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Synthesis of γ-Oxo α-Amino Acids from L-Aspartic Acid[1]

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Abstract: The synthesis of different γ-oxo α-amino acids from hexafluoroacetone protected L-aspartic acid chloride **1** via Stille cross coupling reaction is described. Stille reaction of **1** with vinyltributyltin followed by Lewis acid catalyzed intramolecular Michael addition provides access to 4-substituted pipecolic acid derivatives. An efficient synthesis of 5-hydroxy-4-oxo-L-norvaline **7** and a new approach to the 4-oxo-L-ornithine skeleton starting from **1** have been elaborated. Copyright © 1996 Elsevier Science Ltd

Key words: L-aspartic acid, γ-oxo α-amino acids, 5-hydroxy-4-oxo-norvaline, 4-oxo-L-pipecolic acid, Stille reaction, intramolecular Michael addition, hexafluoroacetone

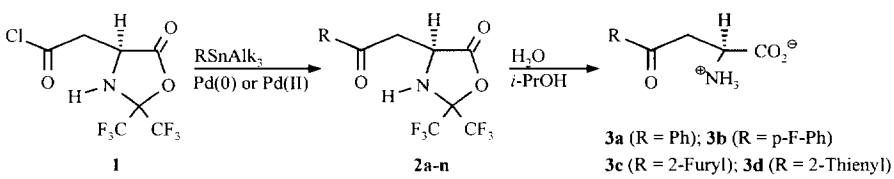
Introduction

γ-Oxo α-amino acids form a class of natural compounds. L-Kynurenine is a key intermediate in the metabolism of L-tryptophan.[2] 5-Hydroxy-4-oxo-L-norvaline [(-)-HON] (RI-331) exhibits antibiotic and antifungal activity.[3] 4-Oxo-L-pipecolic acid is a constituent of the virginiamycins, a family of cyclopeptides with antibiotic activity.[4] 3-(2-Furoyl)-L-alanine[5] and 4-oxo-L-norleucine[6] are naturally occurring compounds. Several tripeptides containing L-3-(2- and 4-methoxybenzoyl)alanines are candidates for incorporation into antiinflammatory drugs.[7]

The development of new convenient approaches to these amino acids from naturally occurring α-amino acid precursors (chiral pool) is of current interest.[8] For example, L-aspartic acid and L-serine are readily available at low cost. Our approach to γ-oxo α-amino acids starts from L-aspartic acid as homochiral precursor and hexafluoroacetone (HFA) as protecting reagent.[9] The protected L-aspartic acid derivative **1** is easily obtained in two steps in 72 % overall yield starting from L-aspartic acid.[10] As previously shown, the acid chloride **1** reacts with aromatic compounds in the presence of Lewis acids to give HFA-protected γ-aryl γ-oxo α-amino acids without racemization.[11] Simultaneous deprotection of the vicinal amino and carboxylic functions proceeds under mild conditions (H_2O/*i*-PrOH; rt). Various aromatic γ-oxo α-amino acids can be obtained via this straightforward approach in only four steps. However, the limitations inherent in the Friedel-Crafts reaction and low yields often observed for the acylation step prompted us to search for another possibility for the transformation of **1** into the γ-oxo α-amino skeleton. The Stille coupling reaction is one of the most promising protocols for this purpose. This approach has been previously used for the synthesis of L-kynurenine and (2S)-nicotinylalanine starting from another L-aspartic acid synthon: (S)-(3-(benzyloxy-carbonyl)-5-oxo-4-oxazolidinyl)acetyl chloride.[12,13]

