164. Application of the Gold(I)-Catalyzed Aldol Reaction to a Stereoselective Synthesis of (2*S*,3*R*,4*R*,6*E*)-3-Hydroxy-4-methyl-2-(methylamino)oct-6-enoic Acid (= MeBmt[1])), Cyclosporin's Unusual Amino Acid

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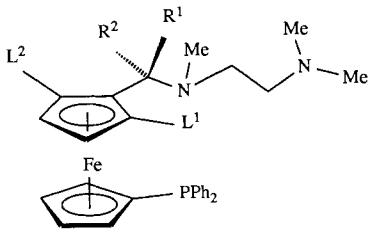
The title compound **8** was prepared in three steps starting from the optically pure aldehyde (2*R*,4*E*)-2-methylhex-4-enal (**3**), thus constituting the shortest synthetic approach reported. Two of the three stereogenic centers in the product were generated in a coupling reaction of **3** with ethyl isocyanoacetate, catalyzed by a gold(I)/chiral ferrocenylphosphine system, giving the dihydrooxazole **5** in 85% diastereoselectivity *(mismatched case)*. The weak effect of double stereodifferentiation in this reaction *(matched case* 90% ds) is discussed. *N*-Methylation and hydrolytic ring opening of **5** gave the protected form **7** of MeBmt. The X-ray diffraction study carried out on **7** confirms the absolute configuration of the two stereogenic centers formed in the gold(I)-catalytic reaction.

1. Introduction. – Stereoselective C–C bond forming reactions catalyzed by chiral transition-metal complexes are a topic of fundamental importance [1]. In 1986, *Hayashi* and *Ito* reported an elegant asymmetric synthesis of dihydrooxazoles by an efficient gold(I)-catalyzed coupling of aldehydes with 2-isocyanoacetates in the presence of chiral ferrocenylphosphines of type **1** and the gold(I) complex **2** as a catalyst precursor [2]. The high diastereo- and enantioselectivity obtained in this type of aldol reaction constitutes a powerful approach to optically active β-hydroxy-α-amino acids.

Hayashi and *Ito* reported subsequently the design of more sophisticated ferrocenylphosphine ligands [3] but investigated only to a limited extent the influence of



(*R*,*S*)-**1** R[1]=Me, R[2]=H, L[1]=PPh_2, L[2]=H
(*S*,*R*)-**1** R[1]=H, R[2]=Me, L[1]=H, L[2]=PPh_2

[Au(CN-*cyclo*-C_6H_{11})$_2$]BF_4

2

[1]) (4*R*)-4-[(*E*)-But-2-enyl]-4,*N*-dimethyl-L-threonine = MeBmt (IUPAC/IUB three-letter amino-acid notation).
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structural variations of the substrates. In particular, they did not use chiral aldehydes or isocyanoacetates. In contrast, our own research effort was directed towards the definition of the scope and limitations of this reaction and the elucidation of the nature of its stereoselective step [4]. Making use of the most readily available ligand **1**, we widely varied the structure of the substrates.

We previously reported the introduction of heteroatom substituents into the aldehyde being crucial and able to severely alter the catalyst stereoselectivity [4c]. In addition, we described the large effect of double stereodifferentiation (for definitions and examples, see [5]) observed in the reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde and pointed out the possible concurrent influence of both the chirality and the α-heteroatom in determining diastereoselectivity in that specific case. In an attempt to evaluate the effect of aldehyde chirality in an environment free of heteroatom substituents and, at the same time, implement the Au(I)-catalytic step into a total synthesis of a natural product, we chose (2*R*,4*E*)-2-methylhex-4-enal (**3**) [6a] as a model substrate. Aldehyde **3** is chiral at C(α), bears no heteroatom substituent, and is readily available in optically pure form.

We describe herein the shortest known synthesis of (2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)oct-6-enoic acid (= MeBmt[1]; **8**), the unusual amino acid in the immunosuppressive undecapeptide cyclosporine (for a review, see [7]), starting from **3** and constructing the C(2) and C(3) stereogenic centers in a single stereoselective homogeneous transition-metal-catalyzed step.

