{4A,5B} = J_{4B,5A} = 9.4$, $^4J_{4A,1'} = {}^4J_{4B,1'} =$ 0.8 Hz, 2 H, 4-H), 4.01 (dd, $J_{1',2'A} = 6.0$, $^2J_{2'A,2'B} = 8.7$ Hz, 1 H, 2'-H_A), 4.23 (dd, $J_{1',2'B} = 6.8$, $^2J_{2'A,2'B} = 8.7$ Hz, 1 H, 2'-H_B), 4.32 – 4.40 (2 "ddd", $J_{4A,5A} = J_{4B,5B} = 11.1$, $J_{4A,5B} = J_{4B,5A} = 9.4$, $^2J_{5A,5B} = 8.0$ Hz, 2 H, 5-H), 4.97 (ddt, $^4J_{4,1'} = 0.8$, $J_{1',2'A} = 6.0$, $J_{1',2'B} = 6.8$ Hz, 1 H, 1'-H). – ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 25.5$, 26.6 (2 q, C(CH_3)$_2$), 34.4 (t, C-4), 67.5 (t, C-2'), 69.2 (t, C-5), 71.5 (d, C-1'), 110.7 (s, $C(CH_3)_2$), 158.6 (s, C-3). – $C_8H_{13}NO_3$ (171.2): calcd. C 56.13, H 7.65, N 8.18; found C 56.01, H 7.62, N 8.09.

*(1'S)-3-(1',2'-Cyclohexylidenedioxyethyl)-4,5-dihydro-1,2-oxazole (***13***)*

a) 2,3-*O*-Cyclohexylidene-D-glyceraldoxime (**11**): Prepared according to ref. [41] from 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol by periodate cleavage and oximation of the aldehyde **10**. – 36.5 mmol run, yield of colorless, oily

oxime **11**, 11.8 g (87%, *E/Z* 65:35). – $[\alpha]_D^{20} = 55.0$ ($c = 1.35$, $CHCl_3$). – Spectroscopic data in agreement with literature data [17f, 41].

b) 2,3-*O*-Cyclohexylidene-D-glycerohydroximoyl chloride (**12**): As described above for **8**, the oxime **11** (7.46 g, 40.3 mmol) in DMF (150 ml, abs.) with NCS (5.92 g, 44.3 mmol) and moist HCl vapor (20 ml) gave crude **12** (8.75 g, 96% yield corrected for impurities DMF (2.5%) and ether (0.7%). The product was used without further purification in the subsequent cycloaddition step.

c) Isoxazoline **13**: Prepared in analogy to **9** as described above. Hydroximoyl chloride **12** (8.71 g, content 96.8%, *ca.* 38.4 mmol), toluene (250 ml), ethylene saturation at 0 °C, triethylamine in toluene (42.2 ml of 1.00 M solution, addition time 47 h with rate 0.015 ml/min. The crude product 8.12 g of a yellow oil, was purified by chromatography (column 7 cm × 20 cm, petrol ether/EtOAc 7:3) to afford analytically pure, colorless, crystalline **13** (7.56 g, 93%, 74% from oxime **11**).

M. p. 45 °C. – $[\alpha]_D^{20} = -3.7$ ($c = 0.50$, CH_2Cl_2); $[\alpha]_D^{20} = -4.1$ ($c = 0.60$, CH_2Cl_2) [2b]. – IR (KBr): ν = 2920, 2840, 1440 (C=N), 1150, 1090, 910, 850 cm^{-1}. – ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.40 - 1.64$ (m, 10 H, $C(CH_2)_5$), 2.98 – 3.13 (m, 2 H, 4-H), 3.99 (dd, $J_{1',2'A} = 6.0$, $^2J_{2'A,2'B} = 8.6$ Hz, 1 H, 2'-H_A), 4.22 (dd, $J_{1',2'B} = 6.8$, $^2J_{2'A,2'B} = 8.6$ Hz, 1 H, 2'-H_B), 4.32 – 4.40 (m, 2 H, 5-H), 4.97 (dd, $J_{1',2'A} = 6.0$, $J_{1',2'B} = 6.8$ Hz, 1 H, 1'-H). – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 23.8, 24.0, 25.0, 34.1, 34.6 (5 t, $C(CH_2)_5$), 35.9 (t, C-4), 66.8 (t, C-2'), 68.8 (t, C-5), 70.7 (d, C-1'), 111.0 (s, $C(CH_2)_5$), 158.4 (s, C-3). – $C_{11}H_{17}NO_3$ (211.3): calcd. C 62.54, H 8.11, N 6.63; found C 62.74, H 8.11, N 6.62.

*(1'S)-3-(1',2'-Isopropylidenedioxyethyl)-2-methyl-4,5-dihydro-1,2-oxazolium tetrafluoroborate (***16***)*

See General Procedure A: isoxazoline **9** (125 mg, 0.73 mmol), Me_3OBF_4 (119 mg, 0.80 mmol), CH_2Cl_2 (10 ml, abs.). The crude product, a brown oil (233 mg) was triturated as above, to yield slightly impure (NMR; *cf.* elemental analysis) **16** as a yellowish oil (148 mg, "86%"). – $[\alpha]_D^{20} = -7.8$ ($c = 0.90$, MeOH). – IR (Film): ν = 2992, 2944, 1635 (C=N), 1380, 1208, 1148, 1056, 928, 837 cm^{-1}. – ^1H NMR (500.1 MHz, CD_3OD): δ = 1.89, 1.98 (2 s, each 3 H, $C(CH_3)_2$); 4.14 – 4.42 (m, 4-H), 4.33 (t, $^5J_{4,1''} = 1.9$ Hz, NCH_3) – sum 5 H; 4.73 (dd, $J_{1',2'A} = 4.7$, $^2J_{2'A,2'B} = 9.6$ Hz, 1 H, 2'-H_A), 4.91 (dd, $J_{1',2'B} = 7.3$, $^2J_{2'A,2'B} = 9.6$ Hz, 1 H, 2'-H_B), 5.22 – 5.31 (m, 2 H, 5-H), 5.81 (dd, $J_{1',2'A} = 4.7$, $J_{1',2'B} = 7.2$ Hz, 1 H, 1'-H). – ^{13}C NMR (125.8 MHz,): δ = 25.4, 26.6 (2 q, $C(CH_3)_2$), 38.6 (t, C-4), 40.4 (q, NCH_3), 68.5 (t, C-2'), 72.1 (d, C-1'), 72.5 (t, C-5), 114.4 (s, $C(CH_3)_2$), 170.3 (s, C-3). – $C_9H_{16}BF_4NO_3$ (273.0): calcd. C 39.59, H 5.91, N 5.13; found C 37.96, H 5.91, N 5.09.

