228. Synthesis of Cyclosporine. I. Synthesis[1]) of Enantiomerically Pure (2*S*,3*R*,4*R*,6*E*)-3-Hydroxy-4-methyl-2-methylamino-6-octenoic Acid Starting from Tartaric Acid

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Summary

Starting from *R,R*-(+)-tartaric acid, the synthesis of (2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-methylamino-6-octenoic acid in 24 steps is reported. This novel amino acid is found in the cyclic undecapeptide cyclosporin A, isolated from the fungal strain *Tolypocladium inflatum* GAMS. Its stereospecific synthesis allowed, for the first time, the isolation and characterization of the new amino acid previously reported as the 'C-9-amino acid' [1].

1. Introduction. – The previously reported C-9-amino acid [1] [2], now also designated as (4*R*)-4-((*E*)-2-butenyl)-4,*N*-dimethyl-L-threonine (MeBmt)[2])[3]), was the only unknown amino acid in cyclosporine[4]), and there had previously been no means for its isolation. For this reason and because it is possible that this amino acid could play a significant role in determining the pharmacological activity of cyclosporine, the synthesis of this amino acid in enantiomerically pure form was initiated.

In the (4*R*)-4-butenyl-4-*N*-dimethyl-threonine **25** (MeBmt, in a simplified staggered projection (**i**) and in a *Fischer* projection (**ii**), MeNH- and OH-groups are in a *threo*-configuration as it is the case in *N*-methyl-L-threonine (**iii**) and the OH- and CH_3-groups in an *erythro*-configuration; the double bond is *trans* (*E*)-configurated. The

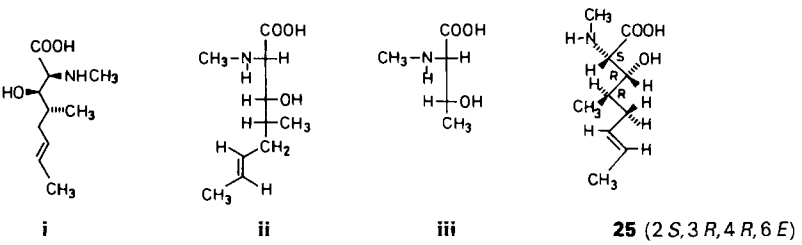
[1]) Part of this work has been presented at the 'Seventh Symposium on Synthesis in Organic Chemistry' organized by the Royal Society of Cambridge Perkin Division in Oxford, 21–23 July 1981, and at an 'International Symposium on Cyclosporin A' held at Cambridge (England) from 16–18 September 1981.

[2]) Previously reported as MeC9, for details see [3].

[3]) The new abbreviation MeBmt is, in accordance with conventional practice, to be understood for an amino acid of the L-configuration. The Me represents the *N*-methylated residue of Bmt as MeLeu means *N*-methyl-L-leucine. Bmt is the abbreviation of (4*R*)-4-((*E*)-2-butenyl-4-methyl-L-threonine.

[4]) The name cyclosporine is used for the cyclic undecapeptide that has been named initially [1] 'cyclosporin A', see [3] (previously, the name cyclosporin was proposed for the structure of 'cyclosporin A'; now that the USAN name cyclosporine has been accepted in the USA, this name will be adopted for this basic structure).

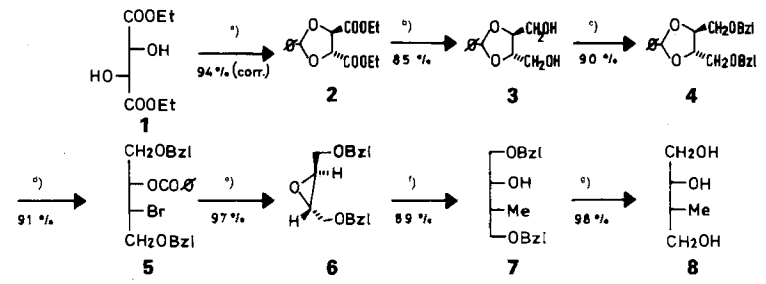
amino acid **25** is specified as (2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-methylamino-6-octenoic acid by the *Cahn-Ingold-Prelog* [4] rules.



The relative and absolute configuration was established by X-ray crystallographic analysis of an iodinated cyclic derivative of cyclosporin A [2]. The (*E*)-configuration of the double bond is proved by measurement of a coupling constant of 16 Hz between the vinyl protons from the 360-MHz-NMR spectrum of cyclosporine in (D_6)benzene [1]. The structural assignments have eventually been confirmed by an X-ray crystallographic analysis of cyclosporine itself [5].

2. Strategy of the Synthesis. – (*R*,*R*)-(+)-Tartaric acid was used as the basic chiral building block[5]) and modified in three major operations to introduce the features of the butenyl-4,*N*-dimethyl-threonine **25**. In the first operation, summarized in *Scheme 1*, one OH-group of the (*R*,*R*)-(+)-tartaric acid molecule is incorporated with the correct configuration, and the other OH-group is replaced by a CH_3-group accompanied by inversion of configuration. This provides the asymmetric centres C(3) and C(4) of the amino acid **25**. The second operation consists of introducing the (*E*)-butenyl moiety *(Scheme 2)* and of oxidizing the diol **14** to the hydroxy aldehyde **19** *(Scheme 3)*. In the third operation the MeNH- and the COOH-groups are introduced *via* a cyclic inter-

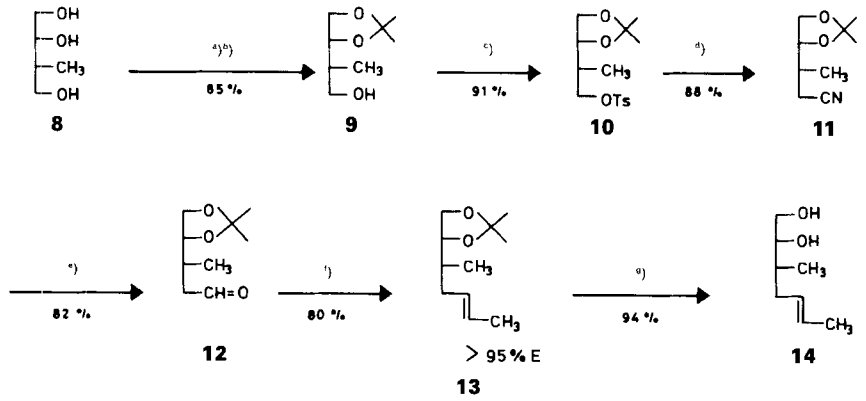
Scheme 1. *Synthesis of* (R,R)-*3-Methyl-1,2,4-butanetriol* (**8**)



[a]) PhCHO/HC(OEt)$_3$/TsOH. [b]) $LiAlH_4$. [c]) BzlBr/KOH. [d]) NBS. [e]) KOH/EtOH. [f]) 2 MeLi/CuI. [g]) Pd/H_2.

[5]) For the use of tartaric acid as an ideal source of chiral building blocks for syntheses, see the recently published review by *Seebach & Hungerbühler* [6].

Scheme 2. *Synthesis of* (R,R,E)-*3-methyl-5-heptene-1,2-diol* (**14**)



[a]) $Me_2C(OMe)_2$/TsOH/C_6H_6, reflux, 2 h. [b]) Acetone, TsOH, reflux, 15 h. [c]) TsCl/Py, 35°, 4 h. [d]) KCN/DMSO, 20°, 3 days. [e]) DIBAH/hexane, −75°, 2 h. [f]) Ph_3EtPBr/BuLi, *Schlosser* conditions. [g]) 1.1 equiv. of 1N HCl, THF/H_2O 4:1, 20°, 2 days.

mediate permitting stereochemical control during the formation of the asymmetric centre at C(2) *(Scheme 4)*.

2.1. *Synthesis of (*R,R*)-3-Methyl-1,2,4-butanetriol* (**8**). *Formation of the Asymmetric Centres at C(3) and C(4).* The OH-groups of diethyltartrate (**1**) are protected by acetalization to **2** with benzaldehyde in the presence of triethyl orthoformate and *p*-toluenesulfonic acid (TsOH)hydrate. Subsequent reduction with $LiAlH_4$ in tetrahydrofuran (THF) to the diol **3** and benzylation (benzyl bromide, toluene, KOH) furnishes the dioxolane **4**. The overall yield from **1** is 72%, and the three steps are partly described by *Erlenmeyer* [7], *Collet et al.* [8], *Curtis et al.* [9], and *Jones* [10]. For the replacement of one of the OH-groups of tartaric acid by a CH_3-group with inversion of configuration, the epoxide **6** is first prepared following a procedure described by *Seeley & McElwee* [11] for the conversion of acetals of 1,2-diols into epoxides. Due to the symmetry of **4** it is immaterial on which of the two secondary C-atoms the displacement occurs. Thus, treatment of **4** with *N*-bromosuccinimide (NBS) in CCl_4 for three days at room temperature in the absence of light produces the bromo ester **5**, which upon alcaline hydrolysis is directly converted to the optically active and therefore *trans*-disubstituted oxirane **6** (88%). The alkylation of the C_2-symmetrical epoxide is achieved according to *Johnson et al.* [12] with excess MeLi (CuI) in Et_2O at −15° to give a single product **7** in 89% yield. The benzyl protecting groups are removed by hydrogenolysis in EtOH. The triol **8** is isolated in an overall yield of 56% from diethyl tartrate (**1**; 7 steps).