Aldehyde **3** has been previously exploited as intermediate for total syntheses of MeBmt in connection with the use of either a chiral (*Evans* and coworkers [6] and *Seebach* and coworkers[3]) [8]) or non-chiral glycine synthon (*Rich* and coworkers [9] and *Schmidt* and *Siegel* [10]), respectively. Other approaches to **8** made use of the *Sharpless'* epoxidation methodology and diastereoselective oxazolidinone formation (*Tung* and *Rich* [11] and *Rama Rao et al.* [12]). The first reported, laborious total synthesis of MeBmt started from (+)-(*R*,*R*)-tartaric acid (*Wenger* [13]). No asymmetric homogeneous transition-metal-catalyzed route to this amino acid has been so far described.

2. Results and Discussion. – 2.1. *Synthesis.* In order to test the selectivity induced by the stereogenic center C(α) of the substrate, the (*R*)-aldehyde **3** was reacted with ethyl isocyanoacetate under gold(I)-catalytic conditions in the presence of both enantiomeric ligands (*R*,*S*)-**1** and (*S*,*R*)-**1**, respectively (see *Scheme 1*). The dihydrooxazoles formed were isolated and purified by distillation (77% yield). The formation of the preferred diastereoisomer in each of the two reactions is clearly dominated by the induction due to the catalyst. Thus, the use of (*S*,*R*)-**1** corresponds to a *matched case* [5] giving the *trans*-diastereoisomer **4** in 90% diastereoselectivity (ds), whereas (*R*,*S*)-**1** leads to the formation of the desired diastereoisomer **5** in nevertheless 85% ds, constituting the *mismatched case* (see the *Table*). We attribute the only weak effect of double stereodifferentiation to the absence of heteroatom substituents in the substrate **3** [4c].

The fact that a high chiral induction is dominated by a single homochiral (= enantiomerically pure) component (here the catalyst) is, for synthetic purposes, to be understood as an advantage, as it allows more predictable stereochemical outcomes in

[3]) *Seebach*'s synthesis of MeBmt is to be considered a formal total synthesis. It was namely thwarted by the inability to hydrolyze the methyl amide obtained in the course of the preparation and which would have given the final product.

Scheme 1

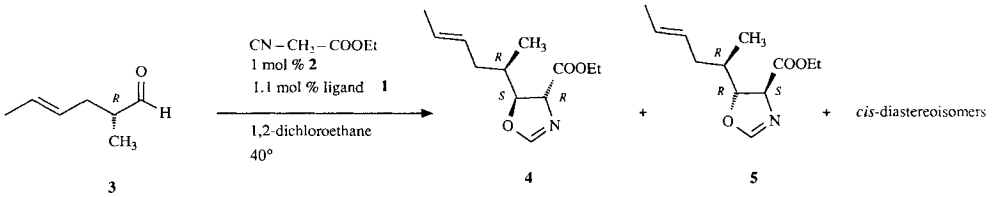

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Table. *Distribution of Diastereoisomers Depending on the Ligand as Determined by GLC*[a])

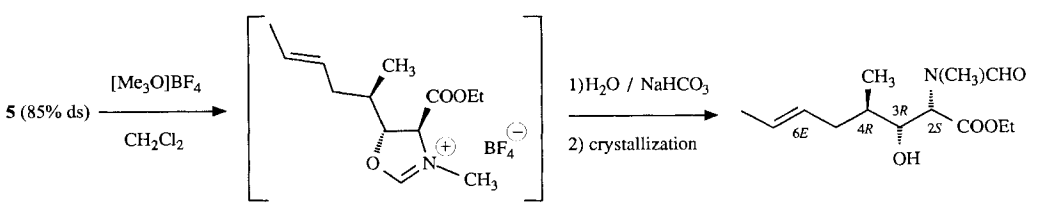
Ligand	*trans*-Dihydrooxazole		*cis*-Dihydrooxazoles [%]
	4 [%]	**5** [%]	
(*R*,*S*)-**1**	10	85	5
(*S*,*R*)-**1**	90	6	4

[a]) 50-m *Chirasil*-L-*Val* column.

transformations where two homochiral reagents are reacted with one another. The present synthesis is an example thereof. Thus, due to the only weak effect of double stereodifferentiation observed, the two diastereoisomeric pairs of enantiomeric dihydrooxazoles (**4**, **5** and their mirror images) are, in principle, equally accessible in comparable optical yields.

