135. Stereoselective Synthesis of Masked Amino-polyols *via* Osmylation of 4,5-Dihydro-5-vinylisoxazoles

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Variously substituted 4,5-dihydro-5-vinylisoxazoles, obtained by regio- and stereospecific cycloaddition of nitrile oxides to dienes, undergo smooth OsO_4-catalyzed *cis*-hydroxylation to give amino-polyol precursors. The reaction is *'anti'*-selective, the diastereoisomeric ratios ranging from 73:27 up to $\geq$ 99:1. Thus, the cycloaddition/osmylation sequence allows the control of the relative configuration of up to four contiguous asymmetric centers. A sulfoxide-mediated approach to enantiomerically pure compounds is also described.

Introduction. – The versatility of 4,5-dihydroisoxazoles (Δ^2-isoxazolines) for the construction of variously substituted acyclic carbon skeletons is well established. Indeed, as demonstrated especially by the extensive work of *Jäger* and *Kozikowski* [1], a number of latent functionalities disguised in this heterocyclic ring can be unmasked in a highly stereocontrolled fashion, to deliver, *inter alia*, β-ketols [2], γ-aminoalcohols [3], polyols [4], and aminosugars [5].

We have recently developed a new approach to enantiomerically pure 4,5-dihydroisoxazoles [6] and studied the stereoselective generation of additional asymmetric centers outside of the heterocyclic ring [7]. We report here on the OsO_4-promoted *cis*-hydroxylation of 4,5-dihydro-5-vinylisoxazoles.

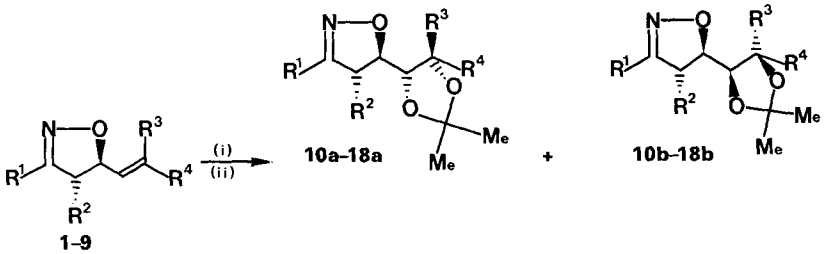
Results and Discussion. – Trapping of nitrile oxides [8], generated *in situ* from nitroethane [9] or from the appropriate hydroximoyl chloride [10], with a variety of commercially available dienes [11] gave 4,5-dihydroisoxazoles **1–9** in high yields. The cycloaddition proceeded, as expected [8] [10], regioselectively[1]) on the less substituted and/or less hindered double bond of the dienes *via* a stereospecific *cis*-attack. As reported in part in a preliminary note [12], compounds **1–9** underwent catalytic osmylation [13] to give mixtures of the corresponding diols.

Since conversion of the latter into the acetals **10–18**, respectively, allowed ready isomer separation and thus direct diastereoisomeric-ratio (d.r.) evaluations, it was routinely performed *(Scheme 1)*. In *Table 1*, yields, physical properties, and isomer ratios are collected.

The data found indicates that the osmylation is always *'anti'*-selective [14], in agreement with the stereochemical course of the OsO_4 oxidation of allylic alcohols and ethers as proposed earlier on empirical [15] as well as on theoretical grounds [16] [17].

[1]) In the synthesis of compound **7**, less than 5% of the isomeric 4,5-dihydroisoxazole was formed (see *Table 1, Footnote f*).

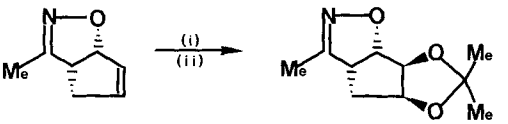
Scheme 1



1–9 **10a–18a** + **10b–18b**

1, 10a, b R^1=Me, R^2=R^3=R^4=H
2, 11a, b R^1=CO_2Et, R^2=R^3=R^4=H
3, 12a, b R^1=Ph, R^2=R^3=R^4=H
4, 13a, b R^1=NO_2Ph, R^2=R^3=R^4=H
5, 14a, b R^1=R^3=Me, R^2=R^4=H
6, 15a, b R^1=R^4=Me, R^2=R^3=H
7, 16a, b R^1=R^2=R^3=Me, R^4=H
8, 17a, b R^1=R^2=R^4=Me, R^3=H
9, 18a, b R^1=R^3=R^4=Me, R^2=H

(*i*) OsO_4, $Me_3N{\rightarrow}O$; (*ii*) $Me_2C(OMe)_2$, TsOH.
Only one enantiomer is indicated for simplicity



19 **20**

Table 1. *Stereoselective Synthesis of Acetals* **10–18**[a])

Entry	Starting material	Product	Yield[b]) [%]	d.r.[c]) **a**/**b**	Isomer **a** m.p. [°C] (n_D^{23})	Isomer **b** m.p. [°C] (n_D^{23})
A	**1**	**10a, b**	80	78:22	44–45	63–64
B	**1**	**10a, b**	72[d])	78:22	–	–
C	**2**	**11a, b**	83	77:23	(1.4659)	(1.4710)
D	**2**	**11a, b**	65[d])	76:24	–	–
E	**3**	**12a, b**	74[e])	75:25	69–70	74–75
F	**4**	**13a, b**	82[e])	73:27	162–164	96–98
G	**5**	**14a, b**	80	86:14	(1.4590)	(1.4669)
H	**6**	**15a, b**	70	75:25	(1.4569)	(1.4591)
I	**7**	**16a, b**	70	92:8	–[f])	–[f])
J	**8**	**17a, b**	69	73:27	(1.4522)	50–51
K	**9**	**18a, b**	70	89:11	58–60	(1.4643)

[a]) Unless otherwise stated, all reactions were carried out on a 1 to 5-mmol scale at 0 °C for 5 h.
[b]) Overall yield of **10–18** from **1–9**, respectively.
[c]) Diastereoisomeric ratios (d.r.) evaluated by isomer separation and, if necessary, by 200-MHz-^{1}H-NMR analysis (see *Exper. Part*).
[d]) Reaction carried out at −20 °C.
[e]) Reaction time 15 h.
[f]) These products contain small amounts of their isomer (see text, *Footnote 1*).