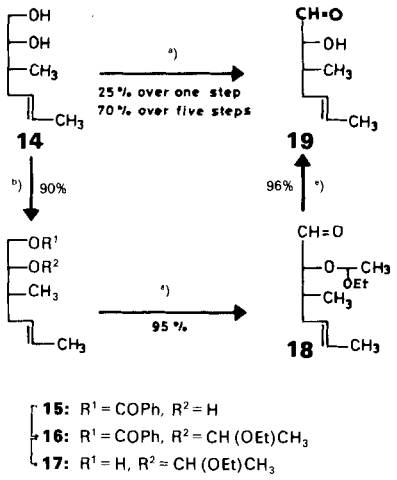
2.2. *Synthesis of (*R,R,E*)-3-Methyl-5-heptene-1,2-diol* (**14**). *Chain Elongation with Introduction of the* trans*-Double Bond.* The two vicinal OH-groups of the triol **8** are selectively[6]) protected by formation (2,2-dimethoxypropane/benzene/TsOH) of the

[6]) For similar cases of 5-membered ring acetonide formation, which is favoured over the 6-membered ring acetonide see [13] [14] (formation of the 5-membered ring acetonide from 1,2,4-butanetriol and of 1,2:5,6-*O*-diisopropylidene-D-mannitol from D-mannitol, respectively).

acetal **9**, which can be purified by chromatography or by distillation (85%). The formation of 10–15% of the isomeric 1,3-dioxane besides the desired dioxolane **9** could not be avoided. The ratio of the isomers is easily determined from the NMR spectrum. The dioxolane **9** is converted (tosylchloride (TsCl)/pyridine (Py)/$CHCl_3$/35°) to the tosylate **10**[7]) in 91% yield. Subsequent carbon-chain elongation with KCN in dimethylsulfoxide (DMSO) at room temperature gives the nitrile **11** (88%) which is reduced to the aldehyde **12** (82%) with excess diisobutylaluminium hydride (DIBAH) at −75°. This aldehyde is subjected to a *Wittig* reaction with ethyl(triphenyl)phosphonium bromide under the conditions recommended by *Schlosser & Christmann* [16]. The olefin **13** is isolated in a 80% yield and in a configurational purity of over 95%[8]). Frequently, this type of transformation of aldehydes to olefins has produced 1:1 mixtures of (*Z*)- and (*E*)-isomers. The successful formation of the (*E*)-double bond in **13** requires, that the procedure described in [16] is closely followed. The isopropylidene protecting group of **13** is removed (94%) with 1N HCl in THF/H_2O 4:1. The overall yield of the six steps leading from the triol **8** to the olefinic diol **14** is 42%.

2.3. *Synthesis of (*R,R,E*)-2-Hydroxy-3-methyl-5-heptenal* (**19**). *Oxidation of* **14** *to* **19**. Although the oxidation can theoretically be performed in one step, the fast rate of

Scheme 3. *Synthesis of* (R,R,E)-*2-Hydroxy-3-methyl-5-heptenal* (**19**)



[a]) DCC/DMSO/C_6H_6/Py/TFA, 20°, 2 h. [b]) PhCOCl/Py, 20°, 1 h. [c]) CH_2=CHOEt/TFA, 20°, 1–3 days. [d]) 10N KOH/EtOH, 20°, 1½ h. [e]) 1N HCl/THF, 20°, 2 h.

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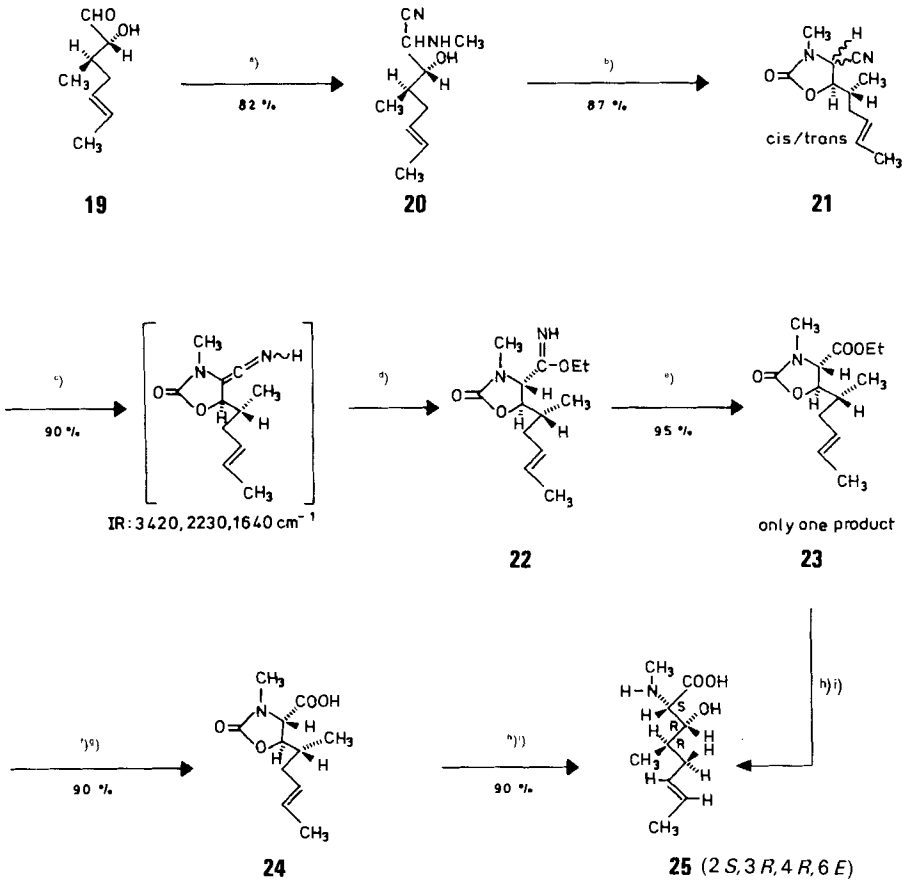
[7]) After the synthesis of **25** was completed (see the total synthesis of cyclosporine by *Wenger* [15a], *Mori & Iwasawa* [15b] published their synthesis of δ-multistriatin using the same intermediate **10**, which they synthesized by a related route.

[8]) In the 360-MHz NMR spectrum in $CDCl_3$ no trace of (*Z*)-isomer was observed. The (*Z*)-isomer obtained by working at room temperature during the *Wittig* reaction absorbs at 0.87 (CH_3–C(5)); 1.37 and 1.40 ((CH_3)$_2$C); 1.62 (3 H–C(1)); 1.80, 2.0, and 2.24 (2 H–C(4) and H–C(5)); 3.6 and 3.9 (H–C(6) and 2 H–C(7)); 5.45 (H–C(2) and H–C(3)).

isomerization of an α-hydroxy aldehyde to the most stable α-hydroxy ketone[9]) and the high reactivity of the aldehyde **19** suggested that the selective conversion might be difficult. Indeed, the oxidation of the diol **14** can be effected by the *Pfitzner-Moffatt* method [18–20] in one step, but only in low yield (25%)[10]). To obtain the hydroxy aldehyde **19** in high yield, it is necessary to protect the secondary OH-group of **14**. This is done by monobenzoylation (→ **15**, 90%), followed by protection of the secondary

Scheme 4



19 **20** **21** **22** **23** **24** **25** (2*S*,3*R*,4*R*,6*E*)

[a]) KCN/$MeNH_2$ · HCl/MeOH/H_2O, 20°, 2 h. [b]) 1,1'-Carbonyldiimidazol/CH_2Cl_2, 20°, 16 h. [c]) K_2CO_3/EtOH, 20°, 6 h. [d]) EtOH. [e]) 1 equiv. of 1 N HCl/EtOH, 20°, 1½ h. [f]) 0.1 N KOH/dioxane, 20°, 1 h. [g]) HCl (pH 2). [h]) 2 N KOH/H_2O, 80°, 3 h. [i]) HCl (pH 5).

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[9]) *Cf.* the isomerization of glucose to fructose and [17].

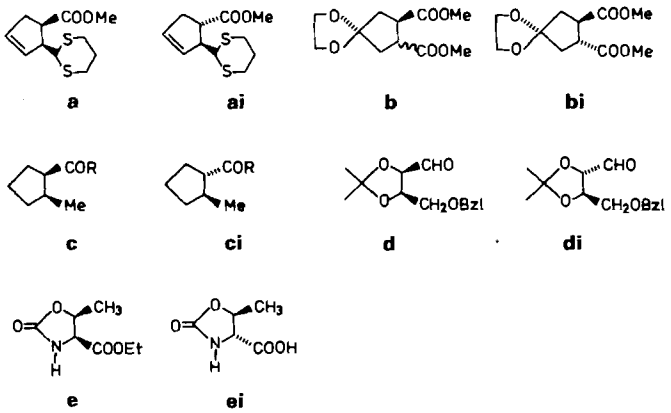
[10]) The formation of the α-hydroxy ketone $CH_3CH{=}CH{-}CH(CH_3)COCH_2OH$ (probably by isomerization of **19**) and of other by-products could not be avoided.

OH-group as the ethoxyethyl derivative **16** (ethylvinyl ether/trifluoroacetic acid (TFA)) according to a procedure described by *Seebach & Hungerbühler* [21], and alkaline hydrolysis of the benzoate to give the primary alcohol **17**. Oxidation of **17** to the aldehyde **18** is then realized as above in 95% yield. The ethoxyethylprotecting group is removed with 1 N HCl in THF at room temperature yielding the hydroxy aldehyde **19** in a total yield over five steps of 70%.

2.4. *Synthesis of (2 S,3 R,4 R,6 E)-3-Hydroxy-4-methyl-2-methylamino-6-octenoic Acid* (**25**). *Introduction of the Methylamino and of the Carboxy Group.* Freshly prepared hydroxy aldehyde **19** treated at room temperature with KCN and $MeNH_2 \cdot HCl$ in $MeOH/H_2O$ 4:1 yields the cyanamine **20** as a mixture of diastereomers (82%). The use of the unprotected α-hydroxy aldehyde **19** as starting material for introduction of the CN- and MeNH-groups is prefered to the use of the protected **18** because of the sensitivity of the product **20** to acids (fast decomposition giving **19** and by-products). The mixture **20** is converted (1,1'-carbonyldiimidazol/CH_2Cl_2/20°/12 h) to the oxazolidine-2-one diastereomers **21** (6:1/*cis*:*trans* rel. to ring, 87%). This oxazolidinone protecting group is chosen because of the ease of its preparation under mild neutral conditions (conversion of **20** to a 2,2-dimethyloxazolidine with acetone in the presence of acid is not possible). Both diastereomers of **21** can be converted in high yield to the same carboximidate **22** by treatment with K_2CO_3 in EtOH. The intermediate didehydroimine *(Scheme 4)* can be characterized by a band at 2230 cm^{-1} in the IR spectrum of a crude product. This *N*,α-didehydroimine[11]) reacts with EtOH stereospecifically to yield the thermodynamically more stable *trans*-configurated (rel. to the ring) carboximidate **22** as a 3:1 mixture (NMR) of (*E*/*Z*)- or (*Z*/*E*)-isomers (rel. to the C=N bond). Hydrolysis of **22** with 1 N HCl (1 equiv.) gives the enantiomerically pure *N*-methylamino-acid derivative **23** with the O- and N-functional groups in the desired *threo*-configuration. Similar conversion of *cis*-5-membered ring derivatives into thermodynamically more stable *trans*-derivatives have precedents in the literature [23–28][12]). Both protecting

[11]) Analogous didehydroimines have already been isolated as dimethyl(*tert*-butyl)silyl derivatives, for details s. [22].