The dihydrooxazole **5** (85% ds) was treated with trimethyloxonium tetrafluoroborate in CH_2Cl_2 at room temperature *(Scheme 2)*, yielding the dihydrooxazolium tetrafluoroborate **6**. Imidates of type **6** are known [14] to undergo fast hydrolytic ring opening giving the corresponding formamido alcohol (see **7**) under workup conditions with aqueous $NaHCO_3$ solution. The formamido alcohol obtained from **5** *via* **6** was purified by distillation giving 92% yield of a mixture of diastereoisomers as a viscous, yellowish oil. The optically pure (2*S*,3*R*,4*R*,6*E*)-diastereoisomer **7** was obtained by crystallization of the oil in Et_2O (79% from the oil), as colorless platelets. This intermediate was characterized by X-ray diffraction *(vide infra)* and ^1H- and ^{13}C-NMR spectra.

Scheme 2



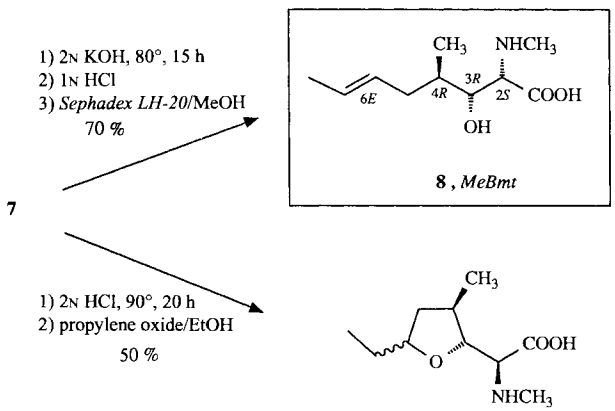
6 7 (73% overall), (2*S*,3*R*,4*R*,6*E*)

The ^1H- and ^{13}C-NMR spectra of **7** show at r.t. two sets of resonances due to the (*Z*)- and (*E*)-conformer of the *N*-formyl group in a ratio of 7:3 (see *Exper. Part*). In the ^1H-NMR, the signals due to the CHO and CH_3N group are very diagnostic for the presence of amide rotamers. They each show 2 signals with a $\Delta\delta$ of 0.02 and 0.08 ppm, respectively, in $CDCl_3$, and 0.03 and 0.20 ppm, respectively, in (D_6)DMSO. In the latter solvent, complete coalescence was observed at 423 K, although at this temperature, the *s* of the CH_3N group still appears broadened.

We tentatively interpret this observation as indicative of slow N–C(2) bond rotation, on the NMR time scale. Slow rotation around the *sec*-alkyl–N bond in amides has been previously observed [15]. Upon cooling to r.t., a 57:43 mixture of the two formamide rotamers is formed, constituting the equilibrium mixture. The temperature-dependent behavior is reversible. In the ^{13}C-NMR spectrum at r.t., all C-atoms of the two rotamers, except for the COOEt and *Me*–C(4) groups, appear at different chemical shifts.

The hydrolysis of **7** to MeBmt (**8**) proved problematic. Initial attempts to obtain **8** by an acid-catalyzed hydrolysis (2N HCl) of its precursor **7** generated, in 50% yield, the same cyclic MeBmt isomer **9** as previously observed by *Rüegger et al.* [16] upon hydrolysis of cyclosporine in 6N HCl. Basic conditions (2N KOH, 80°, over night), followed by acidification to pH 5 and chromatography on *Sephadex LH-20* (a procedure similar to those used by *e.g., Wenger* [13] or *Evans* and *Weber* [6a] for the hydrolysis of oxazolidinone derivatives), gave the desired product in 70% yield (see *Scheme 3*).

Scheme 3



9 (3:1 mixture of epimers)

The present synthesis is suitable to scale-up owing to *a*) the availability of the aldehyde **3**, *b*) the possibility to purify the crystalline precursor **7** of MeBmt, and, in particular, *c*) the efficiency and productivity of the easy-to-handle gold(I) catalyst. The gold(I)/ferrocenylphosphine system at hand can easily be recycled and also reused a number of times without any loss of activity and/or selèctivity on a kg scale[4]) [17].