*(1'S)-3-(1',2'-Cyclohexylidenedioxyethyl)-2-methyl-4,5-dihydro-1,2-oxazolium tetrafluoroborate (***17***)*

The General Procedure A was followed; isoxazoline **13** (2.60 g, 12.3 mmol), Me_3OBF_4 (2.00 g, 13.5 mmol), CH_2Cl_2 (30 ml, abs.). The crude product was a brownish solid, which on re-crystallization from ethanol gave analytically pure, colorless crystals of the isoxazolinium salt **17** (3.25 g, 84%). – M. p. 105 – 106 °C. – $[\alpha]_D^{20} = -12.9$ ($c = 0.96$, CH_2Cl_2). – IR (KBr): ν = 2939 (s), 2858 (m), 2361 (w), 1634 (w, C=N^+), 1450 (m), 1368 (m), 1335 (w), 1289 (m), 1237 (m), 1163 (s), 1057 (vs), 923 (s), 848 (w), 830 (w) cm^{-1}. – ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.35 - 1.76$ (m, 10 H, $C(CH_2)_5$), 3.68 – 3.85 (m, 2 H, 4-H), 3.88 (t, $^5J_{4,1''} = 2.1$ Hz, 3 H, NCH_3), 4.33 (dd, $J_{1',2'A} = 4.1$, $^2J_{2'A,2'B} = 10.1$ Hz, 1 H, 2'-H_A), 4.42 (dd, $J_{1',2'B} = 6.9$, $^2J_{2'A,2'B} = 10.1$ Hz, 1 H, 2'-H_B), 4.78 – 4.92 (m, 2 H, 5-H), 5.25 (dd, $J_{1',2'A} = 4.1$, $J_{1',2'B} = 6.9$ Hz, 1 H, 1'-H). – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 23.6, 23.9, 24.8, 33.7, 35.6 (5 t, $C(CH_2)_5$), 36.6 (t, C-4), 39.4 (q, NCH_3), 66.5 (t, C-2'), 69.5 (d, C-1'), 70.5 (t, C-5), 113.4 (s, $C(CH_2)_5$), 166.7 (s, C-3). – $C_{12}H_{20}BF_4NO_3$ (313.1): calcd. C 46.03, H 6.44, N 4.47; found C 45.93, H 6.44, N 4.45.

*(2S,3R)/(2S,3S)-3-Amino-1,2-O-cyclohexylidene-1,2,5-pentanetriol (***22***/***23***; L-erythro/D-threo) from isoxazoline* **13** *by $LiAlH_4$ reduction*

According to ref. [17a, 32] the isoxazoline **13** (100 mg, 0.47 mmol) in ether (5 ml, abs.) was added to a suspension of $LiAlH_4$ (37 mg, 0.95 mmol) in ether (5 ml, abs.) and stirred under nitrogen at room temp. for 1.5 h. Hydrolysis was effected with water (0.04 ml). NaOH solution (0.03 ml, 20%), and again water (0.13 ml) [42], then CH_2Cl_2 (10 ml) was added and stirring was continued for 30 min. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 ml), the combined organic solutes were dried ($MgSO_4$) and rota-evaporated to leave a colorless, somewhat impure hygroscopic oil of the amino alcohols **22**/**23** (83 mg, "81%", d. r. 44:56), which was transformed to analytically pure *Z*-derivatives **24**/**25** (*vide infra*).

$[\alpha]_D^{20} = 0.3$ ($c = 0.27$, CH_2Cl_2). – IR (film): ν = 3357, 2934, 1592, 1106, 1066, 1041 cm^{-1}. – ^1H NMR (250.1 MHz, $CDCl_3$, **22**/**23** = 44 : 56): **22** (*erythro*): δ = 2.87 (ddd, J = 9.1, 6.2, 4.1 Hz, 3-H), 3.63 ("dd", J = 8, 6.4 Hz, 1-H_a), other signals coinciding with those of major isomer. – **23** (*threo*): $\delta = 1.30 - 1.78$ (m, 4-H, $C(CH_2)_5$), 2.35 (sb, NH_2, OH), 3.05 "ddd", J = 10.1, 5.0, 3.4 Hz, 3-H), 3.71 – 4.07 (m, 1-H, 2-H, 5-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, **22**/**23** = (44 : 56); **22** (*erythro*): δ = 34.5, 34.8, 36.0 (3 t, C-4, $C(CH_2)_5$), 54.5 (d, C-3), 60.6 (t, C-5), 66.0 (t, C-1), 79.4 (d, C-2), 109.4 (s, $C(CH_2)_5$); other signals overlapping with those of major isomer. **23** (*threo*): δ = 23.4, 23.7, 24.8, 34.3, 34.5, 35.8 (6 t, C-4, $C(CH_2)_5$), 53.4 (d, C-3), 60.9 (t, C-5), 64.7 (t, C-1), 78.8 (d, C-2), 109.3 (s, $C(CH_2)_5$). –

$C_{11}H_{21}NO_3$ (215.3): calcd. C 61.37, H 9.83, N 6.51; found C 59.80, H 9.38, N 6.16.

*(+)-(2S,3R)- and (−)-(2S,3S)-3-Benzyloxylcarbonylamino-1,2-O-cyclohexylidene-1,2,5-pentanet riol (***24** *and* **25***; D-erythro and L-threo)*

The mixture of *erythro*/*threo*-amino alcohols **22**/**23** (242 mg, 1.30 mmol; d. r. = 44 : 56) was dissolved in dioxane/water (10 ml, 7:3) and treated with benzyl chloroformate (333 mg, 1.95 mmol), then $NaHCO_3$ (218 mg, 2.60 mmol) was added in portions. After stirring at room temp. for 1 d CH_2Cl_2 (50 ml) was added and the organic phase was washed with water and bicarbonate solution (50 ml of each) and dried ($MgSO_4$). After rota-evaporation the remaining oil was separated by MPLC (column type B, eluent CH_2Cl_2/MeOH 98:2; flow 20 ml/min at 13 bar).

Erythro isomer **24**: colorless oil, 112 mg, 25%, $[\alpha]_D^{20} = 42.9$ ($c = 1.70$, CH_2Cl_2). – IR (film): $\nu = 3335, 2936, 1699, 1506, 1252, 1096$ cm^{-1}. – ^{1}H NMR (250.1 MHz, $CDCl_3$): $\delta = 1.40 - 1.91$ (m, 12 H, 4-H, $C(CH_2)_5$), 3.23 (sb, 1 H, OH), 3.56 – 3.60 (m, 2 H, 5-H), 3.68 ("dd", $^2J = 8.0$, $J_{1a,2} = 7.1$ Hz, 1-H_a), 3.92 (m, 1 H, 3-H), 4.03 ("dd", $^2J = 8.0$, $J_{1b,2} = 6.8$, 1 H, 1-H_b), 4.17 ("ddd" as "dt", $J_{2,3} = 1.9$ Hz, 1 H, 2-H), 5.06 (d, $J_{3,NH} = 9.9$ Hz, NH), 5.06, 5.15 (A, B of AB, $^2J = 12.2$ Hz, CO_2CH_2Ph), together 3 H, 7.26 – 7.45 (m, 5 H, C_6H_5). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 23.6$, 23.9, 25.0, 35.9, 36.7 (5 t, $C(CH_2)_5$), 34.2 (t, C-4), 48.1 (d, C-3), 58.4 (t, C-5), 66.1, 67.2 (t, C-2, CO_2CH_2Ph), 76.8 (d, C-2), 109.9 (s, $C(CH_2)_5$), 128.0, 128.2, 128.6 (3 d; *o*-, *m*-, *p*-C of C_6H_5), 136.1 (s, *i*-C of C_6H_5), 157.6 (s, CO_2CH_2Ph).