Results and Discussion

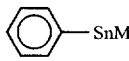
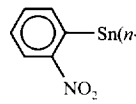
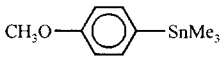
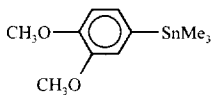
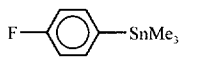
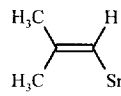
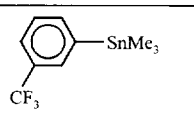
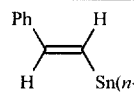
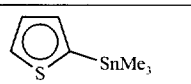
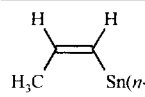
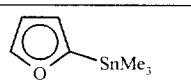
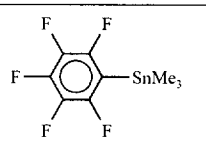
We investigated the cross-coupling reaction[14] of acid chloride **1** with various tin compounds [$RSnMe_3$ and RSn-*n*-Bu_3 (R = aryl-, alkenyl-, alkynyl-, alkyl-)] in the presence of different palladium catalysts [(Pd(0): $Pd_2(DBA)_3$·$CHCl_3$, $Pd(PPh_3)_4$; Pd(II): $PhCH_2Pd(PPh_3)_2Cl$ and $(PPh_3)_2PdCl_2$)] (Scheme 1, Table 1).



Scheme 1

The best yields of the aryltrimethyltin coupling with **1** are obtained by slow and portionwise addition of a solution of $Pd_2(DBA)_3$·$CHCl_3$ in toluene to a solution of the substrate in toluene at rt over a period of 24-36 h under argon. Aryl rests with both electron-donating and electron-withdrawing *para*- and *meta*-substituents can be transferred in good to excellent yields to afford the corresponding γ-aryl γ-oxo α-amino acid derivatives **2a-e**. Heteroaryl derivatives **2f,g** are obtained in slightly lower yields under these conditions. As a rule, the coupling reactions proceed faster (3-6 h) in dimethoxyethane in the presence of $PhCH_2Pd(PPh_3)_2Cl$ at elevated temperatures (40-60°C), however, at the expense of yields.

Table. Conditions and yields of the Stille cross-coupling reaction of acyl chloride **1** with tin reagents.

Product	R-Sn(Alk)$_3$	Method[#]	Yield [%]	Product	R-Sn(Alk)$_3$	Method[#]	Yield [%]
2a		1	85	**2i**		1-3	0
2b		2	75	**2j**	CH_2=CH-$SnMe_3$	1	67
2c		1	70	**2j**	CH_2=CH-Sn(*n*-Bu)$_3$	2	75
2d		1	91	**2k**		1	37
2e		1	71	**2l**		1	77
2f		1	57	**2m**[¶]		1	75
2g		1	59	**2n**	Ph-C≡C-Sn(*n*-Bu)$_3$	3	40
2h		1	10	**2o**	(*t*-Bu)Me_2SiOCH_2-Sn(*n*-Bu)$_3$	1-3	0
					$MOMOCH_2$-Sn(*n*-Bu)$_3$	1-3	0

[#] Method 1. $Pd_2(DBA)_2$·$CHCl_3$, toluene, 20°C, slow addition of catalyst. - Method 2. $PhCH_2Pd(PPh_3)_2Cl$, dimethoxyethane, 60°C. - Method 3. $Pd_2(DBA)_2$·$CHCl_3$, N-methylpyrrolidone, tri(2-furyl)phosphine.

[¶] A mixture of (*E*)- and (*Z*)-enones is obtained; the latter can be isomerized into pure (***E***)-**2m**.

An electron-withdrawing *ortho*-substituent on the aryl rests slows down the transfer reaction or prevents it at all. For example, $C_6F_5SnMe_3$ provides the corresponding ketone **2h** in very low yield, and our attempts to cross-couple *o*-$NO_2C_6H_4$Sn(*n*-Bu)$_3$ with **1** (as an approach to L-kynurenine) failed with any catalyst tested. Coupling of **1** with alkenyltrialkyltins proceeds readily to provide the corresponding α,β-unsaturated ketones **2j-m** in fair to good yields. Because substantial amounts of derivative **2j** were needed for further transformations we optimized the reaction of vinyltributyltin with acid chloride **1**. Compound **2j** is obtained in 75 % yield on a 10 g scale by heating the components in dimethoxyethane at 60°C for 8 h in the