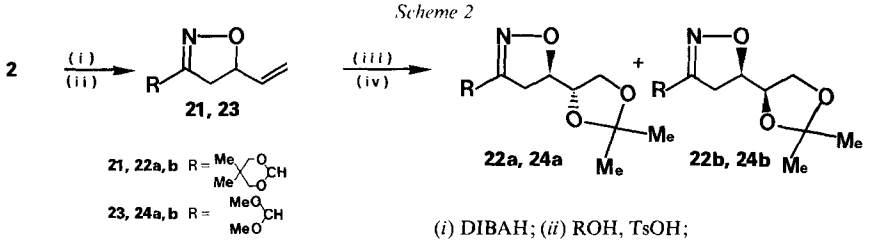
As far as the extent of the stereoselection is concerned, neither the nature of the R^1 group (*Entries A, C, E,* and *F*) nor a variation of the reaction temperature *(Entries A–D)* seem to exert any appreciable effect. The d.r. observed in the case of the *cis*-hydroxylation of monosubstituted double bonds (*Entries A, C, E,* and *F*) can conveniently be compared with those observed in the cycloaddition of corresponding nitrile oxides to *O,O*-isopro-

pylidene-3-butene-1,2-diols [4] [18]. Also in this case, the *'anti'*-isomers are predominant, the d.r. for compounds **10–13** ranging from 80:20 to 88:12.

The substitution pattern at the double bond affects the stereochemical outcome of the process in a well definite way. Indeed, while the presence of a CH_3 group *trans*-arranged with respect to the isoxazolinyl moiety has apparently no effect *(Entries A vs. H)*, the steric congestion brought about by a *cis*-methyl substituent markedly increases the d.r., boosting the *'anti'/'syn'* ratios up to 92:8 (*Entries G, I,* and *K*). Also this behaviour is in line with the proposed model [15]. It is worth mentioning that in the case of compound **16**, an almost complete control of the relative configuration at four contiguous asymmetric centers is achieved by the cycloaddition/osmylation. A stereospecific reaction was observed in a case with less flexibility. Thus, cycloaddition of acetonitrile oxide [9] to cyclopentadiene [8] gave dihydroisoxazole **19**, in which the double bond is specifically attacked from the less hindered side to give *one* diastereoisomer **20** as the product of the *'anti'*-attack.

As mentioned in the introduction and as pointed out by several authors, compounds of the type of **10–18** and **20** represent useful synthons for aminosugars [1] [5] [18], since reduction of the dihydroisoxazole ring produces γ-amino alcohols with high degrees of stereoselectivity [3] [6]. Therefore, we briefly investigated the osmylation of some selected derivatives of **1–9**.

Scheme 2



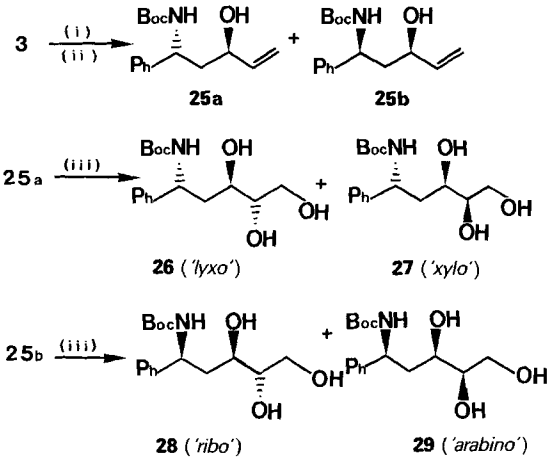
(*i*) DIBAH; (*ii*) ROH, TsOH;
(*iii*) OsO_4, $Me_3N \rightarrow O$; (*iv*) $Me_2C(OMe)_2$, TsOH

As shown in *Scheme 2*, compound **2** was converted into the protected aldehyde **21**. *cis*-Hydroxylation of the latter, followed by acetalization gave **22a, b** as a 72:28 *'anti'/'syn'* mixture of separable isomers. From compound **22a**, racemic lividosamine was obtained by *Jäger* [5b]. A slight increase in the stereoselection of osmylation was observed for the dimethyl acetal **23** which produced **24a, b** in 75:25 *'anti'/'syn'* ratio. Compound **22a, b** has been obtained as a 77:23 *'anti'/'syn'* mixture by the cycloaddition approach [5b].

We studied also the reaction sequence outlined in *Scheme 3*. $LiAlH_4$ reduction of **3** followed by protection of the amino group as Boc derivative allowed the isolation of **25a** *('anti')* and **25b** *('syn')* in a 13:87 ratio. Isomer **25a** was converted by the usual procedure into a 75:25 mixture of **26** *('lyxo')* and **27** *('xylo')*. Similarly from **25b**, **28** *('ribo')* and **29** *('arabino')* were obtained in a 70:30 ratio. Thus, as the result of the combined diastereoselectivities of the two processes, the four isomeric amino polyols **28**, **29**, **26**, and **27** are produced in a 61:26:10:3 ratio. Analogous diastereoisomeric ratios were obtained by *Jäger* [5b] *via* a cycloaddition/reduction sequence.

In a final attempt to improve the stereoselectivity of the osmylation reaction of 4,5-dihydro-5-vinylisoxazoles, oxydation of **1** employing a stoichiometric amount of

Scheme 3



(*i*) $LiAlH_4$;
(*ii*) $(t\text{-}BuOCO)_2O$;
(*iii*) OsO_4, $Me_3N{\rightarrow}O$

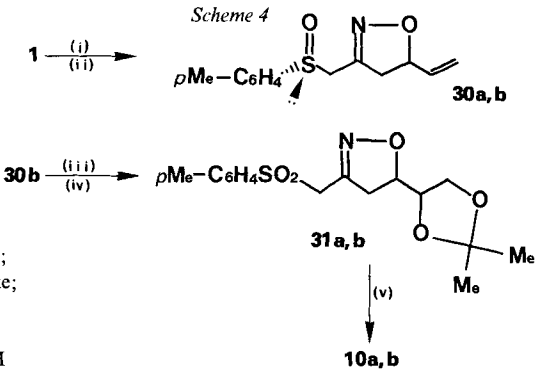
Table 2. *Stereoselective Synthesis of* **10a, b** via *Stoichiometric Osmylation*

Base[a])	Yield[b]) [%]	Diastereoisomeric ratio **10a**/**10b**
Pyridine	50	63:37
2,6-Dimethylpyridine	30	67:33
$Et(i\text{-}Pr)_2N$	28	66:34
Et_3N	44	75:25
1,4-Diazabicyclo[2.2.2]octane (DABCO)[c])	45	79:21
Dihydroquinine acetate	51	75:25

[a]) Unless otherwise stated, 2 mol-equiv. of base per mol of substrate employed.
[b]) Overall yield of **10a, b** from **1**.
[c]) 1 mol-equiv. of base.