Threo isomer **25**: colorless oil, 173 mg, 38%, $[\alpha]_D^{20} = -24.0$ ($c = 1.50$, CH_2Cl_2). – IR (film): $\nu = 3328, 2936, 1695, 1537, 1252, 1100, 1070, 1042$ cm^{-1}. – ^{1}H NMR (250.1 MHz, $CDCl_3$): $\delta = 1.22 - 1.61$ (m, 11 H, 4-H_a, $C(CH_2)_5$), 1.83 – 1.97 (m, 1 H, 4-H_b), 3.10 (very br, 1 H, OH), 3.68 (m, 2 H, 5-H), 3.79 ("dd", $^2J = 8.6$, $J_{1a,2} = 5.6$ Hz, 1 H, 1-H_a), 3.89 (m, 1 H, 3-H), 4.03 ("dd", $^2J = 8.6$, $J_{1b,2} = 6.7$ Hz, 1 H, 1-H_b), 4.14 ("ddd" als "q", $J_{2,3} = 5.3$ Hz, 1 H, 2-H), 5.10 (s, 2 H, CO_2CH_2Ph), 5.19 (d, $J_{3,NH} = 9.0$ Hz, 1 H, NH), 7.26 – 7.43 (m, 5 H, C_6H_5). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 23.7$, 23.9, 25.0, 34.4, 35.9 (5 t, $C(CH_2)_5$), 33.1 (t, C-4), 50.6 (d, C-3), 58.7 (t, C-5), 66.1, 67.1 (t, C-1, CO_2CH_2Ph), 77.1 (d, C-2), 110.3 (s, $C(CH_2)_5$), 128.1, 128.2, 128.5 (3 d; *o*-, *m*-, *p*-C of C_6H_5), 136.2 (s, C_{ipso}), 157.1 (s, CO_2CH_2Ph). – $C_{19}H_{27}NO_5$ (349.4): calcd. C 65.31, H 7.79, N 4.01; found for **24** (*erythro*) C 64.85, H 7.85, N 3.99; found for **25** (*threo*) C 65.16, H 7.88, N 4.08.

D-(+)Homoserinolactone hydrobromide **27**

a) Amino alcohols **22**/**23** from isoxazoline **13** by reduction with $NaBH_4/NiCl_2 \cdot 6H_2O$: In analogy to ref. [35] the isoxazoline **13** (253 mg, 1.20 mmol) in methanol (36 ml) was treated with $NiCl_2 \cdot 6H_2O$ (569 mg, 2.40 mmol) and $NaBH_4$ (227 mg, 6.00 mmol; added in portions) at −30 °C. The solution immediately turned black; after 10 min methanol was cautiously rota-evaporated. The residual mixture was treated with conc. ammonia (36 ml) and CH_2Cl_2 (36 ml) and stirred with air contact, until the organic phase had taken a yellow-brown color. After separation of the layers, the aqueous phase was extracted with CH_2Cl_2 (2 × 36 ml); the combined organic solutes were dried (Na_2SO_4) and concentrated (15 Torr). The product, a brown-yellow oil (251 mg, "97%") consisted of a mixture of amino alcohols **22**/**23** (*erythro*/*threo*= 35 : 65) and *ca.* 10% of unidentified impurities. ^{13}C NMR data were in accordance with those of **22**/**23** given above.

b) *N*-Z-Amino alcohols **24** (L-*erythro*) and **25** (D-*threo*): Preparation as above; amino alcohol mixture **22**/**23** (251 mg, crude product obtained above), *Z*-Cl (200 mg, 1.17 mmol), Et_3N (118 mg, 1.17 mmol). MPLC separation afforded colorless, analytically pure samples of **24** (L-*erythro*; 101 mg, 25%) and **25** (D-*threo*; 187 mg, 46%). – L-*erythro* isomer **24**: $[\alpha]_D^{20} = 43.0$ ($c = 0.345$, CH_2Cl_2). – L-*threo* isomer **25**: $[\alpha]_D^{20} = -24.1$ ($c = 0.840$, CH_2Cl_2). – $C_{19}H_{27}NO$ (349.4): calcd. C 65.31, H 7.79, N 4.01; found for **24**: C 65.25, H 7.52, N 3.88; found for **25**: C 65.08, H 7.86, N 3.90. – Spectroscopic data in complete agreement with those reported above.

c) (+)-D-*N*-Benzyloxycarbonylhomoserinolactone **26**: The Z-aminotriol derivative **25** (115 mg, 0.33 mmol) was dissolved in THF and treated with hydrochloric acid (10%, 0.5 ml) for 5 h at room temp. Then $NaIO_4$ (77 mg, 0.36 mmol) was added and the mixture continued stirring for 1.5 d. After addition of saturated NaCl (20 ml), the mixture was extracted with ether (3 × 20 ml), the organic solutes were dried ($MgSO_4$) and concentrated *in vacuo*. The remainders were taken up in acetic acid (3 ml) and CrO_3 (36 mg, 0.36 mmol) was added in 3 portions within 3 h. After another 4.5 h, the volatiles were removed by rota-evaporation and the remaining oil was filtered through silica (7 g, column 2 cm × 3 cm) by means of EtOAc (40 ml). The solvent was evaporated to give a yellow oil, which was dried (10^{-2} Torr/KOH) and chromatographically purified (MPLC, column type B, eluent petrol ether/EtOAc 1:1, 12 bar, flow rate 40 ml/min). The Z-aminolactone **26** was obtained as an analytically pure, colorless solid (11 mg, 14%).

M. p. 126 – 128 °C; m. p. [17f] 121 – 122 °C. – $[\alpha]_D^{20} = 3.5$ ($c = 0.90$, $CHCl_3$); $[\alpha]_D^{20} = 1.11$($c = 2.00$, $CHCl_3$) [17f]. – IR (CCl_4): 3240, 1732, 1499, 1172, 1063, 1019 cm^{-1}. – ^{1}H NMR (250.1 MHz, $CDCl_3$): $\delta = 2.21$ ("ddt", $^2J = 24.0$, $^3J = 11.6$, $^3J = 8.9$ Hz, 1 H, 3-H_a), 2.79 (m, 1 H, 3-H_b), 4.25 (ddd, $^3J = 11.2$, $^3J = 9.3$, $^3J = 5.8$ Hz, 1 H, 2-H), 4.35 – 4.50 (m, 2 H, 4-H), 5.13 ("s", 2 H, CO_2CH_2Ph), 5.34 (bs, 1 H, NH), 7.30 – 7.39 (m, 5 H, C_6H_5). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 30.4$ (t, C-3), 50.5 (d, C-2), 65.8, 67.3 (2 t, C-4,

CO_2CH_2Ph), 128.2, 128.3, 128.6 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 135.8 (s, *i*-C of C_6H_5), 156.0 (s, NCO_2CH_2Ph), 174.9 (s, C-1). – $C_{12}H_{13}NO$ (235.2): calcd. C 61.27, H 5.57, N 5.95; found C 61.41, H 5.69, N 5.67.

d) D-Homoserinolactone hydrobromide (**27**·HBr): Z-Protected homoserinolactone **26** {73 mg, 0.33 mmol; sample with $[\alpha]_D^{20} = +1.11$ ($c = 2.00$ in $CHCl_3$), m. p. 121–122 °C, analytically pure} was treated with HBr/glacial acetic acid (0.5 ml), causing immediate gas evolution. After 6 h ether (5 ml) was added, the mixture was cooled to −20 °C and the precipitate (hydrobromide) filtered off. After washing with ice-cold ether and drying *in vacuo* (P_2O_5, 10^{-3} Torr), pale-orange crystals of **27**·HBr (43 mg, 72%) were isolated. – M. p. 241 °C, m. p. [43] 242–244 °C. – $[\alpha]_D^{27} = 19.5$ ($c = 1.02$, H_2O); $[\alpha]_D^{27}$ (lit. [43] = 21 ($c = 1.0$, H_2O). – IR (KBr): 2990 (b), 2870 (b), 1775 (C=O), 1210, 1022 cm^{-1}. – ^1H NMR (400.1 MHz, D_2O; mixture of lactone and hydroxy amino acid *ca.* 75:25, insufficient resolution); lactone **27**·HBr: $\delta = 2.27$, 2.63 (m, 2 H, 3-H), 4.29, 4.46 (m, 2 H, 4-H), 4.5 (s, b; OH, NH, 3-H). – Acid: $\delta = 1.9 - 2.1$ (m, 2 H, 3-H), 3.61, 3.95 (m, 2 H, 4-H). – ^{13}C NMR (100.6 MHz, D_2O, d_6-acetone; 75:25 mixture); lactone **27**·HBr: $\delta = 26.9$ (C-3), 48.8 (C-2), 67.6 (C-4); acid: $\delta = 32.0$ (C-3), 52.2 (C-2), 58.4 (C-4); C=O not identified. – $C_4H_9BrNO_2$ (182.0): calcd. C 26.40, H 4.43, N 7.70; found C 25.78, H 4.21, N 7.48.