[12]) As examples: transformation of the compounds **a**, **b**, **c**, **d**, and **e** into the *trans* products **ai** [23], **bi** [24], **ci** [25], **di** [26], and **ei** [27], [28], respectively.



groups of the *N*-methylamino acid **23** can be removed in one step (90%) by treatment with 2N KOH at 80° or stepwise using the following procedure. The ester group of **23** is selectively hydrolyzed with excess of 0.1N KOH in dioxane at room temperature giving the acid **24** in 90% yield. The oxazolidine-2-one group of **24** is cleaved with 2N KOH (80°, 3 h, 90%). The desired *N*-methylamino acid **25** crystallizes from the reaction mixture following acidification to pH 5 with 1N HCl (m.p. 240–241°, $[\alpha]_D = +13.5°$ ($c = 0.50$, H_2O, pH 7)). The yield of **25** is 48% after six steps from the α-hydroxy aldehyde **19** or 7.8% after 24 steps from diethyl (*R,R*)-(+)-tartrate (**1**; average yield of 90% per step). The *Figure* shows bristly crystals of **25** (from MeOH).

The stereospecific synthesis described here allows for the first time the characterization of the new amino acid (4*R*)-4-((*E*)-2-butenyl)-4,*N*-dimethyl-L-threonine (**25**) and opens the way for a total synthesis of cyclosporine.

We thank *Kurt Martin* and *Louis Walliser* for their capable technical assistance. Thanks also due to Dr. *H. Braunschweiger* and *F. Seemann* for the supply of ample quantities of intermediates. We appreciate the valuable help by *H.R. Loosli, M. Ponelle* and *T. Zardin* (NMR spectra), *W. Pfirter* (analysis), *C. Quiquerez* (MS), *R. Knoepfli* (photographs), *H. Stocker* (for drawing the schemes) and *C. Weber* (for typing the manuscript). It is a pleasure to acknowledge with sincere thanks the encouragement of Prof. Dr. *D. Seebach* and his help in improving the manuscript.

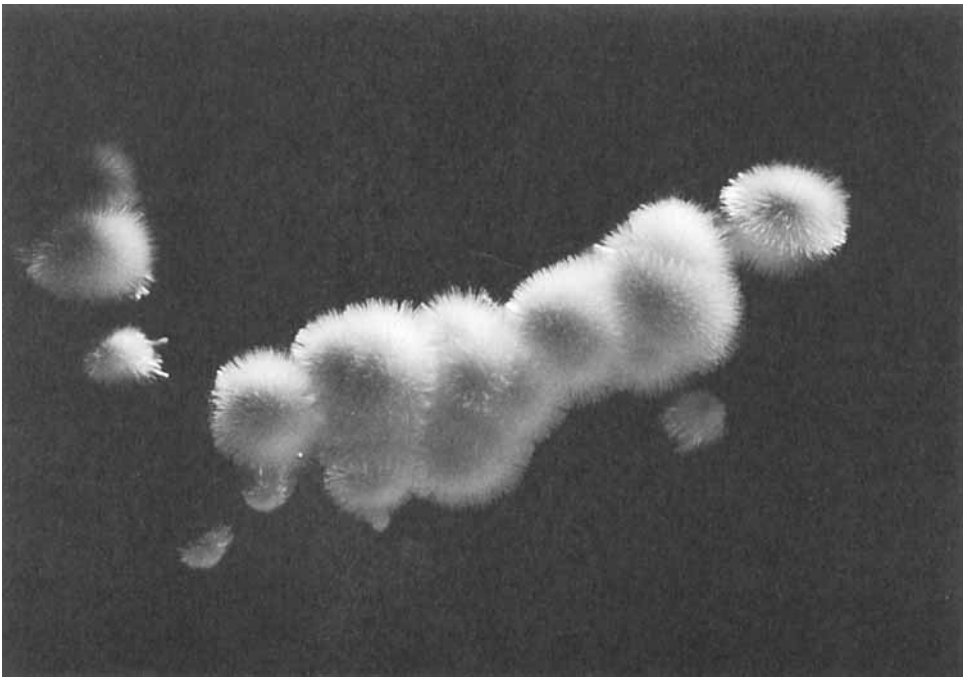


Figure. *Crystals of the Synthetic New Amino Acid MeBmt*[3]) (crystallized from MeOH and photographed under red light by *R. Knoepfli*, Photo Dept. at *Sandoz*)

Experimental Part

General. Melting points (m.p.): *Büchi 510;* all m.p. and b.p. are uncorrected. IR: *Perkin Elmer 720* (data in cm^{-1}); intensities as weak (*w*), medium (*m*), strong (*s*); broad (br.), shoulder (sh). ^{1}H-NMR: *Varian A60* (60 MHz), *Bruker HX90* (90 MHz), *Varian HA* (100 MHz), *Bruker WH360* (360 MHz); chemical shifts are given in ppm with internal tetramethylsilane (TMS) reference at 0.0 ppm, multiplicities as singlet (*s*), doublet (*d*), triplet (*t*), quadruplet (*q*), multiplet (*m*), coupling constants (*J*) in Hz. Optical rotation: polarimeter *Perkin Elmer 241.* MS: *AEI MS30* for low resolution (LR) and *Varian MAT 212* for high resolution (HR) and field desorption (FD), measurements effected at 70 eV (electron energy). For column chromatography, silica gel 0.063–0.2 mm is used.

1. *Diethyl (4 R,5 R)-2-Phenyl-1,3-dioxolane-4,5-dicarboxylate* (**2**). To a mixture of 191 g (0.93 mol) of (*R,R*)-(+)-diethyl tartrate (**1**; *Fluka, Purum*), 145 g (0.98 mol) of $HC(OEt)_3$ and 104 g (0.98 mol) of benzaldehyde, 100 mg (0.53 mmol) of $TsOH \cdot H_2O$ are added. After 2 to 3 min, the temp. rises from 22 to 40° and is maintained at 40° with a cooling bath until the exothermic reaction has stopped. The mixture is then heated to 100–120° for 4 h so that the alcohol formed slowly distills over. The mixture is then cooled to r.t., diluted with 1000 ml of CH_2Cl_2 and shaken with 200 ml of sat. aq. $NaHCO_3$. The aq. phase is reextracted with 500 ml of CH_2Cl_2, the combined org. phase dried over Na_2SO_4 and the solvent evaporated. The light yellow liquid obtained is distilled under vaccum to yield 59.5 g (31.2%) of **1**, b.p. 108°/0.3 Torr, and 173 g (63.4%, corrected 94%) of **2**, b.p. 146°/0.2 Torr, which is crystallized from 100 ml of Et_2O and 500 ml of petroleum ether to yield 141.5 g (51.8%) of crystalline **2**, m.p. 44–46°, $[\alpha]_D^{20} = -33.1°$ (*c* = 1.3, $CHCl_3$). IR (CH_2Cl_2): 2980*w*, 2945*w*, 1760*s*, 1465*m*, 1400 br., 1380*m*, 1220*s*, 1110*s*, 1030*m*, 960*w*, 920*w*, 855*w*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 1.24, 1.28 (2 *t*, *J* = 7, 6 H, 2 CH_3CH_2O); 4.28, 4.34 (2 *q*, *J* = 7, 4 H, 2 CH_3CH_2O); 4.84, 4.92 (2 *d*, *J* = 4.5, 2 H, H–C(4), H–C(5)); 6,16 (*s*, 1 H, H–C(2)); 7.3–7.8 (*m*, 5 H, arom. H). MS (LR): 294 (M^+), 293, 221, 189, 173, 135, 122, 105.

$C_{15}H_{18}O_6$ (294.30) Calc. C 61.2 H 6.2 O 32.6% Found C 61.2 H 6.3 O 33.0%

2. *(4 S,5 S)-2-Phenyl-1,3-dioxolane-4,5-dimethanol* (**3**). Under N_2 and cooling with CO_2/CH_2Cl_2, 1000 ml of abs. THF *(Merck)* are added to 20.9 g (0.55 mol) of $LiAlH_4$ without stirring to avoid that the temp. rises above +10°. Then, 136.5 g (0.46 mol) of **2** in 800 ml of abs. THF are added dropwise with stirring so that the temp. does not rise above +25°. The mixture is stirred for 1 further h at 22°. Then, under a strong N_2 stream and cooling, 70 ml of sat. Na_2SO_4 are added dropwise. After stirring for 1 further h at r.t., the mixture is filtered through talc, the residue stirred 3× with 1000 ml of CH_2Cl_2/MeOH 4:1 during 30 min, and filtered. The combined filtrates are dried over Na_2SO_4, filtered through talc and evapored to yield 89.5 g (85%) of pale yellow **3**, $[\alpha]_D^{20} = +7.4°$ (*c* = 1.0, $CHCl_3$). IR (CH_2Cl_2): 3580*s*, 3450 br. 3030*w*, 2920*m*, 2870*m*, 1460*m*, 1400 br. 1220*m*, 1100*s*, 1070–960*s*, 920–850*w*. ^{1}H-NMR ($CDCl_3$, 100 MHz): 2.70 (*s*, 2 H, 2 OH); 3.70 (*s*, 4 H, 2 CH_2O); 4.10 (*m*, 2 H, H–C(4), H–C(5)); 5.88 (*s*, 1 H, H–C(2)); 7.28–7.60 (*m*, 5 H, arom. H). MS (LR): 210 (M^+), 209, 179, 148, 133 123. MS (HR): 210.0893 (M^+, $C_{11}H_{14}O_4$ calc. 210.0884).