OsO_4 was studied [15]. The results are collected in *Table 2*. Quite surprisingly, no increase in the *'anti'*/*'syn'* product ratios was observed but, on the contrary, stoichiometric oxydations gave almost constantly poorer selectivities and lower chemical yields with respect to those obtained under catalytic conditions. While conversion of dihydroisoxazole to isoxazole can account for the latter observation, the former is, to the best of our knowledge, unprecedented. Since tertiary amines are known to affect the osmylation ratio [19], different bases were tested. Among these, aromatic and hindered aliphatic amines gave rise to less selectivity; the only slight increase in stereoselection with respect to catalytic osmylation was observed with 1,4-diazabicyclo[2.2.2]octane (DABCO) which displays strongly chelating bridgehead N-atoms [20]. The same feature is present in dihydroquinine acetate [21] which is known to coordinate OsO_4 and to promote asymmetric oxydation on olefins [22]. The reaction carried out in the presence of this base produced **10a**/**10b** in a 75:25 ratio and gave low to medium asymmetric induction yielding (+)-**10a** and (−)-**10b** in 21 and 60% enantiomeric excess, respectively (see below for the enantiomeric excess determination).

Scheme 4



(*i*) Lithium diisopropylamide;
(*ii*) menthyl *p*-toluenesulfinate;
(*iii*) OsO_4, $Me_3N \rightarrow O$;
(*iv*) Me_2CO, TsOH;
(*v*) Na/Hg, NaH_2PO_4, MeOH

Therefore, in order to prepare **10a** and **10b** in enantiomerically pure form we exploited our recently reported sulfoxide-mediated approach to enantiomerically pure dihydroisoxazole [6] [12]. Accordingly, from **1** a mixture of 4,5-dihydro 3-((*R*)-*p*-tolylsulfinyl)methyl-5-vinylisoxazoles (**30a, b**), epimeric at C(5), was prepared [6] and separated into the pure individual components [12]. Osmylation and acetalization of **30b** gave the corresponding sulfone **31a, b** which, after Na-amalgam-promoted desulfurization, afforded (–)-**10a** and (–)-**10b** in a 78:22 ratio *(Scheme 4)*. They were separated as usual to give enantiomerically pure (–)-**10a**, $[\alpha]_D^{23} = -79.0°$ ($c = 0.2$, $CHCl_3$), and (–)-**10b**, $[\alpha]_D^{23} = -90.6°$ ($c = 0.2$, $CHCl_3$). It must be noted that when the reaction was performed on a 1:1 mixture of the sulfoxide **30a**/**30b** (epimers at C(5)), racemic **10a** and **10b** were obtained; therefore, in this case the sulfoxide group seems to exert no appreciable effect neither on the diastereo- nor on the enantioselectivity of the process, in contrast with what was observed in an acyclic and conformationally free system [23].

Experimental Part

1. General. Anh. solvents were obtained in the usual way and stored and transferred under Ar. All reagents were commercial products and were used without further purification, unless otherwise indicated. Org. extracts were dried over Na_2SO_4 and filtered before removal of the solvent under reduced pressure. Silica gel was used for TLC and column chromatography. M.p. and b.p. are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on *Varian-EM-390* and *Varian-XL-200* instruments in $CDCl_3$ as solvent, unless otherwise stated (chemical shifts in ppm downfield from internal TMS; coupling constants *J* in Hz). $[\alpha]_D$'s were measured on a *Perkin-Elmer-241* polarimeter. Elemental analyses were performed with a *Perkin-Elmer-240* instrument.

2. 4,5-Dihydro-5-vinylisoxazoles. Compds. **1**, **5**–**9**, and **19** were prepared following the method described in [9] and **2**–**4** following the method described in [10]. Compds. **1** [11], **2** [11], and **3** [24] had physical and spectral data in agreement with those reported.

*2.1. 4,5-Dihydro-3-(*p*-nitrophenyl)-5-vinylisoxazole* (**4**). Yield 77%, m.p. 146–147° (from AcOEt). ^{1}H-NMR: 8.45–7.85 (*AA'BB'*, 4 arom. H); 6.15–5.95 (*m*, CH_2=C*H*); 5.55–5.10 (*m*, C*H*$_2$=CH, H–C(5)); 3.70–3.00 (*m*, CH_2(4)). Anal. calc. for $C_{11}H_{10}N_2O_2$ (202.22): C 65.33, H 4.98, N 13.85; found: C 65.39, H 5.03, N 13.72.

2.2. 4,5-Dihydro-3-methyl-5-((Z)-prop-1'-enyl)isoxazole (**5**). Yield 75%, bulb-to-bulb distillation at 125–130° (bath temp.)/16 Torr, $n_D^{23} = 1.4740$. ^{1}H-NMR: 5.75–5.10 (*m*, H–C(1'), H–C(2'), H–C(5)); 3.30–2.45 (*m*, CH_2); 2.05 (*s*, CH_3–C(3)); 1.80 (*d*, 3H–C(3')). Anal. calc. for $C_7H_{11}NO$ (125.17): C 67.17, H 8.86, N 11.19; found: C 67.25, H 8.91, N 11.10.

2.3. 4,5-Dihydro-3-methyl-5-((E)-prop-1'-enyl)isoxazole (**6**). Yield 78%, bulb-to-bulb distillation at 130–135° (bath temp.)/15 Torr, $n_D^{23} = 1.4750$. ^{1}H-NMR: 5.95–5.30 (*m*, H–C(1'), H–C(2')); 5.00–4.70 (*m*, H–C(5)); 3.20–2.50 (*m*, CH_2); 1.95 (*s*, CH_3–C(3)); 1.70 (*d*, 3H–C(3')). Anal. calc. for $C_7H_{11}NO$ (125.17): C 67.17, H 8.86, N 11.19; found: C 67.28, H 8.86, N 11.25.

2.4. trans-*4,5-Dihydro-3,4-dimethyl-5-((Z)-prop-1'-enyl)isoxazole* (**7**). Yield 59%, bulb-to-bulb distillation at 135–140° (bath temp.)/15 Torr; contaminated by *ca.* 5% of an unseparable isomeric compd., tentatively identified as the product of cycloaddition on the *cis*-double bond of the diene. ^{1}H-NMR: 5.90–5.40 (*m*, H–C(1'), H–C(2')); 4.85–4.65 (*dd*, H–C(5)); 3.1–2.7 (*m*, H–C(4)); 1.95 (*s*, CH_3–C(3)); 1.80 (*d*, 3H–C(3')); 1.25 (*d*, CH_3–C(4)). Anal. calc. for $C_8H_{13}NO$ (139.20): C 69.03, H 9.41, N 10.06; found: C 69.10, H 9.45, N 10.10.