General Procedure B, reduction of isoxazolinium salts (prepared from isoxazolines) with $NaBH_4$ to yield isoxazolidines; two-step/one-pot procedure

To a solution of the isoxazoline (1–10 mmol) in abs. CH_2Cl_2 (5–30 ml) at room temp. Me_3OBF_4 (1.1 eq) was added; after stirring overnight the solvent was removed (15 Torr), the remainders are dissolved in abs. ethanol and treated with 2 eq of $NaBH_4$ with stirring overnight. For work-up the mixture was hydrolyzed with 5% aqueous citric acid and water. After removal of ethanol (rota-evaporation at 15 Torr) the mixture was extracted with EtOAc (4 × 20 ml), the solutes were partitioned against sat. NaCl (30 ml) and dried ($MgSO_4$). For further product purification see individual compounds.

*(3R,1'R)/(3S,1'R)-3-(1'-Benzyloxy-2'-hydroxyethyl)-2-methyltetrahydro-1,2-oxazole (***28***, erythro and* **29***, threo)*

General Procedure B; isoxazoline **4** (420 mg, 1.90 mmol), CH_2Cl_2 (5 ml, abs.), Me_3OBF_4 (308 mg, 2.08 mmol); isoxazolinium salt **14** dissolved in ethanol (5 ml), reduction with $NaBH_4$ (143 mg, 3.78 mmol), 3 h at 0 °C, 3 h at room temp. Work-up gave a colorless oil of **28**/**29** (79:21 from HPLC and NMR), which was filtered through silica (column 2 cm × 12 cm, petrol ether/EtOAc 3:7) and separated by MPLC (column type C, petrol ether/EtOAc 1:9). After removal of the solvent (10^{-3} Torr) analytically pure, colorless oils of **28** (erythro; 221 mg, 53%) and **29** (50 mg, 12%) were obtained.

Erythro isomer **28**: $[\alpha]_D^{20} = 70.2$ ($c = 0.465$, CH_2Cl_2). – IR (Film): $\nu = 3419$ (OH), 2876, 1454, 1067, 740 cm^{-1}. – ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 2.17$ ("dddd", $J_{3,4A} = 3.8$, $^2J_{4A,4B} = 12.6$, $J_{4A,5A} = 8.7$, $J_{4A,5B} = 6.1$ Hz, 1 H, 4-H_A), 2.42 (ddt, $J_{3,4B} = J_{4B,5B} = 8.7$, $^2J_{4A,4B} = 12.6$, $J_{4B,5A} = 6.1$ Hz, 1 H, 4-H_B), 2.66 (s, 3 H, NCH_3), 3.12 (dt, $J_{3,4A} = 3.7$, $J_{3,4B} = J_{3,1'} = 7.9$ Hz, 1 H, 3-H), 3.31 (ddd, $J_{3,1'} = 7.5$, $J_{1',2'A} = 6.1$, $J_{1',2'B} = 3.3$ Hz, 1 H, 1'-H), 3.75 (dd, $J_{1',2'A} = 6.2$, $^2J_{2'A,2'B} = 11.6$ Hz, 1 H, 2'-H_A); 3.82 (dt, $J_{4A,5A} = ^2 J_{5A,5B} = 8.4$, $J_{4B,5A} = 6.1$ Hz, 5-H_A), 3.86 (dd, $J_{1',2'B} = 3.3$, $^2J_{2'A,2'B} = 11.6$ Hz, 2'-H_B) – sum 2 H; 4.01 (ddd, $J_{4A,5B} = 6.1$, $J_{4B,5B} = 9.0$, $^2J_{5A,5B} = 8.1$ Hz, 1 H, 5-H_B), 4.54, 4.67 (A, B of AB, $^2J_{AB} = 11.6$ Hz, 2 H, C$H_2$$C_6H_5$), 7.28–7.37 (m, 5 H, C_6H_5). – ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 31.4$ (t, C-4), 45.2 (q, NCH_3), 63.0 (t, C-2'), 65.3 (t, C-5), 70.4 (d, C-3), 72.5 (t, C$H_2$$C_6H_5$), 79.0 (d, C-1'), 128.3, 128.4, 128.9 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 138.3 (s, *i*-C of C_6H_5).

Threo isomer **29**: $[\alpha]_D^{20} = -56.9$ ($c = 0.45$, CH_2Cl_2). – IR (Film): $\nu = 3408$ (OH), 2876, 1454, 1060 (vs), 740 cm^{-1}. – ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 2.15$ ("ddt", $J_{3,4A} = J_{4A,5B} = 6.2$, $^2J_{4A,4B} = 12.5$, $J_{4A,5A} = 8.4$ Hz, 1 H, 4-H_A), 2.36 (ddt, $J_{3,4B} = J_{4B,5B} = 8.4$, $^2J_{4A,4B} = 12.5$, $J_{4B,5A} = 5.7$ Hz, 1 H, 4-H_B), 2.72 (s, 3 H, NCH_3), 3.13 (dt, $J_{3,4A} = J_{3,1'} = 6.2$, $J_{3,4B} = 8.4$ Hz, 1 H, 3-H); 3.58 ("ddd", $J_{3,1'} = 6.5$, $J_{1',2'A} = 4.4$, $J_{1',2'B} = 5.2$ Hz, 1'-H), 3.61 (dd, $J_{1',2'A} = 4.4$, $^2J_{2'A,2'B} = 11.7$ Hz, 2'-H_A) – sum 2 H; 3.80–3.84 (m, 1 H, 2'-H_B), 3.88 (dt, $J_{4A,5A} = ^2 J_{5A,5B} = 8.3$, $J_{4B,5A} = 5.7$ Hz, 1 H, 5-H_A), 4.00 (dt, $J_{4A,5B} = 6.4$, $J_{4B,5B} = ^2 J_{5A,5B} = 8.2$ Hz, 1 H, 5-H_B), 4.65, 4.69 (A, B of AB, $^2J_{AB} = 11.6$ Hz, 2 H, C$H_2$$C_6H_5$), 7.28–7.39 (m, 5 H, C_6H_5). The OH signal was not identified. – ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 31.0$ (t, C-4), 45.4 (q, NCH_3), 61.8 (t, C-2'), 65.3 (t, C-5), 69.0 (d, C-3), 72.5 (t, C$H_2$$C_6H_5$), 79.4 (d, C-1'), 127.8, 127.9, 128.5 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 138.2 (s, *i*-C of C_6H_5). – $C_{13}H_{19}NO_3$ (237.3): calcd. C 68.50, H 8.07, N 5.90; found for *erythro* isomer **28** C 65.05, H 8.04, N 5.81; found for *threo* isomer **29** C 64.95, H 8.07, N 5.79.

Reduction of **14** (prepared from **4**, 0.74 mmol as above) with $NaBH(OAc)_3$ (2.2 mmol) as described for **17** at 0 °C gave a 83:17 mixture of **28**/**29**. – $[\alpha]_D^{20} = 45.5$ ($c = 1.12$, CH_2Cl_2). – Found: C 65.43, H 8.12, N 5.88.