2.2. *Structure of Ethyl (2*S*,3*R*,4*R*,6*E*)-2-(*N*-Formyl-*N*-methylamino)-3-hydroxy-4-methyloct-6-enoate* (**7**). Previous extensive studies by *Loosli et al.* [18] disclosed the structure of cyclosporine itself. *Petcher et al.* [19] described the solid-state structure of iodocyclosporine, containing the iodinated form of the cyclic isomer **9** of MeBmt. The crystal structure determination described herein is the first being carried out on a simple

[4]) After completion of the catalytic reaction and subsequent evaporation of the solvent, the catalyst can be precipitated by addition of either Et_2O or pentane. Filtration, washing with Et_2O and drying *in vacuo*, furnishes an orange powder of approximate composition [Au(**1**)]BF_4, in up to 95% recovery. This material shows no different activity or selectivity, compared to the freshly, *in situ* prepared catalyst. The operation of recovery can be consistently repeated a number of times, with the same starting material.

derivative of MeBmt. This X-ray diffraction study, the absolute configuration of the aldehyde **3** being known, confirms that of both new stereogenic centers in **7** (2*S*,3*R*), formed by the Au(I)-catalytic reaction, as well as that of the synthetic MeBmt, obtained by hydrolysis of **7**.

The geometry of the molecule and the adopted atom numbering scheme are depicted in *Fig. 1* (ORTEP plot [20]). Relevant interatomic distances and angles are given in the

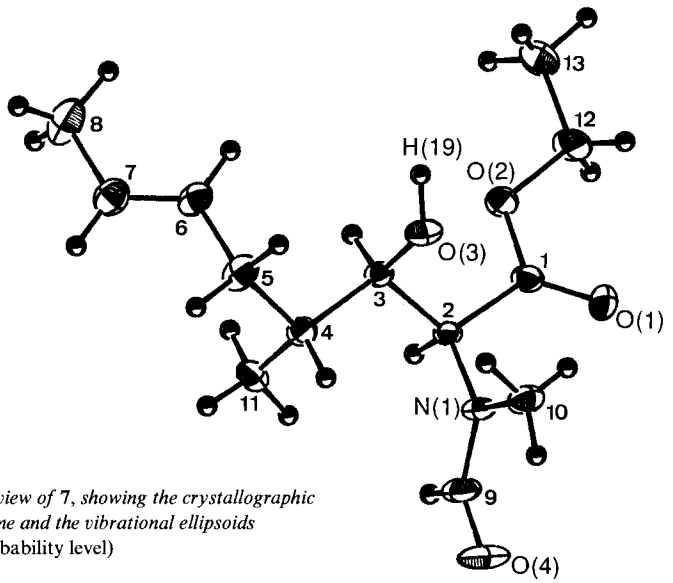


Fig. 1. *ORTEP view of* **7**, *showing the crystallographic numbering scheme and the vibrational ellipsoids* (at the 20% probability level)

Table. *Relevant Interatomic Distances* [Å] *and Angles* [°] *in* **7**[a])

O(1)–C(1)	1.199(7)	C(2)–C(3)	1.567(6)
O(2)–C(1)	1.328(7)	C(3)–C(4)	1.544(7)
O(2)–C(12)	1.472(7)	C(4)–C(5)	1.553(8)
O(3)–C(3)	1.416(6)	C(4)–C(11)	1.525(9)
O(4)–C(9)	1.243(8)	C(5)–C(6)	1.518(9)
N(1)–C(2)	1.458(6)	C(6)–C(7)	1.307(9)
N(1)–C(9)	1.362(7)	C(7)–C(8)	1.52(1)
N(1)–C(10)	1.470(8)	C(12)–C(13)	1.40(1)
C(1)–C(2)	1.537(7)		
C(1)–O(2)–C(12)	116.2(5)	O(3)–C(3)–C(4)	111.1(4)
C(2)–N(1)–C(9)	116.1(5)	C(2)–C(3)–C(4)	109.8(4)
C(2)–N(1)–C(10)	122.7(4)	C(3)–C(4)–C(5)	108.5(4)
C(9)–N(1)–C(10)	121.1(5)	C(3)–C(4)–C(11)	111.7(4)
O(1)–C(1)–O(2)	124.1(5)	C(5)–C(4)–C(11)	112.1(5)
O(1)–C(1)–C(2)	125.0(5)	C(4)–C(5)–C(6)	114.3(5)
O(2)–C(1)–C(2)	110.9(5)	C(5)–C(6)–C(7)	125.4(5)
N(1)–C(2)–C(1)	109.1(4)	C(6)–C(7)–C(8)	125.1(6)
N(1)–C(2)–C(3)	113.8(4)	O(4)–C(9)–N(1)	120.0(6)
C(1)–C(2)–C(3)	110.7(4)	O(2)–C(12)–C(13)	108.9(6)
O(3)–C(3)–C(2)	107.8(4)		