2.5. trans-*4,5-Dihydro-3,4-dimethyl-5-((E)-prop-1'-enyl)isoxazole* (**8**). Yield 43%, purified by flash chromatography (Et_2O/hexane 3:7). ^{1}H-NMR: 5.90–5.50 (*m*, H–C(1'), H–C(2')); 4.45–4.30 (*dd*, H–C(5)); 3.00–2.80 (*m*, H–C(4)); 1.95 (*s*, CH_3–C(3)); 1.75 (*d*, H–C(3')); 1.30 (*d*, CH_3–C(4)). Anal. calc. for $C_8H_{13}NO$ (139.20): C 69.03, H 9.41, N 10.06; found: C 69.18, H 9.34, N 10.01.

2.6. 4,5-Dihydro-3-methyl-5-(2'-methylprop-1'-enyl)isoxazole (**9**). Yield 87%, bulb-to-bulb distillation at 150–155° (bath temp.)/15 Torr, $n_D^{23} = 1.4835$. ^{1}H-NMR: 5.25–4.90 (*m*, H–C(1'), H–C(5)); 3.10–2.25 (*m*, CH_2(4)); 1.90 (*s*, CH_3–C(3)); 1.65 (*s*, 2 CH_3–C(2')). Anal. calc. for $C_8H_{13}NO$ (139.20): C 69.03, H 9.41, N 10.06; found: C 69.00, H 9.45, N 9.97.

2.7. 4,6a-Dihydro-3-methyl-3aH-cyclopent[d]isoxazole (**19**). Yield 49%, obtained by flash chromatography with Et_2O/hexane 6:4, containing traces of diphenylurea; purification attempts by fractional distillation resulted in extensive cycloreversion. ^{1}H-NMR: 5.90–5.40 (*m*, H–C(5), H–C(6), H–C(6a)); 3.80–3.55 (*m*, H–C(3a)); 2.85–2.30 (*m*, CH_2); 1.90 (*s*, CH_3–C(3)).

3. General Procedure for Catalytic Osmylation of Dihydro-vinylisoxazoles. To a stirred soln. of dihydro-vinylisoxazole (1–5 mmol) in THF/H_2O 9:1 (5 ml per mmol) cooled at 0°, 2 mol-equiv. of $Me_3N{\rightarrow}O \cdot 2H_2O$ were added, followed by 0.1 mol-equiv. of 0.04M OsO_4 in *t*-BuOH. The mixture was stirred at 0° for 5 h and the reaction quenched by the addition of solid $NaHSO_3$. Vigorous stirring was maintained for 30 min. Then, the mixture was evaporated *in vacuo* and the resulting dark solid residue filtered through a short silica-gel column with Et_2O/MeOH mixtures to give the mixtures of isomeric diols which were converted as such into their acetals.

4. General Procedure for Stoichiometric Osmylation of Dihydro-vinylisoxazoles. To a stirred soln. of dihydro-vinylisoxazole (1 mmol) and tertiary amine (2 mmol) in anh. toluene (2 ml) cooled to −78°, 2.5 ml of 0.4M OsO_4 in toluene (1 mmol) were added. After 2 h stirring at −78°, the mixture was allowed to warm up to r.t. and stirred for 5 h. Solid $NaHSO_3$ was added and, after 3 h stirring, the reaction was worked up as described above to give mixtures of diols which were converted as such into their acetals.

5. General Procedure for the Synthesis of Acetals **10–18** *and* **20**. To a stirred soln. of the diol in 2,2-dimethoxypropane, a spatula tip of TsOH was added and the mixture stirred for 2 h at r.t. Solid $NaHCO_3$ was then added and the mixture filtered and concentrated *in vacuo* to give an oily residue. Flash chromatography with Et_2O/hexane separated the isomers. *'anti'*-Products constantly showed higher R_f and larger J(H–C(5), H–C–O) (6.7–7.8 Hz) than their *'syn'*-counterparts (J = 3.3–5.3 Hz), in agreement with previous observations [4b] [5b]. Overall yields, isomer ratios, and physical properties for **10–18** are reported in *Table 1*. Compds. **10a, b, 11a, b,** and **12a, b** were reported elsewhere [4b] [18].

5.1. 5-(2',2'-Dimethyl-1',3'-dioxolan-4'-yl)-4,5-dihydro-3-(p-nitrophenyl)isoxazole (**13**). Chromatography with Et_2O/hexane 4:1. Anal. calc. for $C_{14}H_{16}N_2O_5$ (292.30): C 57.75, H 5.52, N 9.59; found: C 57.87, H 5.62, N 9.48.

(5RS,4'SR)-**13a**: ^{1}H-NMR: 8.25–7.82 (*AA'BB'*, 4 arom. H); 4.76 (*X* of *ABX*, J(H–C(5), H–C(4')) = 7.0, J(H–C(5), H–C(4)) = 7.0, J(H–C(5), H–C(4)) = 10.0, H–C(5)); 4.20–4.10 (*m*, CH_2(5')); 4.10–3.92 (*m*, H–C(4')); 3.44 (*AB* of *ABX*, J(H–C(4), H–C(4)) = 17.5, J(H–C(4), H–C(5)) = 7.0, J(H–C(4), H–C(5)) = 10.0, CH_2(4)); 1.45 (*s*, CH_3); 1.35 (*s*, CH_3).

(5RS,4'RS)-**13b**: ^{1}H-NMR: 8.34–7.72 (*AA'BB'*, 4 arom. H); 5.07–4.67 (*m*, H–C(5)); 4.48–3.92 (*m*, CH_2(5'), H–C(4')); 3.57–3.40 (*m*, CH_2(4)); 1.51 (*s*, CH_3); 1.42 (*s*, CH_3).

5.2. 4,5-Dihydro-3-methyl-5-(2',2',5'-trimethyl-1',3'-dioxolan-4'-yl)isoxazole (**14**). Chromatography with Et_2O/hexane 1:1. Anal. calc. for $C_{10}H_{17}NO_3$ (199.25): C 60.28, H 8.60, N 7.03; found: C 60.27, H 8.69, N 6.99.