*(3R,1'R)- and (3S,1'R)-3-(1',2'-Dibenzyloxyethyl)-2-methyltetrahydro-1,2-oxazole (***30***, erythro and* **31***, threo)*

General Procedures A and B were followed. – Isoxazoline **5** (264 mg, 0.85 mmol), Me_3OBF_4 (138 mg, 0.93 mmol), CH_2Cl_2 (5 ml, abs.); reduction with $NaBH_4$ (64 mg, 1.69 mmol) in EtOH (8 ml, abs.). TLC analysis showed the reduction to be complete after 2 h; work-up then gave a

yellowish oil (286 mg, d. r. 72:28). The mixture was filtered through silica (column 2 cm × 8 cm, petrol ether/EtOAc 8:2) and the resulting colorless oil (172 mg) was separated by MPLC (column type C, petrol ether/EtOAc 1:1). After solvent removal (10^{-3} Torr) colorless, analytically pure compounds **30** (*erythro*, oil, 122 mg, 44%) and **31** (*threo*, oil, 45 mg, 16%) were obtained.

Erythro isomer **30**: $[\alpha]_D^{20} = 42.6$ ($c = 0.55$, CH_2Cl_2). – IR (film): ν = 2954, 2868, 1454, 1097, 1062, 1028, 737 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 2.25$ ("dddd", $J_{3,4A} = 4.7$, $^2J_{4A,4B} = 12.4$, $J_{4A,5A} = 8.5$, $J_{4A,5B} = 6.3$ Hz, 1 H, 4-H_A), 2.33 (ddt, $J_{3,4B} = J_{4B,5B} = 8.5$, $^2J_{4A,4B} = 12.4$, $J_{4B,5A} = 6.0$ Hz, 1 H, 4-H_B), 2.60 (s, 3 H, NCH_3), 3.09 (ddd, $J_{3,4A} = 4.7$, $J_{3,4B} = 8.3$, $J_{3,1'} = 6.8$ Hz, 1 H, 3-H), 3.48 (ddd, $J_{3,1'} = 6.8$, $J_{1',2'A} = 4.9$, $J_{1',2'B} = 3.4$ Hz, 1 H, 1'-H), 3.66 (dd, $J_{1',2'A} = 4.9$, $^2J_{2'A,2'B} = 10.4$ Hz, 1 H, 2'-H_A); 3.73 (dd, $J_{1',2'B} = 3.4$, $^2J_{2'A,2'B} = 10.4$ Hz, 2'-H_B), 3.76 (dt, $J_{4A,5A} = {}^2J_{5A,5B} = 8.3$, $J_{4B,5A} = 6.1$ Hz, 5-H_A) – sum 2 H; 3.96 (dt, $J_{4A,5B} = 6.2$, $J_{4B,5B} = {}^2J_{5A,5B} = 8.3$ Hz, 1 H, 5-H_B), 4.53, 4.56 (A, B of AB, $^2J_{AB} = 12.1$ Hz, 2 H, CH_2C$_6$H$_5$), 4.59, 4.73 (A, B of AB, $^2J_{AB} = 11.7$ Hz, 2 H, CH_2C$_6$H$_5$), 7.22 – 7.37 (m, 10 H, 2 C$_6$H$_5$). – ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 30.6$ (t, C-4), 44.8 (q, NCH_3), 65.0 (t, C-5), 67.7 (d, C-3), 70.1 (t, C-2'), 72.5, 73.3 (2 t, 2 *C*H$_2$C$_6$H$_5$), 78.8 (d, C-1'), 127.5, 127.6, 127.9, 128.1, 128.28, 128.32 (6 d, *o*-, *m*-, *p*-C of 2 C$_6$H$_5$), 138.3, 138.5 (2 s, *i*-C of 2 C$_6$H$_5$).

Threo isomer **31**: $[\alpha]_D^{20} = -29.4$ ($c = 0.38$, CH_2Cl_2). – IR (film): ν = 2956, 2866, 1454, 1097, 1058, 1028, 737 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 2.00$ (ddt, $J_{3,4A} = J_{4A,5B} = 6.7$, $^2J_{4A,4B} = 12.2$, $J_{4A,5A} = 8.3$ Hz, 1 H, 4-H_A), 2.30 (ddt, $J_{3,4B} = J_{4B,5B} = 8.2$, $^2J_{4A,4B} = 12.2$, $J_{4B,5A} = 5.5$ Hz, 1 H, 4-H_B), 2.74 (s, 3 H, NCH_3), 2.98 – 3.03 (m, 1 H, 3-H), 3.56 (dd, $J_{1',2'A} = 5.0$, $^2J_{2'A,2'B} = 10.1$ Hz, 1 H, 2'-H_A), 3.60 (ddd, $J_{3,1'} = 7.3$, $J_{1',2'A} = 5.0$, $J_{1',2'B} = 3.3$ Hz, 1 H, 1'-H), 3.68 (dd, $J_{1',2'B} = 3.3$, $^2J_{2'A,2'B} = 10.1$ Hz, 1 H, 2'-H_B), 3.82 (dt, $J_{4A,5A} = {}^2J_{5A,5B} = 8.2$, $J_{4B,5A} = 5.4$ Hz, 1 H, 5-H_A), 3.94 (dt, $J_{4A,5B} = 6.6$, $J_{4B,5B} = {}^2J_{5A,5B} = 8.0$ Hz, 1 H, 5-H_B), 4.51, 4.57 (A, B of AB, $^2J_{AB} = 12.1$ Hz, 2 H, CH_2C$_6$H$_5$), 4.67, 4.74 (A, B of AB, $^2J_{AB} = 11.6$ Hz, 2 H, CH_2C$_6$H$_5$), 7.25 – 7.37 (m, 10 H, 2 C$_6$H$_5$). – ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 32.4$ (t, C-4), 46.1 (q, NCH_3), 64.9 (t, C-5), 68.5 (d, C-3), 70.6 (t, C-2'), 72.9, 73.5 (2 t, 2 *C*H$_2$C$_6$H$_5$), 80.7 (d, C-1'), 127.5, 127.7, 127.9, 128.3, 128.4 (5 d, *o*-, *m*-, *p*-C of 2 C$_6$H$_5$) 138.1, 138.6 (2 s, *i*-C of 2 C$_6$H$_5$). – $C_{20}H_{25}NO_3$ (327.4): calcd. C 73.37, H 7.70, N 4.28; found for **30**: C 73.17, H 7.75, N 4.24; found for **31**: C 73.25, H 7.78, N 4.29.

*(3S,1'S)- and (3R,1'S)-3-(1',2'-Cyclohexylidenedioxyethyl)-2-methyltetrahydro-1,2-oxazole (***32***, erythro and* **33***, threo)*

Starting with the isoxazoline **13**, the isoxazolinium salt **17** was prepared according to General Procedure A and then reduced according to General Procedure B. Isoxazoline **13** (1.46 g, 6.91 mmol), Me_3OBF_4 (1.12 g, 7.57 mmol), CH_2Cl_2 (30 ml, abs.); then reduction with $NaBH_4$ (523 mg, 13.8 mmol) in EtOH (60 ml, abs.); yellow oil of **32**/**33** (1.46 g, d. r. 81:19). Purification: The crude product was filtered through silica (column 2 cm × 17 cm, solvent petrol ether/EtOAc 1:1), affording 1.45 g of a slightly yellow oil after solvent removal. MPLC separation (column type C, eluent petrol ether/EtOAc 1:1) gave the *erythro* isoxazolidine **32** (1.07 g, 68%) and the *threo* isomer **33** (256 mg, 16%), both as colorless, analytically pure oils.