presence of $PhCH_2Pd(PPh_3)_2Cl$. In the case of (*Z*)-1-propenyltributyltin a mixture of (*E*)- and (*Z*)-isomers **2m** is obtained. This mixture is converted into pure (***E***)-**2m** by heating with $BF_3 \cdot Et_2O$ in toluene. (Phenylethynyl)tributyltin fails to react with **1** in toluene in the presence of $Pd_2(DBA)_3 \cdot CHCl_3$. Nevertheless, the latter catalyzes this reaction in N-methylpyrrolidone in the presence of tri(2-furyl)phosphine.[15d]

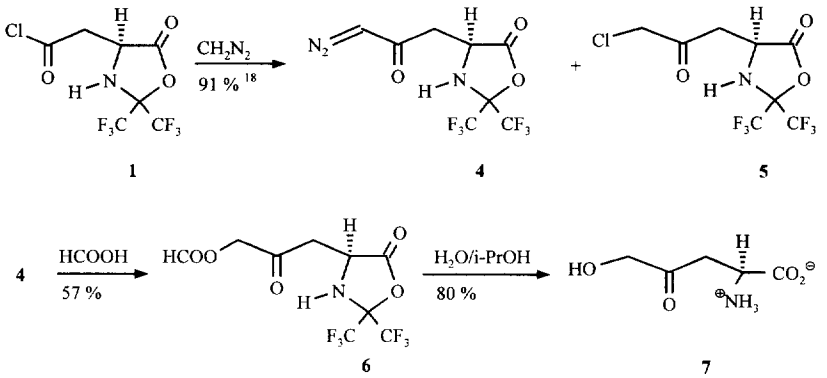
The reactions of (*tert*-butyldimethylsilyloxymethyl)tributyltin and (methoxymethoxymethyl)-tributyltin with **1** (as an approach to 5-hydroxy-4-oxonorvaline) in benzene in the presence of $PhCH_2Pd(PPh_3)_2Cl$ failed. Selective transfer of a single primary alkyl group from tin via Stille reaction often represents a challenge.[14d,e] Some approaches have been developed to overcome this limitation.[15] Unfortunately, neither the addition of CuCN nor of tri(2-furyl)phosphine (N-methylpyrrolidone as solvent) is successful. Other palladium catalysts tested also fail to catalyze this reaction. The coupling of **1** with tetramethyltin and tetrabutyltin gives unsatisfactory results as well. Therefore, further attempts to synthesize γ-alkyl γ-oxo α-amino acids via an alkyl transfer from tin compounds to **1** under Stille reaction conditions were abandoned.

Compounds **2a,d,f,g** have been deprotected on treatment with H_2O/*i*-PrOH at rt. The deprotection under these conditions proceeds rather slowly to provide free amino acids **3a-d** with 30-60 % conversion after stirring for 7-10 days. No side reactions are detected in the deprotection step. Unconverted starting compounds **2a,d,f,g** can be extracted with ethyl acetate and are found unchanged according to NMR data and rotation index measurements. The physical and spectral data of **3a,c** are identical to those quoted in the literature,[5,16] proving that no racemization occurs in any reaction step. Noteworthy, hydrogenolytic deprotection of the Z-protected α-amino group and cleavage of amino acid benzylic esters in γ-aryl γ-oxo α-amino acids applied in other procedures are often accompanied by complete or partial reduction of the γ-oxo group to a methylene group.[8d,17] From this point of view, HFA-protected γ-oxo α-amino acids are advantageous as they can be used directly in peptide synthesis[11] or easily be deprotected to give free amino acids.