[a]) *E.s.d.'s on the last significant digit are given in parentheses.*

Table. Bond lengths and angles agree, in general, with the standard values quoted in the literature. The only exception is the short C–C distance in the ester ethyl group, due to disorder in the crystal.

The ester group shows the expected (*Z*)-conformation [21] (torsion angle [22] C(12)–O(2)–C(1)–O(1), 1.1 (0.9)°), whereas the formamido moiety is (*E*)-arranged (torsion angle C(10)–N(1)–C(9)–O(4), 1.6 (0.9)°), thus allowing for intermolecular H-bond formation between the OH group and the amido O-atom. This interaction, together with *van der Waals* contacts, also determines the crystal packing (see *Fig. 2*).

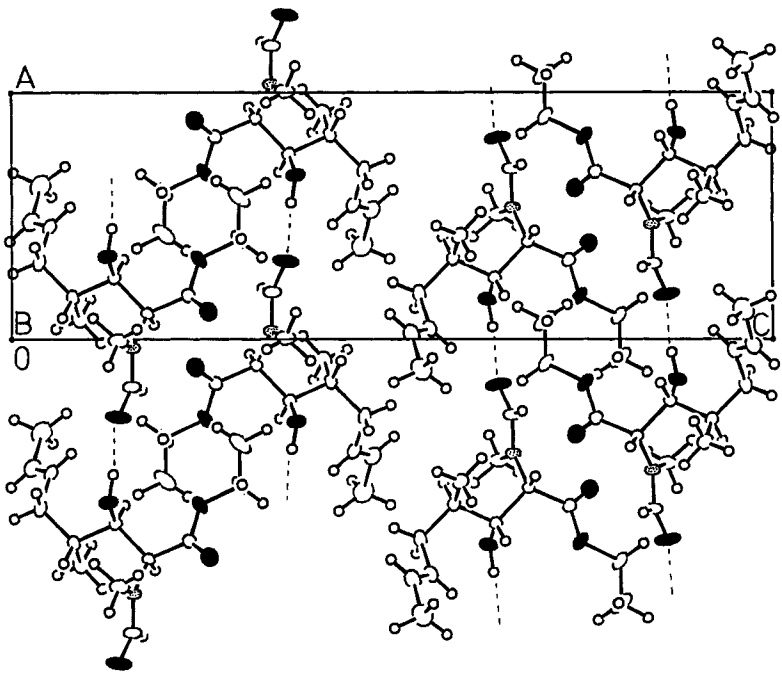


Fig. 2. *Projection along the crystallographic* a-*axis, showing the crystal packing and the intermolecular H-bridges* (dashed lines). Relevant distances and angles: O(3)–H(19) 0.89, H(19)–O(4′) 1.85, O(3)–O(4′) 2.735 Å; O(3)–H(19)–O(4′) 117 and H(19)–O(4′)–C(9′) 147°.

Experimental Part

(The authors wish to thank Mr. *Robert Häusel* for careful experimental work)

General. The ligands **1** [23], complex **2** [24], and (*R*)-aldehyde **3** [6a] were prepared according to published procedures. All reactions with air- or moisture-sensitive compounds were carried out under Ar using standard *Schlenk* techniques. Freshly distilled solvents (THF and Et_2O from Na/benzophenone ketyl, CH_2Cl_2 and 1,2-dichloroethane from powdered CaH_2) were used throughout. All other reagents were used as received. M.p.: *Büchi-510* apparatus; in open capillaries; uncorrected. Optical rotations: *Perkin-Elmer-241* polarimeter using 10-cm cells. GLC: 50-m *Chirasil-L-Val* column, *Carlo Erba* gas chromatograph, model *HRGC 5300 GLC*. ^{1}H-NMR (250.133 or 300.133 MHz) and ^{13}C-NMR (62.896 MHz): *Bruker-AM-300* or *-AC-250* spectrometers, respectively; chemical shifts in ppm relative to internal tetramethylsilane (unless otherwise stated), *J* in Hz. Elemental analyses were performed by Analytical Research Services, *Ciba-Geigy AG*.