Erythro isomer **32**: $[\alpha]_D^{20} = -31.9$ ($c = 0.73$, CH_2Cl_2). – IR (Film): ν = 2936, 2861, 1163, 1101, 1038, 927 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.35 - 1.65$ (m, 10 H, C(CH_2)$_5$), 2.30 ("dddd", $J_{3,4A} = 3.6$, $^2J_{4A,4B} = 12.6$, $J_{4A,5A} = 8.7$, $J_{4A,5B} = 6.2$ Hz, 1 H, 4-H_A), 2.44 (dddd, $J_{3,4B} = 8.1$, $^2J_{4A,4B} = 12.6$, $J_{4B,5A} = 6.0$, $J_{4B,5B} = 8.9$ Hz, 1 H, 4-H_B), 2.63 (s, 3 H, NCH_3), 2.94 (dt, $J_{3,4A} = 3.6$, $J_{3,4B} = J_{3,1'} = 8.2$ Hz, 1 H, 3-H), 3.83 (dd, $J_{1',2'A} = 5.3$, $^2J_{2'A,2'B} = 8.4$ Hz, 1 H, 2'-H_A); 3.90 ("ddd", $J_{4A,5A} = 8.7$, $J_{4B,5A} = 6.0$, $^2J_{5A,5B} = 8.0$ Hz, 5-H_A), 3.94 (ddd, $J_{3,1'} = 8.2$, $J_{1',2'A} = 5.3$, $J_{1',2'B} = 6.1$ Hz, 1'-H) – sum 2 H; 4.04 (ddd, $J_{4A,5B} = 6.2$, $J_{4B,5B} = 9.0$, $^2J_{5A,5B} = 8.0$ Hz, 1 H, 5-H_B), 4.10 (dd, $J_{1',2'B} = 6.1$, $^2J_{2'A,2'B} = 8.4$ Hz, 1 H, 2'-H_B). – ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 23.8$, 24.0, 25.2, 34.8, 36.7 (5 t, C(*C*H$_2$)$_5$), 30.7 (t, C-4), 44.8 (q, NCH_3), 64.9 (t, C-5), 67.7 (t, C-2'), 69.5 (d, C-3), 76.4 (d, C-1'), 109.8 (s, *C*(CH$_2$)$_5$).

Threo isomer **33**: $[\alpha]_D^{20} = 82.2$ ($c = 0.81$, CH_2Cl_2). – IR (Film): ν = 2935, 2861, 1163, 1105, 1041, 928 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.39 - 1.66$ (m, 10 H, C(CH_2)$_5$), 1.89 ("dddd", $J_{3,4A} = 6.5$, $^2J_{4A,4B} = 12.3$, $J_{4A,5A} = 8.7$, $J_{4A,5B} = 5.8$ Hz, 1 H, 4-H_A), 2.33 (ddt, $J_{3,4B} = 8.6$, $^2J_{4A,4B} = 12.3$, $J_{4B,5A} = 6.0$, $J_{4B,5B} = 8.6$ Hz, 1 H, 4-H_B), 2.78 (s, 3 H, NCH_3), 2.80 – 2.85 (m, 1 H, 3-H), 3.66 (dd, $J_{1',2'A} = 6.8$, $^2J_{2'A,2'B} = 8.3$ Hz, 1 H, 2'-H_A), 3.83 ("dddd", $^4J_{3,5A} = 0.5$, $J_{4A,5A} = 8.7$, $J_{4B,5A} = 6.0$, $^2J_{5A,5B} = 8.2$ Hz, 1 H, 5-H_A), 3.96 (ddd, $J_{4A,5B} = 5.8$, $J_{4B,5B} = 8.6$, $^2J_{5A,5B} = 8.2$ Hz, 1 H, 5-H_B), 4.04 (dd, $J_{1',2'B} = 6.4$, $^2J_{2'A,2'B} = 8.3$ Hz, 1 H, 2'-H_B), 4.13 (ddd, $J_{3,1'} = 7.7$, $J_{1',2'A} = 6.8$, $J_{1',2'B} = 6.4$ Hz, 1 H, 1'-H). – ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 23.8$, 24.0, 25.1, 34.8, 36.4 (5 t, C(*C*H$_2$)$_5$), 31.6 (t, C-4), 45.1 (q, NCH_3), 64.9 (t, C-5), 66.5 (t, C-2'), 69.7 (d, C-3), 76.8 (d, C-1'), 110.3 (s, *C*(CH$_2$)$_5$). – $C_{12}H_{21}NO_3$ (227.3): calcd. C 63.41, H 9.31, N 6.16; found for **32**: C 63.51, H 9.38, N 6.14; found for **33** C 63.49, H 9.33, N 6.08.

Isoxazolidines **32** *(erythro) and* **33** *(threo) from* **17** *by sodium triacetoxyborohydride reduction*

A solution of the isoxazolinium salt **17** (295 mg, 0.94 mmol) in THF (5 ml, abs.) was added at −78 °C to a suspension of $NaBH(OAc)_3$ (420 mg, *ca.* 1.88 mmol) in THF

(10 ml, abs.). TLC analysis showed complete consumption of **17** after *ca.* 1 min. For work-up hydrolysis was effected by addition of aqueous citric acid (5%, 5 ml) and water (20 ml). The mixture was extracted with EtOAc (4 × 20 ml); the solution then was washed with aqueous $NaHCO_3$ (saturated, 20 ml) and dried ($MgSO_4$). After rota-evaporation a slightly yellow oil resulted, consisting of a 95:5 mixture of diastereomers **32**/**33**. The product was purified on silica (column 2 cm × 15 cm, eluent petrol ether/EtOAc 1:1) and the solvent was removed *in vacuo* (10^{-3} Torr) to leave **32**/**33** as an analytically pure oil (184 mg, 86%), with spectroscopic data in full agreement with those described above. – Data of **32**/**33** mixture (95:5 from ^{13}C NMR): $[\alpha]_D^{20} = -25.9$ ($c = 1.08$, CH_2Cl_2). – $C_{12}H_{21}NO_3$ (227.3): calcd. C 63.41, H 9.31, N 6.16, found C 63.42, H 9.37, N 6.15.

*(3S,1'S)- 3-(1',2'-Cyclohexylidenedioxyethyl)-2,2-dimethyltetrahydro-1,2-oxazolium-tetrafluoroborate (***34***)*

To a solution of the isoxazolidine **32** (124 mg, 0.55 mmol) in abs. CH_2Cl_2 (5 ml) at room temp. Me_3OBF_4 (89 mg, 0.60 mmol) was added and the mixture was stirred for 16 h. After removal of the solvent (15 Torr) a colorless solid (187 mg) remained, which was recrystallized from ethanol to afford colorless, analytically pure **34** (152 mg, 85%; m. p. 170 – 171 °C). Another recrystallization from ethanol furnished crystals of **34** (m. p. 172 °C) suitable for crystal structure analysis [33].