(5RS,4'SR,5'SR)-**14a**: ^{1}H-NMR: 4.35 (*q*, J(H–C(5), CH_2(4)) = 8.70, H–C(5)); 4.36 (*quint.*, J(H–C(5'), CH_3–C(5')) = 6.5, J(H–C(5'), H–C(4')) = 6.5, H–C(5')); 3.9 (*dd*, J(H–C(4'), H–C(5)) = 8.70, J(H–C(4'), H–C(5')) = 6.5, H–C(4')); 3.00 (*d*, J(CH_2(4), H–C(5)) = 8.70, CH_2(4)); 1.98 (*s*, CH_3–C(3)); 1.40 (*s*, CH_3–C(2')); 1.32 (*d*, J(CH_3–C(5'), H–C(5')) = 6.5, CH_3–C(5')); 1.32 (*s*, CH_3–C(2')).

(5RS,4'RS,5'RS)-**14b**: ^{1}H-NMR: 4.56 (*X* of *ABX*, J(H–C(5), H–C(4)) = 9.1, J(H–C(5), H–C(4)) = 10.6, J(H–C(5), H–C(4')) = 5.3, H–C(5)); 4.34 (*quint.*, J(H–C(5'), H–C(4')) = 6.35, J(H–C(5'), CH_3–C(5')) = 6.35, H–C(5')); 4.04 (*dd*, J(H–C(4'), H–C(5')) = 6.35, J(H–C(4'), H–C(5)) = 5.3, H–C(4')); 2.85 (*AB* of *ABX*, J(H–C(4), H–C(4)) = 15.4, J(H–C(4), H–C(5)) = 10.6, J(H–C(4), H–C(5)) = 9.1, J(CH_2(4), CH_3–C(3)) = 0.9, CH_2(4)); 1.97 (*t*, J(CH_3–C(3), CH_2(4)) = 0.9, CH_3–C(3)); 1.48 (*s*, CH_3–C(2')); 1.36 (*s*, CH_3–C(2')); 1.30 (*d*, J(CH_3–C(5'), H–C(5')) = 6.35, CH_3–C(5')).

5.3. 4,5-Dihydro-3-methyl-5-(2',2',5'-trimethyl-1',3'-dioxolan-4'-yl)isoxazole (**15**). Chromatography with Et_2O/hexane 1:1. Anal. calc. for $C_{10}H_{17}NO_3$ (199.25): C 60.28, H 8.60, N 7.03; found: C 60.40, H 8.51, N 7.07.

(5RS,4'SR,5'RS)-**15a**: ^{1}H-NMR: 4.10 (*X* of *ABX*, *J*(H–C(5), H–C(4)) = 10.3, *J*(H–C(5), H–C(4)) = 7.4, *J*(H–C(5), H–C(4')) = 7.5, H–C(5)); 3.75 (*dq*, *J*(H–C(5'), H–C(4')) = 7.6, *J*(H–C(5'), CH_3–C(5')) = 6, H–C(5')); 3.35 (*t*, *J*(H–C(4'), H–C(5')) = 7.6, *J*(H–C(4'), H–C(5)) = 7.5, H–C(4')); 2.80 (*AB* of *ABX*, *J*(H–C(4), H–C(4)) = 17.7, *J*(H–C(4), H–C(5)) = 10.2, *J*(H–C(4), H–C(5)) = 7.4, CH_2(4)); 1.82 (*s*, CH_3–C(3)); 1.21 (*s*, CH_3–C(2')); 1.18 (*s*, CH_3–C(2')); 1.16 (*d*, *J*(CH_3–C(5'), H–C(5')) = 6, CH_3–C(5')).

(5RS,4'RS,5'SR)-**15b**: ^{1}H-NMR: 4.57 (*X* of *ABX*, *J*(H–C(5), H–C(4')) = 3.3, *J*(H–C(5), H–C(4)) = 10.2, *J*(H–C(5), H–C(4)) = 8.4, H–C(5)); 4.10 (*dq*, *J*(H–C(5'), CH_3–C(5')) = 6, *J*(H–C(5'), H–C(4')) = 8.5, H–C(5')); 3.60 (*dd*, *J*(H–C(4'), H–C(5')) = 8.5, *J*(H–C(4'), H–C(5)) = 3.3, H–C(4')); 2.95 (*AB* of *ABX*, *J*(H–C(4), H–C(4)) = 17.0, *J*(H–C(4), H–C(5)) = 10.2, *J*(H–C(4), H–C(5)) = 8.4, *J*(CH_2(4), CH_3–C(3)) = 0.9, CH_2(4)); 1.98 (*t*, *J* (CH_3–C(3), CH_2(4)) = 0.9, CH_3–C(3)); 1.42 (*s*, CH_3–C(2')); 1.38 (*s*, CH_3–C(2')); 1.30 (*d*, *J*(CH_3–C(5'), H–C(5')) = 6, CH_3–C(5')).

5.4. 4,5-Dihydro-3,4-dimethyl-5-(2',2',5'-trimethyl-1',3'-dioxolan-4'-yl)isoxazole (**16**). Chromatography with Et_2O/hexane 1:1. Anal. calc. for $C_{11}H_{19}NO_3$ (213.28): C 61.95, H 8.98, N 6.57; found: C 62.11, H 8.83, N 6.55.

(4RS,5RS,4'SR,5'SR)-**16a**: ^{1}H-NMR: 3.91 (*dd*, *J*(H–C(5), H–C(4')) = 7.8, *J*(H–C(5), H–C(4)) = 6.9, H–C(5)); 3.90 (*dq*, *J*(H–C(5'), H–C(4')) = 7.8, *J*(H–C(5'), CH_3–C(5')) = 6, H–C(5')); 3.40 (*t*, *J*(H–C(4'), H–C(5)) = 7.8, *J*(H–C(4'), H–C(5')) = 7.8, H–C(4')); 3.10 (*dqq*, *J*(H–C(4), H–C(5)) = 6.9, *J*(H–C(4), CH_3–C(4)) = 8.0, *J*(H–C(4), CH_3–C(3)) = 0.9, H–C(4)); 1.90 (*d*, *J*(CH_3–C(3), H–C(4)) = 0.9, CH_3–C(3)); 1.30 (*s*, CH_3–C(2')); 1.27 (*s*, CH_3–C(2')); 1.26 (*d*, *J*(CH_3–C(5'), H–C(5')) = 6.0, CH_3–C(5')); 1.15 (*d*, *J*(CH_3–C(4), H–C(4)) = 8.0, CH_3–C(4)).