3. *(4 S,5 S)-4,5-Bis(benzyloxymethyl)-2-phenyl-1,3-dioxolane* (**4**). By evaporating 2× with 300 ml of toluene, 15 g (71.4 mmol) of **3** are rendered completely anhydrous. The residual oil is redissolved in 150 ml of toluene, and 30 g of powered KOH (535 mmol) and 71.5 g (418 mmol) of benzyl bromide are added. The mixture is stirred for 15 h at 80°, cooled, the toluene phase decanted, and the org. component removed from the residual phase by stirring with 2 further 200-ml portions of toluene and decanting. The combined toluene phases are filtered through talc, evaporated, and the remaining oil is chromatographed on 2 kg of silica gel with CH_2Cl_2 (fractions containing benzyl bromide are discarded): 25.2 g (90%) of **4**, light yellow fluid, $[\alpha]_D^{20} = +10.1°$ (*c* = 1.4, $CHCl_3$). IR (CH_2Cl_2): 3030*w*, 2950–2850*m*, 1460*w*, 1365*w*, 1220*w*, 1090*s*, 1060*m*, 1020*w*, 980*w*. ^{1}H-NMR ($CDCl_3$, 360 MHz): 3.65–3.75 (*m*, 4 H, 2 CH_2O); 4.16–4.24, 4.25–4.34 (2 *m*, 2 H, H–C(4), H–C(5)); 4.59 (*d*, *J* = 8, 4 H, 2 $PhCH_2$); 5.97 (*s*, 1 H, H–C(2)). MS (LR): 390 (M^+), 299, 283, 269, 193, 180, 133.

$C_{15}H_{26}O_4$ (390.48) Calc. C 76.9 H 6.7 O 16.4% Found C 77.2 H 6.8 O 16.8%

4. *(2 S,3 R)-1,4-Bis(benzyloxy)-3-bromo-2-butylbenzoate* (**5**). The suspension of 10.9 g (61.2 mmol) of NBS in 150 ml of CCl_4 is cooled to 4° and 23.9 g (61.2 mmol) of **4** in 250 ml of CCl_4 added dropwise at 4° within 50 min. The cooling bath is removed, the flask wrapped in aluminium foil and the mixture stirred for 3 days at r.t. The resulting orange suspension is diluted with 1 l of CH_2Cl_2 and shaken with 200 ml of sat. $NaHCO_3$. The aq. phase is extracted with 300 ml of CH_2Cl_2, the combined org. phase dried over Na_2SO_4, and evaporated under vacuum. The residue is chromatographed on 1 kg of silica gel with CH_2Cl_2: 26.2 g (91%) of **5**, colourless oil, $[\alpha]_D^{20} = +18.7°$ (*c* = 1.3, $CHCl_3$). IR (CH_2Cl_2): 3030*w*, 2855*w*, 1725*s*, 1605*w*, 1500*w*, 1455*m*, 1365*w*, 1320*w*, 1280–

1220*m*, 1205*w*, 1180*w*, 1110*s*, 1070*m*, 1020*m*. ^{1}H-NMR ($CDCl_3$, 100 MHz): 3.75–3.90 (*m*, 4 H, 2 CH_2O); 4.45 (*s*, 4 H, 2 PhCH_2); 4.49–4.60 (*m*, 1 H, H–C(3)); 5.45–5.65 (*m*, 1 H, H–C(2)); 7.0–7.50 (*m*, 13 H, arom. H); 7.85–8.0 (*m*, 2 arom. H_o). MS (LR): 470 ($M^+ + 1$), 468 ($M^+ - 1$), 379, 377, 365, 363, 273, 271, 193, 181.

$C_{25}H_{25}BrO_4$ (468.9) Calc. C 63.97 H 5.33 Br 17.04 O 13.65%
Found C 63.6 H 5.4 Br 17.3 O 13.6%

5. *(2 S,3 S)-2,3-Bis(benzyloxymethyl)oxirane* (**6**). To a solution of 25.7 g (54.8 mmol) of **5** in 330 ml of EtOH, 16.5 ml of aq. 10N KOH are added to give a substantially concommitant precipitation of KBr. The mixture is stirred for 30 min at r.t. and then adjusted with 10N HCl to pH 5. The mixture is evaporated under vacuum, the residue taken up in 500 ml of CH_2Cl_2, washed with 200 ml of H_2O and the aq. phase extracted 2× with 200 ml of CH_2Cl_2. The combined org. phases are dried over Na_2SO_4 and evaporated. The residue is distilled under vacuum to yield 14.2 g (92%) of **6**, b.p. 164–168°/0,2 Torr, $[\alpha]_D^{20} = -10.2°$ (c = 1.0, $CHCl_3$), m.p. 30–31° after crystallization from Et_2O/petroleum ether. Instead of purification by distillation, the residue (second batch) can be chromatographed on 1 kg of silica gel with 1% MeOH/CH_2Cl_2 to yield 15.1 g (97%) of **6** of the same quality, $[\alpha]_D^{20} = -10.1°$ (c = 1.0, $CHCl_3$). IR (CH_2Cl_2): 3020*w*, 2850*m*, 1600*w*, 1500*w*, 1455*m*, 1365*m*, 1220*m*, 1100*s*, 1020*w*, 865*w*. ^{1}H-NMR ($CDCl_3$, 360 MHz): 3.11 (*m*, 2 H, H–C(2), H–C(3)); 3.49 (*dd*, J = 5, 11.5, 2 H, CH_2O); 3.74 (*dd*, J = 2.5, 11.5, 2 H, CH_2O); 4.55, 4.59 (2 *d*, J = 12, 4 H, 2 PhCH_2); 7.85 (*s*, 10 H, arom. H). MS (LR): 284 (M^+), 193, 176, 145, 133, 107.

$C_{18}H_{20}O_3$ (284.36) Calc. C 76.0 H 7.1 O 16.9% Found C 76.0 H 6.9 O 17.3%

6. *(2 R,3 R)-1,4-Bis(benzyloxy)-3-methyl-2-butanol* (**7**). To a suspension of 4.64 g (24.37 mmol) of vacuum-dried CuI in 100 ml of abs. Et_2O with dry N_2-gassing are added rapidly at 0° 23.6 ml (47.27 mmol) of 4.4% MeLi/Et_2O. The resulting clear orange-brown solution is cooled immediately to −60°, a solution of 3.0 g (10.56 mmol) of **6** in 25 ml of abs. Et_2O is added and the mixture stirred for 1 h at −60°. To destroy excess MeLi, 5 ml of MeOH are added. The cooling bath is then removed, the mixture warmed to r.t., and 5 ml of H_2O added. The mixture is diluted with 300 ml of CH_2Cl_2, washed 3× with 200 ml of H_2O and the aq. copper-coloured precipitate extracted 3× with 200 ml of CH_2Cl_2. The combined org. phase is dried over Na_2SO_4, filtered through a layer of talc, evaporated under vacuum, and the residue purified by chromatographing on 90 g of silica gel with CH_2Cl_2 to yield 2.82 g (89%) of 7, light-beige oil, $[\alpha]_D^{20} = -4.8°$ (c = 1.0, $CHCl_3$). IR (CH_2Cl_2): 3570*w*, 3470, 3020, 2950–2850*m*, 1500*w*, 1455*m*, 1360*m*, 1090*s*, 1020*w*. ^{1}H-NMR ($CDCl_3$, 100 MHz): 0.95 (*d*, J = 7, 3 H, CH_3–C(3)); 1.82–2.22 (*m*, 1 H, H–C(3)); 3.08 (*d*, J = 4, 1 H, HO–C(2)); 3.40–3.65 (*m*, 4 H, 2 H–C(1), 2 H–C(4)); 3.50–3.85 (*m*, 1 H, H–C(2)); 4.50 (*d*, J = 6, 4 H, 2 PhCH_2); 7.10–7.50 (*m*, 10 H, arom. H). MS (LR): 300 (M^+), 281, 229, 209, 191, 179, 145, 121, 107, 91.

$C_{19}H_{24}O_3$ (300.40) Calc. C 76.0 H 8.1 O 16.0% Found C 75.8 H 8.0 O 16.5%

7. *(2 R,3 R)-3-Methyl-1,2,4-butanetriol* (**8**). At r.t., 4.5 g (15 mmol) of **7** in 120 ml of 95% EtOH are hydrogenated over 0.5 g of 10% Pd/C for 2 h. The product is filtered through talc, evaporated and chromatographed on 120 g of silica gel with CH_2Cl_2/MeOH 4:1 to yield 1.77 g (98%) of **8**, colourless, viscous oil, $[\alpha]_D^{20} = +5.8°$ (c = 1.0, $CHCl_3$). IR (neat): 3300 (br.), 2950–2850*s*, 1455*m*, 1420 br. 1330 br. 1220 br. 1120–970*s*, 920*w*, 870*m*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 0.88 (*d*, J = 7, 3 H, CH_3–C(3)); 1.50–2.10 (*m*, 1 H, H–C(3)); 2.90 (br. *s*, 2 H, 2 OH); 3.0–3.35 (*m*, 1 H, H–C(2)); 3.40–4.0 (*m*, 4 H, 2 H–C(1), 2 H–C(4)); 4.5–4.6 (br. *s*, 1 H, HO–C(2)). ^{1}H-NMR ((D$_6$)DMSO, 60 MHz): 0.80 (*d*, J = 7, 3 H, CH_3–C(3)); 1.40–1.90 (*m*, 1 H, H–C(3)); 3.20–3.60 (*m*, 5 H, 2 H–C(1); H–C(2), 2 H–C(4)); 4.15–4.40 (*m*, 3 H, 3 OH). MS (LR): 121 ($M^+ + 1$), 105, 89, 71, 57.