$[\alpha]_D^{20} = -29.4$ ($c = 0.81$, CH_2Cl_2). – IR (KBr): ν = 2935, 1468, 1112, 1068 cm^{-1}. – ^{1}H NMR (500.1 MHz, CD_3OD): $\delta = 2.69$ (ddt, $J_{3,4A} = J_{4A,5A} = 7.5$, $^2J_{4A,4B}$ = 13.1, $J_{4A,5B} = 4.0$ Hz, 1 H, 4-H_A), 2.77 (ddt, $J_{3,4B}$ = $J_{4B,5B} = 8.6$, $^2J_{4A,4B} = 13.1$, $J_{4B,5A} = 9.9$ Hz, 1 H, 4-H_B), 3.40, 3.52 (2 s, 3 H each, $N(CH_3)_2$), 3.68 (dd, $J_{1',2'A} = 6.4$, $^2J_{2'A,2'B} = 9.1$ Hz, 1 H, 2'-H_A); 4.23 (dd, $J_{1',2'B} = 7.3$, $^2J_{2'A,2'B} = 9.1$ Hz, 2'-H_B), 4.24 (ddd, $J_{3,4A} = 7.4$, $J_{3,4B}$ = 8.7, $J_{3,1'} = 1.3$ Hz, 3-H) – sum 2 H; 4.39 – 4.43 (m, 5-H_A), 4.45 (ddd, $J_{4A,5B} = 4.0$, $J_{4B,5B} = 8.8$, $^2J_{5A,5B} = 7.6$ Hz, 5-H_B) – sum 2 H; 4.70 ("ddd", $J_{3,1'} = 1.3$, $J_{1',2'A} = 6.3$, $J_{1',2'B} = 7.4$ Hz, 1 H, 1'-H). – ^{13}C NMR (125.8 MHz, CD_3OD): δ = 25.4, 25.6, 26.7, 35.7, 37.0 (5 t, C(CH_2)$_5$), 27.7 (t, C-4), 52.6, 56.4 (2 q, $N(CH_3)_2$), 68.5 (t, C-2'), 71.7 (d, C-1'), 72.1 (t, C-5), 80.7 (d, C-3), 114.0 (s, $C(CH_2)_5$). – $C_{13}H_{24}BF_4NO_3$ (329.1): calcd. C 47.44, H 7.35, N 4.26; found C 47.47, H 7.33, N 4.18.

*(2S,3S)-1,2-O-Cyclohexylidene-3-methylamino-1,2,5-pentanetriol (***35***, erythro) by catalytic hydrogenation of the isoxazolidine* **32***; Typical Procedure*

Under nitrogen, to a solution of the isoxazolidine **32** (186 mg, 0.82 mmol) in methanol (5 ml) palladium on carbon (10%, 60 mg) was added and the mixture hydrogenated (3 bar) for 3 d at room temp. The mixture was filtered through celite, the cake was rinsed with methanol, and the combined solutions were put to dryness (10^{-3} Torr). Thus, a colorless, analytically pure oil of **35** (176 mg, 95%) was obtained. – $[\alpha]_D^{20} - 30.4$ ($c = 1.30$, CH_2Cl_2). – IR (film): $\nu = 3316$ (b; NH, OH), 2935, 2861, 1449, 1366, 1103, 1039, 936 cm^{-1}. – ^{1}H NMR (250.1 MHz, $CDCl_3$): $\delta = 1.41 - 1.63$ (m, 10 H, C(CH_2)$_5$), 1.65 - 1.74 (m, 2 H, 4-H), 2.47 (s, 3 H, NHCH_3), 2.66 - 2.74 (m, 1 H, 3-H), 3.13 (sb, 2 H, OH, NHCH_3), 3.73 (dd, $^2J_{1A,1B} = 8.3$, $J_{1A,2} = 6.3$ Hz, 1 H, 1-H_A), 3.79 – 3.86 (m, 2 H, 5-H), 4.07 (dd, $^2J_{1A,1B} = 8.3$, $J_{1B,2}$ = 6.7 Hz, 1 H, 1-H_B), 4.26 (dt, $J_{1A,2} = J_{1B,2} = 6.5$, $J_{2,3} = 4.7$ Hz, 1 H, 2-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.8, 24.0, 25.1, 34.4, 36.0 (5 t, C(CH_2)$_5$), 30.5 (t, C-4), 33.9 (q, $NHCH_3$), 62.5 (d, C-3), 62.6 (t, C-5), 66.2 (t, C-1), 75.4 (d, C-2), 109.6 (s, $C(CH_2)_5$). – $C_{12}H_{23}NO_3$ (229.3): calcd. C 62.85, H 10.11, N 6.11; found C 62.80, H 10.11, N 6.04.

*(2S,3R)-1,2-O-Cyclohexylidene-3-methylamino-1,2,5-pentanetriol (***36***; threo)*

Following the Typical Procedure given above, the *threo* isoxazolidine **33** (122 mg, 0.54 mmol) was hydrogenated using Pd/C (10%, 50 mg) in methanol (5 ml) for 1 d at 3 bar. Work-up gave the amino alcohol **36** (121 mg, 98%), an analytically pure, colorless oil. – $[\alpha]_D^{20} = 12.8$ ($c = 1.46$, CH_2Cl_2). – IR (film): $\nu = 3321$ (br; NH, OH), 2935, 2860, 1448, 1366, 1163, 1104, 1039, 933 cm^{-1}. – ^{1}H NMR (250.1 MHz, $CDCl_3$): $\delta = 1.40 - 1.78$ (m, 12 H, 4-H, C(CH_2)$_5$), 2.49 (s, 3 H, NHCH_3), 2.73 (ddd, $J_{2,3} = 8.3$, $J_{3,4A}$, $J_{3,4B} = 3.6$, 7.1 Hz, 1 H, 3-H), 3.52 (sb, 2 H, OH, NHCH_3), 3.62 (dd, $^2J_{1A,1B} = 8.1$, $J_{1A,2} = 7.0$ Hz, 1 H, 1-H_A), 3.72 – 3.90 (m, 2 H, 5-H), 4.04 (dd, $^2J_{1A,1B} = 8.1$, $J_{1B,2} = 6.2$ Hz, 1 H, 1-H_B), 4.21 (ddd, $J_{1A,2} = 7.0$, $J_{1B,2} = 6.2$, $J_{2,3} = 8.3$ Hz, 1 H, 2-H). [Due to incomplete resolution not all couplings were identified]. – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.8, 24.0, 25.1, 35.0, 36.5 (5 t, C(CH_2)$_5$), 29.4 (t, C-4), 33.1 (q, $NHCH_3$), 61.8 (t, C-5), 62.7 (d, C-3), 66.8 (t, C-1), 76.5 (d, C-2), 109.9 (s, $C(CH_2)_5$). – $C_{12}H_{23}NO_3$ (229.3): calcd. C 62.85, H 10.11, N 6.11; found C 62.82, H 10.07, N 5.99.

*(2S,3S)-3-(N-Benzyloxycarbonyl-N-methylamino)-1,2-O-cyclohexylidene-1,2,5-pentanetriol (N-Z-***35***)*

To a solution of the amino alcohol **35** (*erythro*; 378 mg, 1.65 mmol) in abs. CH_2Cl_2 (15 ml) at 0 °C benzyl chloroformate (326 mg, 1.82 mmol) in abs. CH_2Cl_2 (2 ml) was added, followed by triethylamine (183 mg, 1.81 mmol) in abs. CH_2Cl_2 (2 ml). The mixture was allowed to warm to room temp.; after 2 h water (50 ml) was added and the mixture was extracted with CH_2Cl_2 (4 × 20 ml). The organic layer was washed with saturated NaCl solution (20 ml), dried ($MgSO_4$), and evaporated. The resulting colorless oil (669 mg) was purified on silica (column 3 cm × 18 cm, eluent petrol ether/EtOAc 1:1); after solvent removal

(10^{-3} Torr) colorless, analytically pure ***N*-Z-35** (553 mg, 92%) was isolated.