Synthesis of 5-hydroxy-4-oxo-L-norvaline [(-)-HON]

As demonstrated previously, the HON skeleton can be constructed by reaction of acyl chloride **1** with diazomethane followed by decomposition of diazoketone **4** with various carboxylic acids.[18] An addition of **1** to a three- to fourfold excess of diazomethane seems to be optimal with respect to the yield, allowing to minimize the principal side reaction of **1** with liberated hydrogen chloride to give chloro ketone **5**. Nevertheless, the formation of byproduct **5** (5-7 %) is observed under these conditions, if the synthesis is done on a 10-15 g scale of **1**. The purification of **4** is achieved either by distillation (with partial decomposition) or by column chromatography. Decomposition of **4** with formic acid provides a facile access to fully protected (-)-HON **6** (Scheme 2). The distinct advantage of the formyl group consists of the possibility of a simultaneous deprotection of all three protected functional groups on treatment with H_2O/*i*-PrOH at rt. The final purification can be accomplished by recrystallization from H_2O/acetone to give free (-)-HON[19] **7** in only

5 steps starting from L- aspartic acid in an overall yield of 37 %. The physical and spectral data of **7** are identical to those quoted for the natural antibiotic.[19c]

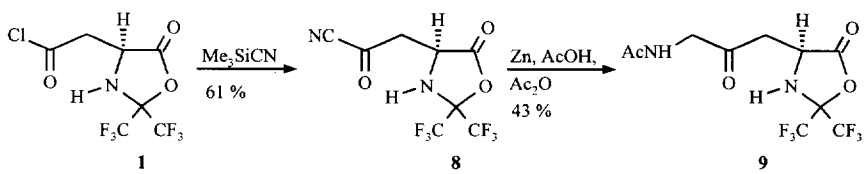


1 **4** **5** **6** **7**

Scheme 2

A new approach to the 4-oxo-L-ornithine skeleton

Protected 4-oxo-L-ornithine[20] is a valuable precursor for (2S,4R)-4-hydroxy ornithine,[21] a component of lower marine animals, plants and of the antibiotic cyclopeptides biphenomycins A and B.[22] We worked out a new approach to the 4-oxo-L-ornithine skeleton starting from acyl chloride **1**. Our initial attempts to substitute chlorine in derivative **5** (and in the analogous bromo ketone) by azide failed. Another known approach towards the synthesis of α-amino ketones from acyl chlorides consists of the reaction of an acyl chloride with a cyanide source followed by selective reduction of the cyano group.[23] The reaction of **1** with trimethylsilylcyanide gives the ketocyanide **8** in 61 % yield. The following reduction is accomplished with zinc in a 1:1 mixture of acetic acid and acetic anhydride to provide the protected 5-amino-4-oxo-norvaline derivative **9** (Scheme 3).



1 **8** **9**

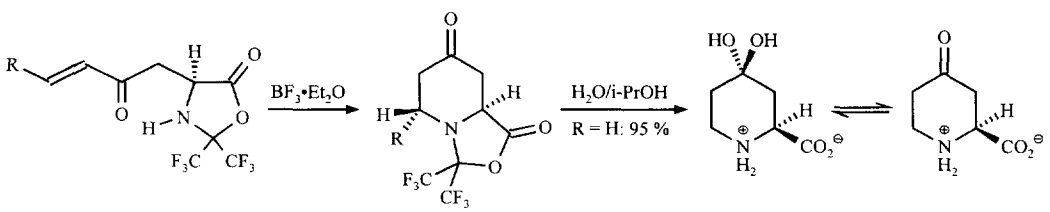
Scheme 3

In spite of only moderate yields in the last two steps this approach to the construction of 4-oxo-L-ornithine skeleton seems to be attractive in terms of simplicity and accessibility of reagents.