$C_5H_{12}O_3$ (120.15) Calc. C 50.0 H 10.1 O 40.0% Found C 50.6 H 10.3 O 39.6%

8. *(2 R,3 R)-3,4-Isopropylidenedioxy-2-methylbutanol* (**9**). A solution of 30.5 g (254 mmol) of **8** in 180 ml benzene is refluxed for 2 h with 39.8 g (383 mmol) of 2,2-dimethoxypropane and 180 mg of TsOH · H_2O. The solvent is evaporated, the remaining oil taken up in 600 ml of acetone, 0.6 g of TsOH · H_2O are added, and the solution is boiled for 16 h under reflux. The resulting yellow solution is evaporated to 100 ml and chromatographed on 1 kg of neutral alumina (act. II) using 2% MeOH/CH_2Cl_2: 34.6 g (85%) of **9**, oil, $[\alpha]_D^{20} = -19.8°$ (c = 1.0, $CHCl_3$), b.p. 56°/0.1 Torr [**9** has been separated from *ca.* 15% of 2,4-isopropylidenedioxy-3-methylbutanol eluted after **9**, with CH_3–C(3) at 0.79 ppm (s. CH_3–C(2) of **9** at 0.85; main difference between the two isomers)]. IR (CH_2Cl_2): 3030*w*, 3000–2840*m*, 1450*m*, 1370*m*, 1200*m*, 1100*m*, 1060*s*, 845*w*. ^{1}H-NMR ($CDCl_3$, 100 MHz): 0.85 (*d*, J = 7, 3 H, CH_3–C(2)); 1.36–1.42 (2 *s*, 6 H, $(CH_3)_2C$); 1.60–2.10 (*m*, 1 H, H–C(2)); 2.80 (*t*,

J = 6, 1 H, OH); 3.50–3.75 (*m*, 2 H, 2 H–C(1)); 3.82–4.20 (*m*, 3 H, H–C(3), 2 H–C(4)). MS (LR): no M^+, 145, 129, 101, 72, 28.

$C_8H_{16}O_3$ (160.215) Calc. C 60.0 H 10.1 O 30.0% Found C 59.5 H 10.1 O 30.2%

9. *(2 R,3 R)-3,4-Isopropylidenedioxy-2-methylbutyl* p-*toluenesulfonate* (**10**). At r.t., 14.3 g (75 mmol) of TsCl are added to a solution of 10.0 g (62.5 mmol) of **9** in 65 ml of $CHCl_3$. Then, 10.1 ml of abs. pyridine are added, whereupon the temp. rises to 31°. The exothermic reaction continues for 45 min before the temp. begins to fall. The mixture is then stirred for 3 h at 35°, the resulting solution diluted with 300 ml of CH_2Cl_2, washed once with 150 ml of sat. Na_2CO_3 and twice with 150 ml of sat. Cu_2SO_4. The aq. phases are extracted with 200 ml of CH_2Cl_2, the combined org. phases dried over Na_2SO_4, filtered through talc and evaporated. The residue is chromatographed on 400 g of neutral alumina (act. II) using CH_2Cl_2. After crystallization from petroleum ether, 17.8 g (91%) of hygroscopic **10** are obtained, $[\alpha]_D^{20} = +14.6$ (*c* = 1.0, $CHCl_3$), m.p. 39–40°. IR (CH_2Cl_2): 3050*w*, 2950–2870*s*, 1600*m*, 1460*m*, 1360*s*, 1240–1150*s*, 1100*s*, 1060*s*, 980–920*s*, 860–800*s*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 0.91 (*d*, J = 7, 3 H, CH_3–C(2)); 1.28, 1.31 (2 *s*, 6 H, $(CH_3)_2C$); 1.75–2.10 (*m*, 1 H, H–C(2)); 2.43 (*s*, 3 H, PhCH_3); 3.40–4.30 (*m*, 5 H, H–C(3), 2 H–C(4), 2 H–C(1)); 7.34, 7.80 (2 *d*, J = 8, 4 H, arom. H). MS (LR): 314 (M^+), 299, 285, 250, 239, 215, 173, 155, 127, 101.

$C_{15}H_{22}O_5S$ (314.403) Calc. C 57.3 H 7.0 O 25.4% Found C 57.0 H 6.9 O 24.9%

10. *(3 R,4 R)-4,5-Isopropylidenedioxy-3-methylpentanenitrile* (**11**). The crystalline, hygroscopic **10** (17.0 g, 54.1 mmol) is immediately dissolved in 90 ml of DMSO, 4.38 g (67.3 mmol) of KCN are added, and the mixture is stirred for 3 days at r.t. under N_2. The obtained solution is diluted with 250 ml of toluene, shaken with 125 ml of H_2O, the aq. phase extracted 2× with 300 ml of CH_2Cl_2, evaporated, and the residue taken up in 100 ml of H_2O. After extracting 2× with 200 ml of toluene, the org. phases are combined with the first toluene phase, dried over Na_2SO_4, concentrated, and distilled under high vacuum to yield 8.2 g (90%) of **11**, colourless oil, $[\alpha]_D^{20} = +11.7°$ (*c* = 1.0, $CHCl_3$), b.p. 60–63°/0.03 Torr. IR (CH_2Cl_2): 2970*m*, 2930*m*, 2870*m*, 2240*w*, 1460*w*, 1375*m*, 1210*s*, 1150*m*, 1060*s*, 840*m*. ^{1}H-NMR ($CDCl_3$, 360 MHz): 1.07 (*d*, J = 7, 3 H, CH_3–C(3)); 1.35, 1.40 (2 *s*, 6 H, $(CH_3)_2C$); 1.93 (*m*, 1 H, H–C(3)); 2.43 (*dd*, J = 8, 17, 1 H) and 2.60 (*dd*, J = 4, 17, 1 H, 2 H–C(2)); 3.64 (*dd*, J = 6, 8, 1 H) and 4.09 (*dd*, J = 6, 8, 1 H, 2 H–C(5)); 3.85 (*q*, J = 6, 1 H, H–C(4)). MS (LR): 168 ($M^+ - 1$), 154, 123, 101, 94.

$C_9H_{15}NO_2$ (169.22) Calc. C 63.9 H 8.9 N 8.3 O 18.9% Found C 63.1 H 9.0 N 8.2 O 19.7%

11. *(3 R,4 R)-3,4-Isopropylidenedioxy-3-methylpentanal* (**12**). A solution of 41 g (243 mmol) of **11** in 1 l of hexane is cooled to −78°, 205 ml of DIBAH (20% solution in hexane) are added dropwise under N_2 within 30 min in such a way that the temp. does not rise over −70°. The mixture is then stirred for 1½ h at −78°. Excess DIBAH is decomposed by the addition of 75 ml of H_2O/THF 1:4 at −70° under N_2. The resulting mixture is poured onto 1 l of H_2O and shaken. The precipitated sediment is removed with a suction filter, the filtrate separated from the aq. phase and shaken 2× with 300 ml of CH_2Cl_2. The combined org. phases are dried over Na_2SO_4 evaporated, and chromatographed on 3 kg of silica gel using 2% MeOH/CH_2Cl_2: 34.2 g (82%) of **12**, colourless oil after high-vacuum distillation under N_2, b.p. 42–45°/0.03 Torr. IR (CH_2Cl_2): 3000–2810*m*, 2730*w*, 1725*s*, 1460*w*, 1380*m*, 1220*m*, 1160*m*, 1065*s*, 855*m*. ^{1}H-NMR ($CDCl_3$, 100 MHz): 0.90 (*d*, J = 7, 3 H, CH_3–C(3)); 1.32, 1.39 (2 *s*, 6 H, $(CH_3)_2C$); 2.0–2.90 (*m*, 3 H, H–C(3), 2 H–C(2)); 3.50–4.20 (*m*, 3 H, H–C(4), 2 H–C(5)); 9.75 (*t*, J = 2, 1 H, H–C(1)). MS (LR): 173 ($M^+ + 1$), 157, 131, 113, 101. MS (HR): 173.1178 (MH^+, $C_9H_{17}O_3$, calc. 173.1178).

$C_9H_{16}O_3$ (172.226) Calc. C 62.8 H 9.4 O 27.9% Found C 62.1 H 9.3 O 28.2%

12. *(5 R,6 R,2 E)-6,7-Isopropylidenedioxy-5-methyl-2-heptene* (**13**). At 110°, 19.0 g (51.1 mmol) of ethyl(triphenyl)phosphonium bromide are dried over-night under high vacuum and then dissolved in 400 ml of THF/Et_2O 3:5 under N_2. Then, 1.1 mol-equiv. of BuLi (24 ml of a 15% solution in hexane) are added under N_2 within 20 min in such a way that the temp. does not rise above 30°. The mixture gets strong red and is stirred for a further 30 min at r.t. before cooling to −78°. Then, 8.0 g (46.5 mmol) of **12** in 50 ml of abs. Et_2O are added dropwise so that the temp. does not rise above −73°. The mixture is then stirred for 30 min and takes on a light-yellow colour. A further 20.8 ml (51.1 mmol) of BuLi in hexane are added at −78°, the red mixture is again stirred for 30 min, then warmed to −30°, and 6.5 ml (69.7 mmol) of *t*-BuOH are added dropwise within 10 min at −30° followed by 7.8 g (69.7 mmol) of *t*-BuOK (all at once). The now yellow solution is warmed to r.t., stirred for 1½ h and poured onto 1 l of H_2O. The aq. phase is separated and shaken 4× with 200 ml of Et_2O. The combined org. phases are dried over Na_2SO_4 and evaporated. The residue is chromatographed on silica gel

using 1% MeOH/CH_2Cl_2: 6.9 g (80.5%) of pure **13**, colourless oil. IR (CH_2Cl_2): 3575*s*, 3400*s*, 2920*s*, 1460*m*, 1380*m*, 1200*w*, 1060*s*, 975*s*, 920*s*, 880*w*. ^{1}H-NMR ($CDCl_3$, 360 MHz): 0.84 (*d*, *J* = 7, 3 H, CH_3–C(5)); 1.37, 1.40 (2 *s*, 6 H, $(CH_3)_2C$); 1.67 (*d*, *J* = 5, 3 H, 3 H–C(1)[13]); 1.71, 1.85, 2.26 (3 *m*, 3 H, 2 H–C(4), H–C(5)); 3.60 (*t*, *J* = 8, 1 H, H–C(7)); 3.87 (*dd*, *J* = 8, 15, 1 H, H–C(6)); 3.98 (*dd*, *J* = 8, 10, 1 H, H–C(7)); 5.44 (*m*, 2 H, H–C(2), H–C(3)).