$[\alpha]_D^{20} = -15.8$ ($c = 0.66$, CH_2Cl_2). – IR (film): $\nu = 3464$ (OH), 2936, 1697 (NC=O), 1450, 1403, 1331, 1283, 1160, 1100, 1044 cm^{-1}. – ^1H NMR (250.1 MHz, CD_3OD), mixture of rotamers (59:41): $\delta = 1.28 - 1.63$ ($C(CH_2)_5$), 1.78 – 2.04 (4-H), 2.82 (NCH_3, minor rotamer), 2.86 (NCH_3, major rotamer), 3.40 – 4.28 (1-H, 2-H, 3-H, 5-H), 5.05 – 5.19 (CO_2CH_2Ph), 7.26 – 7.39 (C_6H_5). – ^{13}C NMR (62.9 MHz, CD_3OD) mixture of rotamers (59:41). Major rotamer: $\delta =$ 26.3, 26.5, 27.7, 37.3, 38.86 (5 t, $C(CH_2)_5$), 31.9 (q, $NHCH_3$), 33.1 (t, C-4), 58.4 (d, C-3), 61.3 (t, C-5), 69.4, 69.9 (2 t, C-1, $CH_2C_6H_5$), 79.41 (d, C-2), 112.9 (s, $C(CH_2)_5$), 130.2, 130.55, 131.0 (3 d, *o*-, *m*-, *p*-C von C_6H_5), 139.6 (s, *i*-C von C_6H_5), 160.1 (s, CO_2CH_2Ph). – Minor rotamer: $\delta = 33.5$ (t, C-4), 38.90 (t, $C(CH_2)_5$), 56.3 (d, C-3), 61.2 (t, C-5), 69.1, 70.0 (2 t, C-1, $CH_2C_6H_5$), 79.44 (d, C-2), 130.5, 130.63 (2 d, *o*-, *m*-, *p*-C von C_6H_5), 139.4 (s, *i*-C von C_6H_5), 159.7 (s, CO_2CH_2Ph); other signals overlapped by those of the major rotamer. – $C_{20}H_{29}NO_5$ (363.5): calcd. C 66.09, H 8.04, N 3.85; found C 66.01, H 8.01, N 3.75.

*(3S,4S)-4,5-Cyclohexylidenedioxy-3-methylamino-pentanoic acid (***37***) and hydrochloride* **37**·*HCl*

a) Amino acid **37**: According to ref. [36] a solution of H_5IO_6/CrO_3 (0.44 M of H_5IO_4) was prepared from H_5IO_6 (10.0 g, 43.9 mmol) and CrO_3 (20.2 mg, 0.20 mmol) in acetonitrile (100 ml, with 0.75% v/v of water) and applied to the oxidation of the alcohol **35**. The latter (309 mg, 0.85 mmol) was dissolved in aqueous acetonitrile (10 ml, 0,75% v/v) and cooled to 0 °C; then within 10 min the solution of the oxidant (5.8 ml, 2.55 mmol of HIO_6) was added. After 2 h the pH of the mixture was brought to 5 by adding a solution of Na_2HPO_4 (0.42 M), then it was extracted with toluene (3×20 ml). The organic phase was washed with aqueous NaCl (half saturated, 2×5 ml), $NaHSO_3$ (0.42 M, 5 ml), and NaCl (saturated, 5 ml) and dried over $MgSO_4$. After concentration (15 Torr) a colorless resin (*N*-Z-acid, 271 mg) was obtained which was taken up in methanol (10 ml). Into this solution under N_2 Pd/C (10%, 120 mg) was placed, then hydrogen was introduced (1 bar) and the mixture was hydrogenated on stirring for 1 d, then filtered (celite, washed with methanol) and rota-evaporated. From this a brownish resin (164 mg, "79%") was obtained which according to NMR analysis consisted of pure amino acid **37**. Since the elemental analysis indicated some impurities, purification and full characterization was done with the hydrochloride **37**·HCl, *vide infra*.

^1H NMR (500.1 MHz, CD_3OD): $\delta = 1.41 - 1.72$ (m, 10 H, $C(CH_2)_5$), 2.48 – 2.54 (m, 2 H, 2-H), 2.75 (s, 3 H, NCH_3), 3.44 – 3.48 (m, 1 H, 3-H), 3.82 (dd, $J_{4,5A} = 5.8$, $^2J_{5A,5B} = 9.1$ Hz, 1 H, 5-H_A), 4.13 (dd, $J_{4,5B} = 7.0$, $^2J_{5A,5B} = 9.1$ Hz, 1 H, 5-H_B), 4.50 (ddd, $J_{3,4} = 3.2$, $J_{4,5A} =$ 5.8, $J_{4,5B} = 7.0$ Hz, 1 H, 4-H). – ^{13}C NMR (62.9 MHz, CD_3OD): $\delta = 26.2$, 26.4, 27.6, 36.4, 38.1 (5 t, $C(CH_2)_5$), 32.6 (q, NCH_3), 34.1 (t, C-2), 61.1 (d, C-3), 67.8 (t, C-5), 75.4 (d, C-4), 113.5 (s, $C(CH_2)_5$), 179.1 (s, C-1).

b) Hydrochloride **37**·HCl: The amino acid **37** (156 mg) was dissolved in CH_2Cl_2 (5 ml, abs.) and moist HCl gas (from supernatant vapour phase of a bottle with conc. HCl) introduced with a syringe until the salt precipitated. The mixture was rota-evaporated (15 Torr), leaving a brownish solid (177 mg) which was recrystallized from acetone/water to afford colorless, analytically pure crystals of **37**·HCl (119 mg, 53% from ***N*-Z-35**). A sample of this proved suitable for crystal structure analysis [37].

M. p. 178 – 181 °C (dec.). – $[\alpha]_D^{20} = -32.3$ ($c = 1.02$, MeOH). – IR (KBr): $\nu = 3435$ (br; NH, OH), 2954 (b), 2851, 2791, 2733, 1724 (C=O), 1585, 1365, 1211, 1098, 1049, 938 cm^{-1}. – ^1H NMR (500.1 MHz, CD_3OD): $\delta =$ 1.41 – 1.71 (m, 10 H, $C(CH_2)_5$), 2.67 (dd, $^2J_{2A,2B} = 18.1$, $J_{2A,3} = 7.5$ Hz, 1 H, 2-H_A); 2.78 (s, NCH_3), 2.80 ("dd", $^2J_{2A,2B} = 18.3$, $J_{2B,3} = 4.2$ Hz, 2-H_b) – sum 4 H; 3.67 ("ddd", $J_{2A,3} = 7.6$, $J_{2B,3} = 4.3$, $J_{3,4} = 2.9$ Hz, 1 H, 3-H), 3.82 (dd, $J_{4,5A} = 5.5$, $^2J_{5A,5B} = 9.3$ Hz, 1 H, 5-H_A), 4.17 (dd, $J_{4,5B} = 7.2$, $^2J_{5A,5B} = 9.3$ Hz, 1 H, 5-H_B), 4.56 (ddd, $J_{3,4} = 3.0$, $J_{4,5A} = 5.5$, $J_{4,5B} = 7.1$ Hz, 1 H, 4-H). – ^{13}C NMR (75.5 MHz, CD_3OD): $\delta = 24.8$, 25.0, 26.2, 34.7, 36.5 (5 t, $C(CH_2)_5$), 31.2 (t, C-2), 31.9 (q, NCH_3), 58.9 (d, C-3), 66.4 (t, C-5), 74.1 (d, C-4), 112.4 (s, $C(CH_2)_5$), 174.3 (s, C-1). – $C_{12}H_{22}ClNO_4$ (279.8): calcd. C 51.52, H 7.93, N 5.01, Cl 12.67; found C 51.39, H 7.92, N 4.89, Cl 12.64.

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