(4RS,5RS,4'RS,5'RS)-**16b**: ^{1}H-NMR: 4.10 (*dq*, *J*(H–C(5'), H–C(4')) = 8.3, *J*(H–C(5'), CH_3–C(5')) = 6.0, H–C(5')); 4.04 (*dd*, *J*(H–C(5), H–C(4)) = 8.3, *J*(H–C(5), H–C(4')) = 3.3, H–C(5)); 3.60 (*dd*, *J*(H–C(4'), H–C(5')) = 8.3, *J*(H–C(4'), H–C(5)) = 3.3, H–C(4')); 3.13 (*dqq*, *J*(H–C(4), CH_3–C(4)) = 8.0, *J*(H–C(4), H–C(5)) = 8.3, *J*(H–C(4), CH_3–C(3)) = 0.9, H–C(4)); 1.90 (*d*, *J*(CH_3–C(3), H–C(4)) = 0.9, CH_3–C(3)); 1.36 (*s*, CH_3–C(2')); 1.34 (*s*, CH_3–C(2')); 1.26 (*d*, *J*(CH_3–C(5'), H–C(5')) = 6.0, CH_3–C(5')); 1.19 (*d*, *J*(CH_3–C(4), H–C(4)) = 8.0, CH_3–C(4)).

5.5. 4,5-Dihydro-3,4-dimethyl-5-(2',2',5'-trimethyl-1',3'-dioxolan-4'-yl)isoxazole (**17**). Chromatography with Et_2O/hexane 1:1. Anal. calc. for $C_{11}H_{19}NO_3$ (213.28): C 61.95, H 8.98, N 6.57; found: C 61.87, H 8.91, N 6.60.

(4RS,5RS,4'SR,5'RS)-**17a**: ^{1}H-NMR: 3.95 (*t*, *J*(H–C(5), H–C(4')) = 7.6, *J*(H–C(5), H–C(4)) = 7.6, H–C(5)); 3.94 (*dq*, *J*(H–C(5'), H–C(4')) = 7.6, *J*(H–C(5'), CH_3–C(5')) = 6.0, H–C(5')); 3.45 (*t*, *J*(H–C(4'), H–C(5)) = 7.6, *J*(H–C(4'), H–C(5')) = 7.6, H–C(4')); 3.10 (*dq*, *J*(H–C(4), H–C(5)) = 7.6, *J*(H–C(4), CH_3–C(4)) = 7.0, H–C(4)); 1.57 (*s*, CH_3–C(3)); 1.32 (*s*, CH_3–C(2')); 1.29 (*s*, CH_3–C(2')); 1.29 (*d*, *J*(CH_3–C(5'), H–C(5')) = 6.0, CH_3–C(5')); 1.18 (*d*, *J*(CH_3–C(4), H–C(4)) = 7.0, CH_3–C(4)).

(4RS,5RS,4'RS,5'SR)-**17b**: ^{1}H-NMR: 4.23 (*dq*, *J*(H–C(5'), CH_3–C(5')) = 6.1, *J*(H–C(5'), H–C(4')) = 8.4, H–C(5')); 3.88 (*dd*, *J*(H–C(5), H–C(4')) = 3.2, *J*(H–C(5), H–C(4)) = 8.1, H–C(5)); 3.63 (*dd*, *J*(H–C(4'), H–C(5)) = 3.2, *J*(H–C(4'), H–C(5')) = 8.4, H–C(4')); 3.18 (*dqq*, *J*(H–C(4), H–C(5)) = 8.1, *J*(H–C(4), CH_3–C(4)) = 7.1, *J*(H–C(4), CH_3–C(3)) = 1.0, H–C(4)); 1.92 (*d*, *J*(CH_3–C(3), H–C(4)) = 1.0, CH_3–C(3)); 1.41 (*s*, CH_3–C(2')); 1.37 (*s*, CH_3–C(2')); 1.30 (*d*, *J*(CH_3–C(5'), H–C(5')) = 6.1, CH_3–C(5')); 1.22 (*d*, *J*(CH_3–C(4), H–C(4)) = 7.1, CH_3–C(4)).

5.6. 4,5-Dihydro-3-methyl-5-(2',2',5',5'-tetramethyl-1',3'-dioxolan-4'-yl)isoxazole (**18**). Chromatography with Et_2O/hexane 1:1. Anal. calc. for $C_{11}H_{19}NO_3$ (213.28): C 61.95, H 8.98, N 6.57; found: C 61.87, H 8.93, N 6.50.

(5RS,4'RS)-**18a**: ^{1}H-NMR: 4.505 (*X* of *ABX*, *J*(H–C(5), H–C(4')) = 8.0, *J*(H–C(5), H–C(4)) = 10.0, *J*(H–C(5), H–C(4)) = 7.8, H–C(5)); 3.62 (*d*, *J*(H–C(4'), H–C(5)) = 8.0, H–C(4')); 3.00 (*AB* of *ABX*, *J*(H–C(4), H–C(4)) = 17.2, *J*(H–C(4), H–C(5)) = 10.0, *J*(H–C(4), H–C(5)) = 7.8, CH_2(4)); 1.99 (*s*, CH_3–C(3)); 1.42, 1.35, 1.31, 1.23 (4*s*, 2 CH_3–C(2'), 2 CH_3–C(5')).

(5RS,4'SR)-**18b**: ^{1}H-NMR: 4.56 (*X* of *ABX*, *J*(H–C(5), H–C(4')) = 7.7, *J*(H–C(5), H–C(4)) = 10.0, *J*(H–C(5), H–C(4)) = 8.0, H–C(5)); 3.81 (*d*, *J*(H–C(4'), H–C(5)) = 7.7, H–C(4')); 2.83 (*AB* of *ABX*, *J*(H–C(4), H–C(4)) = 17.3, *J*(H–C(4), H–C(5)) = 10.0, *J*(H–C(4), H–C(5)) = 8.0, CH_2(4)); 2.01 (*s*, CH_3–C(3)); 1.48, 1.37, 1.33, 1.18 (4*s*, 2 CH_3–C(2'), 2 CH_3–C(5')).

5.7. (3aRS,4aSR,7aSR,7bSR)-3a,4,4a,6,7a,7b-Hexahydro-3,6,6-trimethyl[1',3']dioxolo[4',5':3,4]cyclopent[1,2-d]isoxazole (**20**). Yield 62%, chromatography with Et_2O/hexane 7:3, m.p. 91–92°. ^{1}H-NMR: 4.85 (*d*, *J*(H–C(7b), H–C(3a)) = 8.8 H–C(7b)); 4.74 (*dt*, *J*(H–C(4a), H–C(7a)) = 5.2, *J*(H–C(4a), H–C(4)) = 5.2, *J*(H–C(4a), H–C(4)) = 2.5, H–C(4a)); 4.68 (*d*, *J*(H–C(4a), H–C(7a)) = 5.2, H–C(7a)); 3.64 (*q*, *J*(H–C(3a), H–C(7b)) = 8.8, *J*(H–C(3a), H–C(4)) = 8.8, *J*(H–C(3a), H–C(4)) = 7.6 H–C(3a)); 2.10 (*AB* of *ABX*, *J*(H–C(4), H–C(4)) = 14.5, *J*(H–C(4), H–C(4a)) = 2.5, *J*(H–C(4), H–C(3a)) = 8.8, *J*(H–C(4),

H–C(4a)) = 5.2, *J*(H–C(4), H–C(3a)) = 7.5, CH_2(4)); 1.96 (*s*, CH_3–C(3)); 1.44 (*s*, CH_3–C(6)); 1.30 (*s*, CH_3–C(6)). Anal. calc. for $C_{10}H_{15}NO_3$ (197.24): C 60.89, H 7.66, N 7.10; found: C 61.00, H 7.71, N 7.01.