13. *(2 R,3 R,5 E)-3-Methyl-5-heptene-1,2-diol* (**14**). To a solution of 6.5 g (35.3 mmol) of **13** in 320 ml of THF are added 80 ml of H_2O/1 N HCl 1:1. The mixture is allowed to stand for 2 days at r.t., adjusted to pH 6–7 by the addition of sat. $NaHCO_3$, the THF is evaporated and the aq. solution extracted with CH_2Cl_2 until the test for the presence of diols is negative (on TLC (silica gel) upon spraying with 2% vanillin and 2% H_2SO_4 in EtOH and warming, blue spots for diols). The combined org. phases are dried over Na_2SO_4, evaporated, and filtered through 500 g of silica gel using 10% MeOH/CH_2Cl_2: 4.75 g (94%) of **14**, colourless oil, $[\alpha]_D^{22} = -5.7°$ (*c* = 1.0, $CHCl_3$). IR (CH_2Cl_2): 3600*s*, 3450*s*, 3020*w*, 2950–2800*s*, 1460*m*, 1390*m*, 1200*w*, 1060*s*, 970*s* (C=C, *trans*), 920*w*, 880*w*. ^{1}H-NMR ($CDCl_3$, 360 MHz): 0.85 (*d*, *J* = 7, 3 H, CH_3–C(3)); 1.61 (*m*, 1 H, H–C(3)); 1.66 (*d*, *J* = 5, 3 H, 3 H–C(7)); 1.90, 2.25 (2 *m*, 2 H, 2 H–C(4)); 3.38 (*m*, 2 H, 2 OH); 3.48, 3.68 (2 *m*, 3 H, 2 H–C(1), H–C(2)); 5.37–5.53 (*m*, 2 H, H–C(5), H–C(6)). MS (LR): 144 (M^+), 126, 113, 108, 95, 82, 67, 55, 43, 28, 18.

$C_8H_{16}O_2$ (144.21) Calc. C 66.6 H 11.2 O 22.2% Found C 66.2 H 11.4 O 22.3%

14. *(2 R,3 R,5 E)-2-Hydroxy-3-methyl-5-heptenyl Benzoate* (**15**). Within 10 min, 9.66 g (68.71 mmol) of PhCOCl are added to a solution of 9.0 g (62.5 mmol) of **14** in 90 ml of pyridine, pre-cooled to 0°. The mixture is stirred for 40 min at r.t., diluted with 600 ml of CH_2Cl_2 and washed 3× with 200 ml of sat. $CuSO_4$. The aq. phases are extracted with 200 ml of CH_2Cl_2, the org. phases combined, dried over Na_2SO_4, evaporated, and chromatographed on 500 g of silica gel using 1% MeOH/CH_2Cl_2: 14.0 g (90%) of **15**, colourless oil, $[\alpha]_D^{20} = -11.7°$ (*c* = 1.0, $CHCl_3$). IR (CH_2Cl_2): 3600*m*, 3010*w*, 3000–2800*m*, 1720*s*, 1610*w*, 1460*m*, 1320*m*, 1270*s*, 1180*m*, 1120*s*, 1080*m*, 1030*m*, 970*w*. ^{1}H-NMR ($CDCl_3$, 100 MHz): 1.0 (*d*, *J* = 7, 3 H, CH_3–C(3)); 1.65 (*d*, *J* = 5, 3 H, 3 H–C(7)); 1.7–2.5 (*m*, 3 H, H–C(3), 2 H–C(4)); 2.35 (*d*, *J* = 4, 1 H, HO–C(2)); 3.80 (*m*, 1 H, H–C(2)); 4.40 (*m*, 2 H, 2 H–C(1)); 5.5 (*m*, 2 H, H–C(5), H–C(6)); 7.3–7.7 (*m*, 3 H, *m*- and *p*-arom. H); 7.98, 8.10 (2 *d*, *J* = 2, 2 H, *o*-arom. H). MS (LR): 248 (M^+), 230, 192, 175, 165, 135, 126, 105, 93, 82, 77, 55.

$C_{15}H_{20}O_3$ (248.32) Calc. C 72.6 H 1.8 O 19.3% Found C 72.6 H 8.2 O 19.1%

15. *(2 R,3 R,5 E)-2-(1'-Ethoxyethoxy)-3-methyl-5-heptenyl Benzoate* (**16**). To a solution of 14.0 g (56.5 mmol) of **15** in 200 ml of CH_2Cl_2, 14.4 g (0.2 mol) of ethyl vinyl ether and 1 drop of TFA are added. The mixture is stirred for 3 days at r.t. and the resulting solution chromatographed on 800 g of basic Al_2O_3 (act. II) using 1% MeOH/CH_2Cl_2: 16.8 g (93%) of **16**, colourless oil, $[\alpha]_D^{20} = -3.0°$ (*c* = 1.0, $CHCl_3$). IR (CH_2Cl_2): 2900*m*, 1720*s*, 1450*m*, 1380*m*, 1320*w*, 1270 (br.), 1180*w*, 1120*s*, 1055*w*, 1025, 970*m*. ^{1}H-NMR ($CDCl_3$, 360 MHz, 1:1 mixture of diastereomers): 0.97, 0.99 (2 *d*, *J* = 6, 3 H, CH_3–C(3)); 1.12, 1.20 (2 *t*, *J* = 7, 3 H, OCH_2CH_3); 1.33, 1.35 (2 *d*, *J* = 6, 3 H, 3 H–C(2')); 1.66 (*d*, *J* = 5, 3 H, 3 H–C(7)); 1.9 (*m*, 2 H, 2 H–C(4)); 2.26 (*m*, 1 H, H–C(3)); 3.52, 3.65 (2 *m*, 2 H, OCH_2CH_3); 3.72–3.84 (*m*, 1 H, H–C(3)); 4.29, 4.38 (2 *dd*, *J* = 12, 6, 1 H, H–C(1)); 4.48, 4.52 (2 *dd*, *J* = 12, 4, 1 H, H–C(1)); 4.80, 4.90 (2 *q*, *J* = 5, 1 H, H–C(1')); 5.45 (*m*, 2 H, H–C(5), H–C(6)). MS (LR): 320 (M^+), 305, 291, 274, 247, 230, 219, 209, 185, 153, 123, 105, 93, 73, 55.

$C_{19}H_{28}O_4$ (320.43) Calc. C 71.2 H 8.8 O 20.0% Found C 71.0 H 9.0 O 20.4%

16. *(2 R,3 R,5 E)-2-(1'-Ethoxyethoxy)-3-methyl-5-heptenol* (**17**). To a solution of 16.5 g (51.6 mmol) of **16** in 150 ml of EtOH, 30 ml of 10 N KOH are added. The mixture is stirred for 90 min at r.t. (20°), the solution diluted with 1 l of CH_2Cl_2, washed with 400 ml of H_2O, and the aq. phase extracted with 400 ml of CH_2Cl_2. The combined org. phases are dried over Na_2SO_4 and evaporated: 10.2 g (92%) of **17** colourless oil, $[\alpha]_D^{20} = -30.4°$ (*c* = 1.0, $CHCl_3$). IR (CH_2Cl_2): 3400*m*, 2900*s*, 1450*m*, 1385*m*, 1345*w*, 1135*s*, 1090*s*, 1055*s*, 970*m*, 840*w*. ^{1}H-NMR (CDCl$_3$, 360 MHz, 1:1 mixture of diastereomers) 0.87, 0.89 (2 *d*, *J* = 7, 3 H, CH_3–C(3)); 1.22, 1.24 (2 *t*, *J* = 7, 3 H, OCH_2CH_3); 1.36 (*d*, *J* = 6, 3 H, 3 H–C(2')); 1.66 (*d*, *J* = 6, 3 H, 3 H–C(7)); 1.83 (*m*, 2 H, 2 H–C(4)); 2.17 (*m*, 1 H, H–C(3)); 3.38 (*m*, 1 H, ½ OCH_2CH_3); 3.47–3.68 (*m*, 4 H, ½ OCH_2CH_3, 2 H–C(1), HO–C(1)); 3.75 (*m*, 1 H, H–C(2)); 4.59, 4.85 (2 *q*, *J* = 5, 1 H, H–C(1')); 5.42 (*m*, 2 H, H–C(5), H–C(6)). MS (LR): 216 (M^+), 198, 185, 170, 155, 149, 126, 109, 95, 73, 55.

$C_{12}H_{24}O_3$ (216.32) Calc. C 66.6 H 11.2 O 22.2% Found C 65.3 H 10.8 O 22.6%

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[13]) The (2*Z*)-derivative, obtained by working at r.t., shows the 3 H–C(1) at 1.62 ppm.

17. *(2 R,3 R,5 E)-2-(1'-Ethoxyethoxy)-3-methyl-5-heptenal* (**18**). A solution of 6.3 g (29.2 mmol) of **17** in 120 ml of DMSO/benzene 1:1 is stirred for 2 h at r.t. with 1.66 g (1.12 ml, 14.6 mmol) of TFA, 2.4 ml (2.35 g, 29.7 mmol) of pyridine and 18.5 g (89.67 mmol) of dicyclohexylcarbodiimide. The precipitate formed is filtered off using a suction filter, the filtrate taken up in 500 ml of Et_2O and washed with 250 ml of H_2O. The aq. phase is extracted with 300 ml of Et_2O, the org. phase dried over Na_2SO_4, and evaporated. The residue is chromatographed on silica gel using 0.5% MeOH/CH_2Cl_2: 5.9 g (95%) of **18**, colourless oil. IR (CH_2Cl_2): 3020*w*, 2955*m*, 2920*m*, 2850*m*, 2800*w*, 2700*w*, 1730*s* (CHO), 1450*w*, 1380*m*, 1340*w*, 1125*s*, 1090*s*, 1085*s*, 1055*s*, 970*s*, 940*w*, 920*w*. ^{1}H-NMR ($CDCl_3$, 360 MHz, 1:1 mixture of diastereomers): 0.92, 0.97 (2 *d*, $J \approx 7$, 3 H, CH_3–C(3)); 1.15, 1.18 (2 *t*, $J = 7$, 3 H, OCH_2CH_3); 1.34, 1.36 (2 *d*, $J = 5$, 3 H, 3 H–C(2')); 1.65 (*d*, $J = 6$, 3 H, 3 H–C(7); 1.96 (*m*, 2 H, 2 H–C(4)); 2.21 (*m*, 1 H, H–C(3)); 3.51 (*m*, 2 H, OCH_2CH_3); 3.70, 3.85 (2 *m*, 1 H, H–C(2)); 4.61, 4.79 (2 *q*, $J = 5$, H–C(3)); 5.36, 5.48 (2 *m*, 2 H, H–C(5), H–C(6)); 9.61, 9.63 (2 *d*, $J = 4$, 3, 1 H, H–C(1)).