Ethyl (4S,5R)-5-((1′R,3′E)-1′-Methylpent-3′-enyl)-4,5-dihydrooxazole-4-carboxylate (**5**). A soln. of 75 mg (0.149 mmol) of [Au(CN-*cyclo*-$C_6H_{11})_2$]BF_4 (**2**) and 111 mg (0.163 mmol) of (*R,S*)-**1** in 12 ml of 1,2-dichloroethane was stirred for 10 min. Then 1.33 ml of ethyl isocyanoacetate (11.42 mmol) were added, and the orange soln. was

warmed to 40°. After the addition of 1.5 g (13.37 mmol) of freshly prepared **3**, the mixture was stirred for 18 h at 40°. After evaporation of the solvent and addition of 20 ml of Et_2O, the mixture was stirred vigorously for 5 min. The precipitate formed (catalyst) was filtered off and the solvent evaporated. The residue was distilled yielding 2.32 g (77%) of a clear, colorless liquid. B.p. 69–70°/0.02 mbar. $[\alpha]_D^{22} = +180.4$ ($c = 1.25$, THF). The product was analyzed by GLC (50-m *Chirasil-*L-*Val* column) and shown to be a 85.0:10.0:4.4:0.6 mixture of the four possible diastereoisomers. ^{1}H-NMR ($CDCl_3$, 300 MHz, major stereoisomer): 0.90 (*d*, $^3J = 7$, CH_3–C(1′)); 1.32 (*t*, $^3J = 7$, CH_3CH_2O); 1.67 (*d*, $^3J = 6$, CH_3(5′)); 1.77–2.25 (2 overlapping *m*, CH_2(2′), CH(1′)); 4.25 (*q*, $^3J = 7$, CH_3CH_2O); 4.37 (*dd*, $^3J = 8$, $^4J = 1.5$, CH(4)); 4.54 (*t*, $^3J = 8$, CH(5)); 5.32–5.55 (*m*, CH(4′) = CH(5′)); 6.92 (*d*, $^4J = 1.5$, CH(2)). MS: 225 (M^+), 180, 170, 152, 142, 124, 107, 96, 95, 55. Anal. calc. for $C_{12}H_{19}NO_3$: C 63.98, H 8.50, N 6.22; found: C 63.68, H 8,64, N 6.35.