A new approach to the family of 4-substituted pipecolic acids

Recently there has been an enormous interest in the synthesis of 4-oxo-pipecolic and *cis*-4-hydroxy pipecolic acid.[24] The application of *cis*-4-hydroxy L-pipecolic acid as a constituent of the new potent HIV protease inhibitor *palinavir*[24a] and of 4-oxo-D-pipecolic acid as a building block for *cis*-4(phosphonomethyl)-D-pipecolic acid[24b] (a selective NMDA antagonist) renders this class of α-amino acids an attractive synthetic target. The crucial step of our strategy consists of an intramolecular Michael addition (6-endo-trig[25]) of the enones **2j-m**. Although the two trifluoromethyl groups substantially reduce the nucleophilicity of the nitrogen atom in an 1,3-oxazolidin-5-one, the latter should possess enough residual reactivity to add to an enone double bond. Our expectation was also based on an observation of intramolecular cyclization of diazo derivative **4** effected by HF·pyridine or $[Rh(OAc)_2]_2$ giving the proline skeleton.[26]

Enone **2j** undergoes Michael addition in refluxing benzene in the presence of $BF_3{\cdot}Et_2O$ to give the protected 4-oxo-L-pipecolic acid derivative **10a** in 60 % yield (Scheme 4). We investigated the scope and limitations of this transformation using 6-substituted enones **2k-m**. Enone (*E*)-**2m** gives the corresponding cyclic derivative **10b**. The cyclization reaction proceeds rather slowly but highly stereoselective to provide **10b** in 30 % yield. However, no cyclization products are observed for enones **2k,l** under similar reaction conditions.



2j-m **10a** (R = H): 60 % **10b** (R = CH_3): 30 % **11**

Scheme 4

Deprotection of **10a** (H_2O/*i*-PrOH; 20°C; 2 d) gives 4-oxo-L-pipecolic acid **11**.[27] Purification of **11** can be accomplished by transformation of **11** into its hydrochloride followed by recrystallization. The free amino acid **11** as well as its hydrochloride predominantly exist as geminal diols in D_2O according to the ^1H and ^{13}C NMR spectra.

All protons of **10b** have been assigned unambiguously by a DQF-COSY spectrum (Fig. 1a). A cross-peak in the NOESY spectrum (Fig. 1b) between the signals of the methyl group CH_3-9 and the angular proton H-5 proves the 1,3-diaxial relationship. Therefore, the absolute configuration of **10b** is (5S,9R).

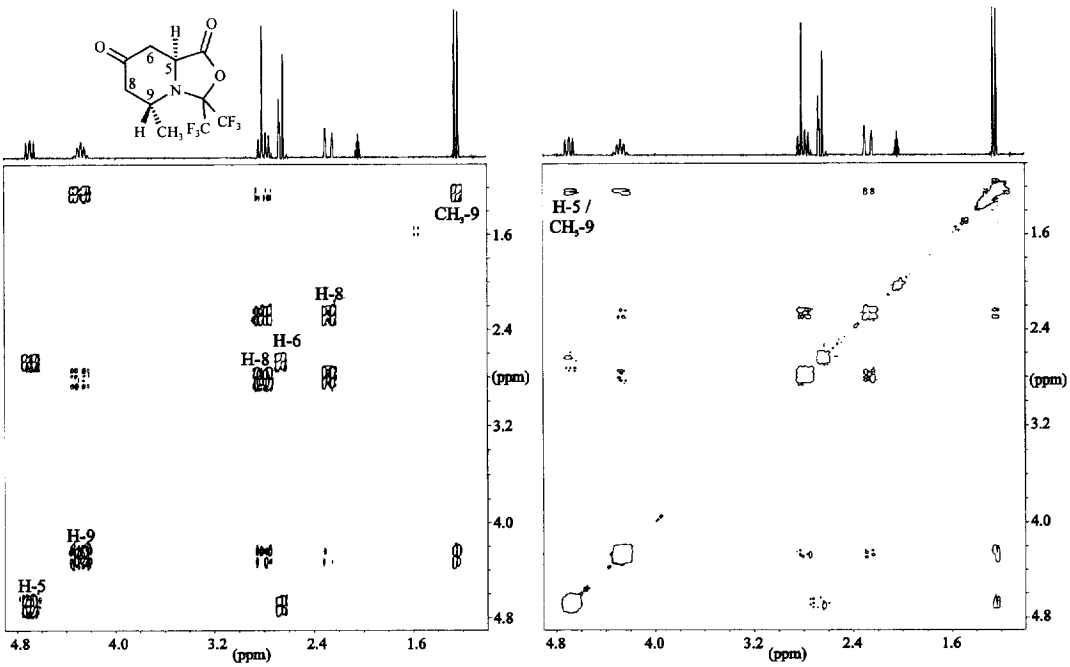
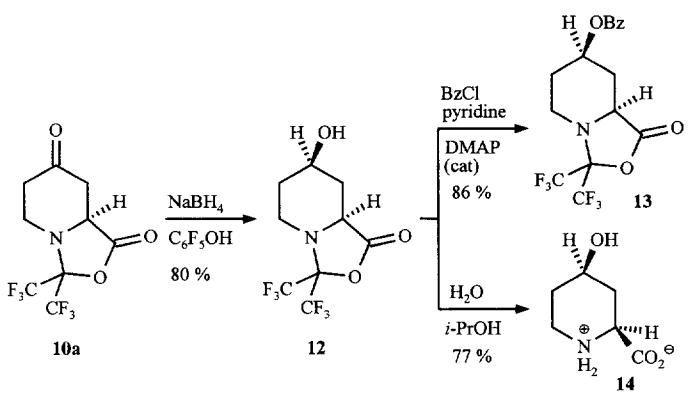