6. 3-(5',5'-Dimethyl-1',3'-dioxan-2'-yl)-4,5-dihydro-5-vinylisoxazole (**21**). To a stirred soln. of **2** (5 mmol, 845 mg) in anh. CH_2Cl_2 (10 ml) cooled at −78°, 5 ml of 1M diisobutylaluminium hydride (DIBAH) in hexane were added dropwise. After 45 min stirring at −78°, the reaction is quenched by the addition of sat. NH_4Cl soln. and then of 4% aq. HCl. The resulting mixture is diluted with CH_2Cl_2 and filtered. Evaporation in a moderate vacuum gave the crude aldehyde. This product was converted into **21** by reaction with 2,2-dimethylpropan-1,3-diol (5 mmol, 520 mg) in refluxing anh. benzene with TsOH as catalyst. Usual workup and flash chromatography (Et_2O/hexane 7:3) gave 83% yield of **21**, m.p. 71–72°. ^{1}H-NMR: 6.05–5.70 (*m*, CH_2=C*H*); 5.40–4.85 (*m*, CH_2=CH); 5.30 (*s*, H–C(2')); 3.60 (*d*, CH_2(4'), CH_2(6')); 3.43–2.71 (*m*, CH_2(4)); 1.20 (*s*, CH_3); 0.80 (*s*, CH_3). Anal. calc. for $C_{11}H_{17}NO_3$ (211.26): C 62.54, H 8.11, N 6.63; found: C 62.51, H 8.21, N 6.54.

7. 3-(Dimethoxy)methyl-4,5-dihydro-5-vinylisoxazole (**23**) was obtained as **21** from **2** in 79% overall yield by refluxing the crude aldehyde in MeOH with TsOH as catalysts. ^{1}H-NMR: 6.05–5.70 (*m*, CH_2=C*H*); 5.40–4.75 (*m*, CH_2=CH); 4.80 (*s*, $(CH_3O)_2$C*H*); 3.75 (*s*, CH_3O); 3.30 (*s*, CH_3O); 2.50–3.20 (*m*, CH_2(4)). Anal. calc. for $C_8H_{13}NO_3$ (171.20): C 56.13, H 7.65, N 8.18; found: C 56.00, H 7.69, N 8.09.

8. 3-(5,5-Dimethyl-1,3-dioxan-2-yl)-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-4,5-dihydroisoxazole (**22**). By the usual catalytic osmylation/diol-protection sequence, **22** was obtained in 65% yield from **21** as a 72:28 mixture of *'anti'/'syn'* isomers. They were separated by flash chromatography with AcOEt/hexane 1:4. ^{1}H-NMR: in agreement with those reported [5b].

9. 3-(Dimethoxy)methyl-5-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)-4,5-dihydroisoxazole (**24**) was obtained from **23** as a 75:25 *'anti'/'syn'* mixture in 60% yield, analogously to **22**. Anal. calc. for $C_{11}H_{19}NO_5$ (257.29): C 56.02, H 7.44, N 5.44; found: C 55.90, H 7.37, N 5.41.

The two isomers **24a, b** were separated by flash chromatography with AcOEt/hexane 1:2. *(5*RS,*4'*SR*)*-**24a**: ^{1}H-NMR: 4.78 (*s*, $(CH_3O)_2$C*H*); 4.70–4.10 (*m*, H–C(5)); 4.05–3.71 (*m*, H–C(4'), CH_2(5')); 3.83 (*s*, CH_3O); 3.39 (*s*, CH_3O); 3.25–2.92 (*m*, CH_2(4)); 1.34 (*s*, CH_3–C(2')); 1.26 (*s*, CH_3–C(2')).

*(5*RS,*4'* RS*)*-**24b**: ^{1}H-NMR: 4.80 (*s*, $(CH_3O)_2$C*H*); 4.70–4.33 (*m*, H–C(5)); 4.25–3.80 (*m*, H–C(4'), CH_2(5')); 3.79 (*s*, CH_3O); 3.31 (*s*, CH_3O); 3.18–2.82 (*m*, CH_2(4)); 1.33 (*s*, CH_3–C(2')); 1.27 (*s*, CH_3–C(2')).

*10. 5-[*N-*(*tert*-Butyloxycarbonyl)amino]-5-phenyl-1-penten-3-ol* (**25**). $LiAlH_4$ reduction of **3** according to [3] gave the mixture of the corresponding amino alcohols which were converted into their Boc derivatives **25** by reaction with a slight excess of di(*tert*-butyl) dicarbonate ($(Boc)_2O$) in CH_2Cl_2 at r.t. for 2 h in the presence of 1.1 mol-equiv. of Et_3N. Evaporation *in vacuo* gave a residue which was purified by column chromatography to give **25** in 76% yield. Anal. calc. for $C_{16}H_{23}NO_3$ (277.37): C 69.28, H 8.36, N 5.05; found: C 69.40, H 8.41, N 5.00.

Flash chromatography (Et_2O/hexane 2:1) gave pure **25b** and **25a** in a 13:87 ratio. *'syn'*-**25b**: M.p. 102–103°. ^{1}H-NMR: 7.30–7.10 (*m*, 5 arom. H); 6.00–5.55 (*m*, H–C(2)); 5.25–4.90 (*m*, 2H–C(1), NH); 4.85–4.55 (*m*, H–C(5)); 4.19–3.88 (*m*, H–C(3)); 2.60 (br. *d*, OH); 2.20–1.64 (*m*, CH_2(4)); 1.36 (*s*, $(CH_3)_3$C).

'anti'-**25a**: M.p. 74–78°. ^{1}H-NMR: 7.30–7.10 (*m*, 5 arom. H); 6.05–5.65 (*m*, H–C(2)); 5.45–4.90 (*m*, 2H–C(1), NH); 4.95–4.65 (*m*, H–C(5)); 4.28–3.88 (*m*, H–C(3)); 3.64 (br. *s*, OH); 2.05–1.63 (*m*, CH_2(4)); 1.36 (*s*, $(CH_3)_3$C).