*Ethyl (2*S*,3*R*,4*R*,6*E*)-2-(*N*-Formyl-*N*-methylamino)-3-hydroxy-4-methyloct-6-enoate* (7). To a soln. of 2.15 g of **5** (9.5 mmol) in 20 ml of CH_2Cl_2 was added a soln. of 1.41 g (9.5 mmol) of Me_3OBF_4 in 20 ml of CH_2Cl_2. The white suspension turned to a clear yellow soln. within 10 min. After stirring it for 20 h at r.t., 15 ml of H_2O and 15 ml of sat. $NaHCO_3$ soln. were added sequentially (→pH 7). The org. phase was washed with H_2O (2 × 100 ml) and brine (100 ml), dried (Na_2SO_4), and evaporated. The residue was bulb-to-bulb distilled yielding 2.26 g (92%) of a light yellow oil. B.p. 180–190°/0.008 mbar. $[\alpha]_D^{22} = +8.5$ ($c = 1.0$, $CHCl_3$). From Et_2O, 1.80 g (79% starting from the oil) of white crystalline platelets of the major compound **7** in the mixture could be obtained. M.p. 114–115°. $[\alpha]_D^{22} = +7.5$ ($c = 1.09$, $CHCl_3$). The crystals were shown by NMR to be a diastereoisomerically (thus also enantiomerically) pure mixture of the two amide conformers ((*Z*/*E*) 7:3). ^{1}H-NMR ($CDCl_3$, 250 MHz, 298 K): 0.85, 0.88 (2 overlapping *d*, $^3J = 6.5$, $CH_3C(4)$); 1.29 (*t*, $^3J = 7$, CH_3CH_2O); 1.46–1.72 (*m*, CH(4)); 1.72 (*d*, $^3J = 5$, $CH_3(8)$); 1.90–2.46 (2 *m*, $CH_2(5)$); 3.01, 3.09 (2 *s*, CH_3N); 2.47, 3.38 (2 *d*, $^3J = 8$, OH); 3.83–4.32 (2 overlapping *m*, CH_3CH_2O, CH(3)); 4.88 (*d*, $^3J = 5.3$, CH(2)); 5.34–5.59 (*m*, CH(6) = CH(7)); 8.12, 8.14 (2 *s*, NCHO). ^{1}H-NMR ($(CD_3)_2SO$, 250.133 MHz, 313 K; δ rel. to DMSO at 2.58 ppm): 0.82, 0.87 (2 *d*, $^3J = 6.8$, $CH_3C(4)$); 1.29, 1.30 (2 *t*, $^3J = 7.1$, CH_3CH_2O); 1.37–1.57 (*m*, CH(4)); 1.71 (br. *d*, $^3J = 4$, $CH_3(8)$); 1.75–1.92 (*m*, CH(5)); 2.32–2.48 (*m*, CH(5)); 2.93, 3.13 (2 *s*, CH_3N); 3.85–3.98 (*m*, CH(3)); 4.10–4.32 (*m*, CH_3CH_2O); 4.48, 5.14 (2 *d*, $^3J = 5.1$, CH(2)); 5.37 (*d*, $^3J = 6.2$, OH, identified by H/D exchange upon addition of D_2O); 5.39–5.59 (*m*, CH(6) = CH(7)); 8.18, 8.21 (2 *s*, NCHO). ^{1}H-NMR ($(CD_3)_2SO$, 250.133 MHz, 423 K; δ rel. to DMSO at 2.58 ppm): 0.97 (*d*, $^3J = 6.7$, $CH_3C(4)$); 1.34 (*t*, $^3J = 7.3$, CH_3CH_2O); 1.58–1.83 (*m*, CH(4)); 1.73 (br. *d*, partially overlapping with previous *m*, $^3J = 3.3$, $CH_3(8)$); 1.80–1.95 (*m*, CH(5)); 2.40 (br. *dq*, $^2J = 12.2$, $^3J = 3.7$, CH(5)); 3.03 (br. *s*, line width 25 Hz, CH_3N); 4.02 (br. *q*, $^3J = 5.8$, CH(3)); 4.28 (*q*, $^3J = 7.3$, CH_3CH_2O); 4.55 (br. *s*, line width 13 Hz, CH(2)); 5.44–5.64 (*m*, CH(6) = CH(7)); 8.21 (*s*, NCHO); signal of OH very br. at *ca.* 4–5. ^{13}C-NMR ($CDCl_3$, 62.896 MHz, 298 K): 14.18 (CH_3CH_2O); 15.70, 16.17 (CH_3(8)); 17.99 (CH_3C(4)); 29.70, 36.02 (CH_3N); 35.02, 35.87 (CH_2(5)); 35.15, 35.29 (CH(4)); 59.07, 63.25 (CH(2)); 61.68, 61.84 (CH_3CH_2O); 74.41 75.27 (CH(3)); 127.24, 127.42 (CH(6)); 128.82, 128.92 (CH(7)); 164.42, 164.52 (NCHO); 169.54, 169,97 (*C*OOEt). MS: 257 (M^+), 239, 212, 184, 174, 145, 128, 116, 107, 99. Anal. calc. for $C_{13}H_{23}NO_4$: C 60.68, H 9.01, N 5.44; found: C 60.73, H 8.92, N 5.58.