$C_{12}H_{22}O_3$ (214.30) Calc. C 67.2 H 10.3 O 22.4% Found C 66.9 H 10.4 O 22.2%

18. *(2 R,3 R,5 E)-2-Hydroxy-3-methyl-5-heptenal* (**19**). To a solution of 1.7 g (7.95 mmol) of **18** in 20 ml of THF, 1.0 ml of 1 N HCl are added. The mixture is allowed to stand for 1½ h at r.t., then shaken with 100 ml of H_2O and 200 ml of CH_2Cl_2, the org. phase separated and washed again with 100 ml of H_2O. The aq. phases are extracted with 200 ml of CH_2Cl_2, the combined org. phases dried over Na_2SO_4, and evaporated: 1.07 g (95%) of **19**, colourless oil. The product is used immediately for the subsequent reaction without further purification.

19. *Compound* **19** *from* **14** *and Isolation as Aminocyanide* **20**. A solution of 0.216 g (1.5 mmol) of **14** in 4 ml of DMSO/benzene 1:1 is stirred for 22 h at r.t. with 0.121 g (1.53 mmol) of pyridine, 87 mg (0.76 mmol) of TFA, and 0.945 g (4.59 mmol) of dicyclohexylcarbodiimide. Then, 0.580 g (4.59 mmol) of oxalic acid in 18 ml of MeOH/Et_2O 1:5 are added, the mixture is stirred for further 25 min, 7 ml of H_2O are added, and the mixture is again stirred for 15 min. The mixture is filtered, the filtrate diluted with 150 ml of Et_2O, washed with 50 ml of aq. 1 N $NaHCO_3$, dried over Na_2SO_4, and evaporated. The residue is dissolved in 5 ml of H_2O/MeOH 2:3, 0.1 g (1.48 mmol) of $MeNH_2 \cdot HCl$ and 0.10 g (1.53 mmol) of KCN are added to the mixture, which is then stirred for 21 h at 20° and then evaporated. The residue is dissolved in 50 ml of CH_2Cl_2, 10 ml of H_2O are added, the H_2O is alcalinized by addition of a few drops of 1 N $NaHCO_3$, the H_2O phase extracted with 20 ml of CH_2Cl_2, the combined org. phase dried over Na_2SO_4 and evaporated. The residue is dissolved in 50 ml of Et_2O, filtered and chromatographed on 60 g of silica gel using 5% MeOH/CH_2Cl_2: 0.068 g (25% calc. on **14**) **20** as an oil (s. *chap. 20*).

20. *(2 RS,3 R,4 R,6 E)-3-Hydroxy-4-methyl-2-methylamino-6-octenenitrile* (**20**). At 20°, 0.52 g (7.9 mmol) of KCN and 0.54 g (7.9 mmol) of $MeNH_2 \cdot HCl$ are added with stirring to 1.1 g (7.7 mmol) of freshly prepared **19** in 50 ml of MeOH. After addition of 7.5 ml of H_2O, the mixture is stirred for 2 h at r.t. and then evaporated to ½ of its volume (water-bath temp. < 40°). The concentrate is shaken with 500 ml of CH_2Cl_2/H_2O 3:2, and the separated org. phase is shaken with a further 100 ml of H_2O. The aq. phases are extracted separately using 2×100 ml of CH_2Cl_2, the CH_2Cl_2 phases are combined, dried over Na_2SO_4, and evaporated. The residue is chromatographed on 100 g of silica gel using 5% MeOH/CH_2Cl_2, to yield 1.15 g (82%) of **20**, which crystallizes from Et_2O as a diastereomeric mixture, m.p. 106–107°. IR (CH_2Cl_2): 3665*w*, 3600*w*, 3400*w*, 2950*w*, 2910*m*, 2855*m*, 2850*m*, 1460*m*, 1380*m*, 1150*m*, 1120*m*, 1040*m*, 1010*m*, 970*m*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 0.94 (*d*, $J = 7$, 3 H, CH_3–C(4)); 1.68 (*d*, $J = 4$, 3 H, 3 H–C(8)); 1.50–2.50 (*m*, 5 H, H–C(4), 2 H–C(5), OH, NH); 2.60 (*s*, 3 H, NCH_3); 3.55 (*m*, 2 H, H–C(2), H–C(3)); 5.54 (*m*, 2 H, H–C(6), H–C(7)). MS (LR): 182 (M^+), 167, 156, 140, 126, 95, 70, 55.

$C_{10}H_{18}N_2O$ (182.27) Calc. C 65.9 H 10.0 N 15.4 O 8.8% Found C 65.7 H 9.9 N 15.1 O 9.2%

21. *(4 RS,5 R)-3-Methyl-5-((1' R,3' E)-1'-methyl-3'-pentenyl)-2-oxooxazolidine-4-carbonitrile* (**21**). To a solution of 630 mg (3.46 mmol) of **20** in 30 ml of CH_2Cl_2 are added 840 mg (5.2 mmol) of 1,1'-carbonyldiimidazole. The mixture is stirred overnight at r.t., then diluted with 100 ml of CH_2Cl_2 and shaken with 50 ml of H_2O. The aq. phase is extracted with 100 ml of CH_2Cl_2, the org. phase dried over Na_2SO_4, and evaporated. The residue is chromatographed on 110 g of silica gel using 1% MeOH/CH_2Cl_2: 628 mg (87%) of **21** as a 6:1 mixture of *cis*/*trans* isomers (rel. to ring). IR (CH_2Cl_2): 2950*m*, 2945*m*, 2885*m*, 2850*m*, 1760*s*, 1440*m*, 1410*m*, 1300*m*, 1210*s*, 1140*m*, 1040*s*, 970*s*, 940*w*, 880*w*, 840*w*. MS (LR): 208 (M^+), 193, 163, 139, 128, 101, 95, 84, 69, 55.

For the separation of the diastereomers, **21** (628 mg) is chromatographed on 150 g of silica gel using 0.5% MeOH/CH_2Cl_2: 88 mg of *trans*-**21** and 532 mg of *cis*-**21**. *cis*-**21**: m.p. 67–68°, $[\alpha]_D^{20} = -6.3°$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 90 MHz, *trans*-**21** (4 *R*,5 *R*,1' *R*,3'*E*)): 0.96 (*d*, $J = 7$, 3 H, CH_3–C(1')); 1.53 (*d*, $J = 5$, 3 H, 3 H–C(5')); 1.80–2.40 (*m*, 3 H, 2 H–C(2'), H–C(1')); 2.95 (*s*, 3 H, NCH_3); 4.20 (*d*, $J = 6$, 1 H, H–C(4)); 4.45

(*t*, $J = 6$, 1 H, H–C(5)); 5.45 (*m*, 2 H, H–C(3'), H–C(4')). ^{1}H-NMR ($CDCl_3$, 90 MHz, *cis*-**21** (4*S*,5*R*,1'*R*,3'*E*)): 0.95 (*d*, $J = 7$, 3 H, CH_3–C(1')); 1.62 (*d*, $J = 5$, 3 H, 3 H–C(5')); 2.18 (*m*, 2 H, 2 H–C(2'), H–C(1')); 2.96 (*s*, 3 H, NCH_3); 4.19 (*t*, $J = 8$, 1 H, H–C(5)); 4.45 (*d*, $J = 8$, 1 H, H–C(4)); 5.45 (*m*, 2 H, H–C(3'), H–C(4')).

$C_{11}H_{16}N_2O_2$ (208.26) Calc. C 63.4 H 7.7 N 13.5 O 15.4% Found C 63.2 H 7.9 N 13.4 O 15.0%

22. *Ethyl (4*S,*5*R*)-3-Methyl-5-((1'*R*,3'*E*)-1'-methyl-3'-pentenyl)-2-oxooxazolidine-4-carboximidate* (**22**). To a solution of 0.85 g (4.09 mmol) of **21** (*cis*/*trans* mixture) in 40 ml of 95% EtOH, 1.12 g (8.18 mmol) of K_2CO_3 are added, and the mixture is stirred for 6 h at r.t. The suspension obtained is shaken with 600 ml of CH_2Cl_2/H_2O 5:1, the aq. phase extracted with 300 ml of CH_2Cl_2, the combined org. phases dried over Na_2SO_4, and evaporated: 0.940 g (90%) of **22**, colourless oil, $[\alpha]_D^{20} = +15.8°$ ($c = 1.0$, $CHCl_3$). IR (CH_2Cl_2): 3400*w*, 2960–2850*m*, 1760*s*, 1670*m*, 1480*w*, 1460–1430*w*, 1410*m*, 1395*w*, 1340*w*, 1300–1260*w*, 1230*w*, 1100*m*, 1050*m*, 975*m*, 860*w*, 830*w*. ^{1}H-NMR ($CDCl_3$, 360 MHz; 1:3 mixture of (*E*/*Z*)- or (*Z*/*E*)-isomers (rel. to C=N)): 0.96 (*d*, $J = 6$, 3 H, CH_3–C(1')); 1.32 (*t*, $J = 6$, 3 H, CH_3CH_2O); 1.67 (*d*, $J = 5$, 3 H, 3 H–C(5')); 1.85, 1.95, 2.20 (3 *m*, 3 H, 2 H–C(2'), H–C(1')); 2.83, 2.88 (2 *s*, 3 H (1:3), NCH_3); 3.80 (*d*, $J = 6$, 1 H, H–C(4)); 4.13 (*t*, $J = 6$, 1 H, H–C(5)); 4.25 (*dd*, $J = 18$, 6, 2 H, CH_3CH_2O); 5.35, 5.51 (2 *m*, 2 H, H–C(3'), H–C(4')); 7.33, 7.39 (2 *s*, 1 H (1:3), HN). MS (HR): 254.1649 (M^+, $C_{13}H_{12}N_2O_3$, calc. 254.1631).