*11. 5-[*N-*(*tert*-Butyloxycarbonyl)amino]-5-phenylpentane-1,2,3-triols* (**26**/**27**). By catalytic osmylation of **25a**, a 75:25 mixture **26**/**27** was obtained in 87% yield. The isomer ratio was determined by ^{13}C-NMR of the mixture. ^{13}C-NMR: **26** *('lyxo')*: 156.3 (C=O); 142.0, 128.6, 127.3, 126.2 (arom. C); 80.2 (C(3)); 74.1 (C(2)); 69.9 (C(5)); 63.7 (C(1)); 51.6 (C(4)); 40.4 ($(CH_3)_3C$); 28.3 ($(CH_3)_3$C). **27** *('xylo')*: 156.3 (C=O); 142.0, 128.6, 127.3, 126.2 (arom. C); 79.9 (C(3)); 74.1 (C(2)); 69.3 (C(3)); 63.7 (C(1)); 51.6 (C(4)); 40.4 ($(CH_3)_3C$); 29.6 ($(CH_3)_3$C). Anal. calc. for $C_{16}H_{25}NO_5$ (311.39): C 61.71, H 8.09, N 4.50; found: C 61.85, H 8.18, N 4.38.

*12. 5-[*N-*(*tert*-Butyloxycarbonyl)amino]-5-phenylpentane-1,2,3-triols* (**28**/**29**). By catalytic osmylation of **25b**, a 70:30 mixture **28**/**29** was obtained in 83% yield. The isomer ratio was determined by ^{13}C-NMR of the mixture. **28** *('ribo')*: 155.8 (C=O); 142.5, 128.6, 127.3, 126.5 (arom. C); 79.9 (C(3)); 74.5 (C(2)); 70.9 (C(5)); 63.2 (C(1)); 53.7 (C(4)); 39.8 ($(CH_3)_3C$); 28.3 ($(CH_3)_3$C); **29** *('arabino')*: 155.6 (C=O); 142.5, 128.6, 127.3, 126.5 (arom. C); 79.9 (C(3)); 73.9 (C(2)); 70.0 (C(5)); 63.2 (C(1)); 53.7 (C(4)); 40.7 ($(CH_3)_3C$); 28.3 ($(CH_3)_3$C). Anal. calc. for $C_{16}H_{25}NO_5$ (311.39): C 67.71, H 8.09, N 4.50; found: C 61.70, H 8.17, N 4.40.

*13. 4,5-Dihydro-3-((*R*)-*p*-tolylsulfinyl)methyl-5-vinylisoxazole* (**30a, b**) was obtained following procedure [6], *75% yield* from **1** and menthyl (−)-(*S*)-*p*-toluenesulfinate. Anal. calc. for $C_{13}H_{15}NOS$ (249.33): C 62.62, H 6.06, N 5.62; found: C 62.48, H 5.99, N 5.62.

The two epimers at C(5) were separated by flash chromatography with Et_2O. **30a**: M.p. 92–94°, $[\alpha]_D^{23} = +357.3°$ ($c = 0.2$, $CHCl_3$). ^{1}H-NMR: 7.45–7.05 (*AA'BB'*, 4 arom. H); 5.88–5.64 (*m*, CH_2=CH); 5.30–5.06 (*m*, CH_2=CH); 4.80–4.98 (*m*, H–C(5)); 3.72 (*AB*, $J = 16$, CH_2SO); 3.16–2.58 (*AB* of *ABX*, J(H–C(4), H–C(4)) = 17.6, CH_2(4)); 2.32 (*s*, CH_3).

30b: M.p. 45–47°, $[\alpha]_D^{23} = +187.0°$ ($c = 0.2$, $CHCl_3$). ^{1}H-NMR: 7.42–7.10 (*AA'BB'*, 4 arom. H); 5.70–5.48 (*m*, CH_2=C*H*); 5.21–4.98 (*m*, C*H*$_2$=CH); 4.91–4.72 (*m*, H–C(5)); 3.66 (*AB*, $J = 16$, CH_2SO); 3.04–2.50 (*AB* of *ABX*, J(H–C(4), H–C(4)) = 17.6, CH_2(4)); 2.13 (*s*, CH_3).

*14. 5-(2,2-Dimethyl-1,3-dioxolan-4-yl)-4,5-dihydro-3-[(*p*-toluenesulfonyl)methyl]isoxazole* (**31a, b**) was obtained in 78% overall yield from **30b** by catalytic osmylation carried out with 3 mol-equiv. of $Me_3N{\rightarrow}O \cdot 2H_2O$, followed by acetalization (acetone was used instead of 2,2-dimethoxypropane to ensure solubility of the dihydroxysulfone). The crude *'anti'/'syn'* mixture was used as such for the subsequent desulfurization.

15. Optically Active 5-(2,2-Dimethyl-1,3-dioxolan-4-yl)-4,5-dihydro-3-methylisoxazole (**10a** *and* **10b**). To a soln. of anh. MeOH (15 ml per mmol), anh. NaH_2PO_4 (1 g per mmol) was added. To the resulting suspension cooled at 0°, 8% Na-Hg (1.5 g per mmol) was added in 1 portion and stirring continued for 1 h. The mixture was then filtered through *Celite* and sat. aq. NH_4Cl soln. added to the filtrate. The org. solvent was evaporated *in vacuo* and the aq. phase extracted 3 times with CH_2Cl_2. Evaporation *in vacuo* gave crude (–)-**10a, b**. The two isomers were separated by flash chromatography with Et_2O/hexane 4:1. (–)-**10a** *('anti')*: Yield 66%, m.p. 52–53°, $[\alpha]_D^{23} = -79.0°$ ($c = 0.2$, $CHCl_3$). (–)-**10b** *('syn')*: Yield 18.6%, m.p. 55–56°, $[\alpha]_D^{23} = -90.6°$ ($c = 0.2$, $CHCl_3$).

(+)-**10a**, $[\alpha]_D^{23} = +17.0°$ ($c = 0.2$, $CHCl_3$), and (–)-**10b**, $[\alpha]_D^{23} = -54.0°$ ($c = 0.2$, $CHCl_3$) were obtained by stoichiometric osmylation carried out in the presence of dihydroquinine acetate [21] [22]. Their e.e. (21.5 and 60%, resp.) were evaluated by comparison with the values obtained for enantiomerically pure (–)-**10a** and (–)-**10b** (see above).

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