*(2*S*,3*R*,4*R*,6*E*)-3-Hydroxy-4-methyl-2-(methylamino)oct-6-enoic Acid* (= MeBmt; **8**). Overnight, 257 mg of **7** were heated at 80° in 2.3 ml of 2N KOH. The mixture was allowed to cool to r.t. and the pH adjusted to 5 by the addition of 1N HCl. After evaporation, the colorless residue was chromatographed on 40 g of *Sephadex LH-20* with MeOH. The material thus obtained was recrystallized from EtOH/H_2O, yielding 141 mg (70%) of **8**. M.p. 239–241°. $[\alpha]_D^{22} = +11.0$ ($c = 0.5$, 1M phosphate buffer pH 7.00). ^{1}H-NMR (D_2O, 250 MHz, r.t.): 0.96 (*d*, $^3J = 6$, $CH_3C(4)$); 1.66 (*d*, $^3J = 6$, $H_3C(8)$); 1.67–1.79 (*m*, partially overlapping with previous *d*, CH(4)); 1.82–1.98 (*m*, CH(5)); 2.24–2.36 (br. *d*, $^2J = 13$, CH(5)); 2.75 (*s*, CH_3N); 3.65 (*d*, $^3J = 6$, CH(2)); 3.78 (*t*, $^3J = 6$, CH(3)); 5.41–5.66 (*m*, CH(6) = CH(7)). Anal. calc. for $C_{10}H_{19}NO_3$: C 59.68, H 9.52, N 6.96; found: C 59.39, H 9.61, N 6.91. Physical and spectral properties in good agreement with reported ones [13] [6a].

Acid Hydrolysis of **7**. To a soln. of 217 mg (0.84 mmol) of **7** in 15 ml H_2O, 5 ml of conc. HCl soln. were added and stirred at 90° for 24 h. The mixture was evaporated, leaving a thick but colorless oil. The latter was dissolved in 1.56 ml of EtOH, and an equivalent volume of propylene oxide was added dropwise, forming a white suspension. The solvent was evaporated and the residue recrystallized from EtOH/H_2O, giving 85 mg (50%) of **9** as white needles. M.p. 232–234°. $[\alpha]_D^{22} = -25.7$ ($c = 0.39$, 1M phosphate buffer pH 7.00). ^{1}H-NMR (D_2O, 250 MHz, r.t.): 0.88 (*t*, $J = 7$, CH_3CH_2); 1.05 (*d*, $J = 6$, CH_3CH); 1.09–1.84 (complex *m*, 3.2 H); 2.24–2.42 (*m*, 1.8 H); 2.72 (*s*, $NHCH_3$); 3.45, 3.53 (2 *d*, $J = 7.3$, *CH*COOH); 3.64–3.76 (2 overlapping *dd*, *CH*CHOOH); 3.88–4.08 (complex *m*, $CHCH_2CH_3$); *ca.* 3:1 mixture by integration of epimers at C(3), in contrast with the findings by *Rüegger et al.* [16] (1:1 epimeric mixture from cyclosporine). MS: 202, 201 (M^+), 194, 172, 157, 156, 128, 125, 114, 113, 95. Anal. calc. for $C_{10}H_{19}NO_3$: C 59.68, H 9.52, N 6.96; found: C 59.52, H 9.49, N 7.12.

X-Ray Analysis of **7**. Suitable crystals, in the form of thin transparent platelets, were grown from Et_2O. Crystal data: $C_{13}H_{23}NO_4$, $M_r = 257.33$, orthorhombic space group $P2_12_12_1$, $a = 7.810(1)$, $b = 7.890(1)$, $c = 24.059(2)$ Å,

$V = 1482.5$ Å^3, $Z = 4$, calc. density 1.153 gcm^{-3}. Cu$K\alpha$ radiation, graphite monochromator, $\lambda = 1.5418$ Å. A crystal of dimensions $0.59 \times 0.29 \times 0.10$ mm was used for data collection. Space-group and cell-constants determination as well as collection of intensity data were effected on *a Nonius-CAD4* diffractometer. The $\Theta/2\Theta$ mode was used. There was no significant intensity variation for 3 standard reflections measured every h. 2Θ range 4–150°, scan time ≤ 45 s, depending on intensity of reflection, scan width 1.2°. Of the 1798 unique reflections measured, 1547 were considered observed ($I > 2\sigma(F_0)$). The structure was solved by the direct methods using the program SDP MULTAN 82 [25]. All H-atoms could be localized from difference *Fourier* maps. Full-matrix-least-squares refinements were carried out with anisotropic thermal parameters for non-H-atoms and isotropic ones for H-atoms. Including H-atoms in the refinement, final $R = 0.055$.

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