23. *Ethyl (4*S,*5*R*)-3-Methyl-5-((1'*R*,3'*E*)-1'-methyl-3'-pentenyl)-2-oxooxazolidine-4-carboxylate* (**23**). A solution of 0.870 g (3.4 mmol) of **22** in 90 ml of 95% EtOH is stirred with 4.5 ml of 1 N HCl for 2 h at r.t. The resulting solution is adjusted to pH 7 by the addition of 1 N $NaHCO_3$ and extracted with 400 ml of CH_2Cl_2 after addition of 200 ml of H_2O. The aq. phase is extracted again with 300 ml of CH_2Cl_2, the combined org. phase dried over Na_2SO_4 and evaporated. The residue is chromatographed on 200 g of silica gel using 1% MeOH/CH_2Cl_2: 0.830 g (95%) of **23**, $[\alpha]_D^{20} = +29.5$ ($c = 1.0$, $CHCl_3$). IR (CH_2Cl_2): 2930 (br.), 1760*s*, 1440*m*, 1400*m*, 1210*m*, 1140*w*, 1040*m*, 970*m*, 830*w*. ^{1}H-NMR ($CDCl_3$, 360 MHz): 0.95 (*d*, $J = 7$, 3 H, CH_3–C(1')); 1.32 (*t*, $J = 7$, 3 H, CH_3CH_2O); 1.67 (*d*, $J = 6$, 3 H, 3 H–C(5')); 1.83–2.04, 2.22 (2 *m*, 3 H, 2 H–C(2'), H–C(1')); 2.92 (*s*, 3 H, NCH_3); 2.95 (*d*, $J = 5$, 1 H, H–C(4)); 4.25 (*t*, $J = 5$, 1 H, H–C(5)); 4.27 (*m*, 2 H, CH_3CH_2O); 5.37, 5.50 (2 *m*, 2 H, H–C(3'), H–C(4')). MS (LR): 255 (M^+), 241, 198, 182, 138, 128, 100, 84, 55.

$C_{13}H_{21}NO_4$ (255.317) Calc. C 61.2 H 8.3 N 5.5 O 25.1% Found C 61.1 H 8.5 N 5.5 O 25.7%

24. *(4*S,*5*R*)-3-Methyl-5-((1'*R*,3'*E*)-1'-methyl-3'-pentenyl)-2-oxooxazolidine-4-carboxylic Acid* (**24**). A solution of 0.680 g (2.67 mmol) of **23** in 35 ml of 1,4-dioxane is stirred for 1 h at r.t. with 92 ml of 0.1 N KOH. The solution is adjusted to pH 2 by the addition of 1 N HCl, extracted twice with 300 ml of CH_2Cl_2, the extract dried over Na_2SO_4, and evaporated. The residue is crystallized from Et_2O to yield 0.545 g (90%) of **24** in pure enantiomeric form, m.p. 81–82°, $[\alpha]_D^{22} = +33.5°$ ($c = 1.0$, $CHCl_3$). IR (CH_2Cl_2): 3450*m*, 3200–2500*s*, 1765*s*, 1700*m*, 1530*w*, 1480*m*, 1400*s*, 1330*m*, 1310*m*, 1240*m*, 1215*m*, 1140*w*, 1095*m*, 1060*s*, 1035*m*, 970*m*, 925*m*, 860*w*, 820*s*. ^{1}H-NMR ($CDCl_3$, 360 MHz): 0.99 (*d* = 7, 3 H, CH_3–C(1')); 1.67 (*d*, $J = 7$, 3 H, 3 H–C(5')); 1.95 (*m*, 2 H, 2 H–C(2')); 2.25 (*m*, 1 H, H–C(1')); 3.02 (*s*, 3 H, CH_3N); 4.04 (*d*, $J = 5$, 1 H, H–C(4)); 4.38 (*dd*, $J = 5$, 6, 1 H, H–C(5)); 5.38, 5.52 (2 *m*, 2 H, H–C(3'), H–C(4')); 8.56 (*s*, 1 H, COOH). MS (LR): 227 (M^+), 211, 182, 170, 138, 128, 100, 84, 68, 55.

$C_{11}H_{17}NO_4$ (227.26) Calc. C 58.1 H 7.5 N 6.2 O 28.2% Found C 57.9 H 7.6 N 6.4 O 28.1%

25. *(2*S,*3*R,*4*R,*6*E*)-3-Hydroxy-4-methyl-2-methylamino-6-octenoic Acid* (**25**). a) *Starting from* **24**. The solution of 172 mg (0.76 mmol) of **24** in 2.0 ml of 2 N KOH is warmed for 3 h at 80°, cooled, adjusted to pH 5 by the addition of 1 N HCl, and evaporated. The residue is taken up in MeOH, filtered through 50 g of *Sephadex LH 20* and evaporated. The residue is crystallized from EtOH to yield 144 mg (94%) of pure **25**, m.p. 240–241°, $[\alpha]_D^{20} = +13.5°$ ($c = 0.50$, H_2O at pH 7 (phosphate buffer *Titrisol* pH 7.00 from *Merck*)).

b) *Starting from* **23**. The suspension of 194 mg (0.76 mmol) of **23** in 4 ml of 2 N KOH is warmed up to 80°, the resulting solution stirred for 3 h at 80°, then cooled to 20°, adjusted to pH 5 by addition of 1 N HCl, and evaporated. The residue is taken up in H_2O, filtered through 7 g of ion exchange resin *(BIO-RAD AG 3-X4* (100–200 mesh) in the OH^--form) and evaporated. The residue is crystallized from MeOH to yield 138 mg (90%) of pure **25**, m.p. 240–241°, $[\alpha]_D^{20} = +13.0$ ($c = 0.46$, H_2O at pH 7, s. above). IR (KBr): 3400*m*, 3200*m*, 3025*w*, 2960*w*, 2940*w*, 2870*w*, 2750–2300 (br.), 1615*s*, 1585*s*, 1460*m*, 1450*m*, 1430*m*, 1410*m*, 1380*s*, 1330*w*, 1320*w*, 1310*w*, 1260*w*, 1245*w*, 1140*m*, 1110*m*, 1075*w*, 1060*w*, 1045*w*, 1035*w*, 990*w*, 970*s*, 930*w*, 895*w*, 850*w*, 680*w*. IR (Nujol): 3200*m*, 2950–2850*s*, 2650 (br.), 2500–2250 (br.), 1620*s*, 1585*s*, 1460*m*, 1445*m*, 1430*m*, 1410*m*, 1380*s*, 1330*w*, 1320*w*, 1310*w*, 1290*w*, 1260*w*, 1245*w*, 1140*m*, 1110*m*, 1075*w*, 1060*w*, 1045*w*, 1030*m*, 990*w*, 970*s*, 930*w*, 895*w*, 850*w*, 880*w*, 870*w*, 850*w*, 675*w*. ^{1}H-NMR (D_2O, 20°; 360 MHz): 0.96 (*d*, $J = 8$, 3 H, CH_3–C(4)); 1.67 (*d*,

J = 6, 3 H, 3 H–C(8)); 1.70 (*m*, 1 H, H–C(4)); 1.90 (*m*, 1 H, H–C(5)); 2.30 (br. *d*, J = 14, 1 H, H–C(5)); 2.75 (*s*, 3 H, CH_3N); 3.65 (*d*, J = 6, H–C(2)); 3.79 (*t*, J = 6, 1 H, H–C(3)); 5.75 (*m*, 2 H, H–C(6), H–C(7)). Irradiation at 1.67 ppm: 5.50 (*m*, 1 H, H–C(6)); 5.85 (*d*, J = 15, H–C(7)). Irradiation at 2.30 ppm: 5.49 (*dd*, J = 15, 6, H–C(6)); 1.90 (*m* (less complicated), 1 H, H–C(5)). ^{1}H-NMR ((D_6)DMSO, 20°; 360 MHz): 0.82 (*d*, J = 6, 3 H, CH_3–C(4)); 1.15 (*s*, 2 H, OH, NH); 1.63 (*d*, J = 4, 3 H, 3 H–C(8)); 1.79 (*m*, 2 H, H–C(4), H–C(5)); 2.28 (*m*, 1 H, H–C(5)); 2.50 (*s*, 3 H, CH_3N); 3.11 (*d*, J = 5, 1 H, H–C(2)); 3.56 (*t*, J = 5, 1 H, H–C(3)); 5.49 (*m*, 2 H, H–C(6), H–C(7)). ^{1}H-NMR ((D_6)DMSO, 120°; 360 MHz, **25** is not stable at 180°): 0.84 (*d*, J = 6, 3 H, CH_3–C(4)); 1.63 (*d*, J = 4, 3 H, 3 H–C(8)); 1.78 (*m*, 1 H, H–C(4)); 1.80, 2.28 (2 *d*, J = 12, 2 H, 2 H–C(5)); 2.44 (*s*, 3 H, CH_3N); 3.06 (*d*, J = 4, 1 H, H–C(2)); 3.54 (*t*, J = 4, 1 H, H–C(3)); 4.40 (br. *s*, 2 H, NH, OH); 5.41 (*m*, 2 H, H–C(6), H–C(7)). MS (LR): 201 (M^+), 156, 138, 118, 89, 79, 55.

$C_{10}H_{19}NO_3$ (201.27) Calc. C 59.7 H 9.5 N 7.0 O 23.8% Found C 59.5 H 9.6 N 6.9 O 24.3%

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