Fig. 1a: Phase sensitive DQF-COSY spectrum of **10b** Fig. 1b: Phase sensitive NOESY spectrum of **10b**

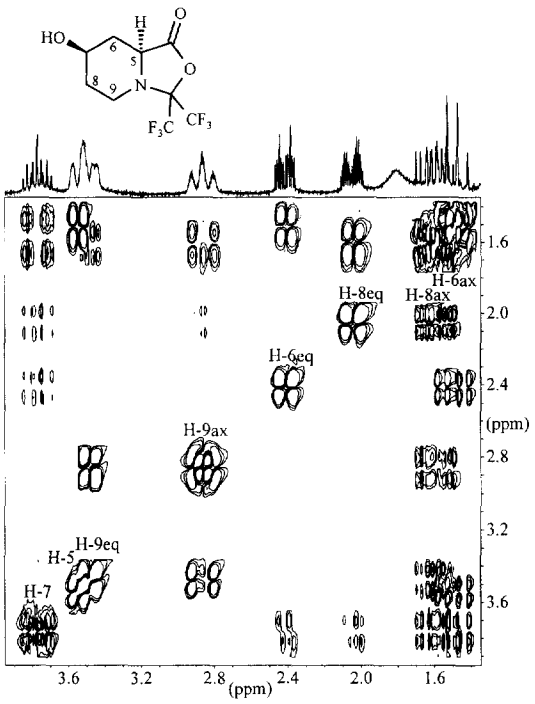
The reduction of compound **10a** with $NaBH_4$ in the presence of C_6F_5OH[28] at -30°C affords the protected *cis*-4-hydroxy-L-pipecolic acid derivative **12** in 80 % yield (Scheme 5). The formation of the *trans*-isomer can not be detected under these conditions.



Scheme 5

However, if the reduction is performed at 0°C, substantial amounts (up to 30 %) of two byproducts are detected. We were not able to isolate these compounds. Their ^1H NMR spectra (doublet at 5.26 with J = 6.5 Hz and doublet at 5.48 with J = 4.3 Hz) and ^{13}C NMR spectra (signals at 98.17 and 102.39 ppm) let us conclude, that they are products of a reduction of the lactone into the corresponding lactol. (Reduction of the

lactone ring in (S)-4-(3-methylpropyl)-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one to the lactol is accomplished with DIBALH to give a product with a similar pattern for the lactol hydrogen and carbon atoms in the NMR spectra[29]).



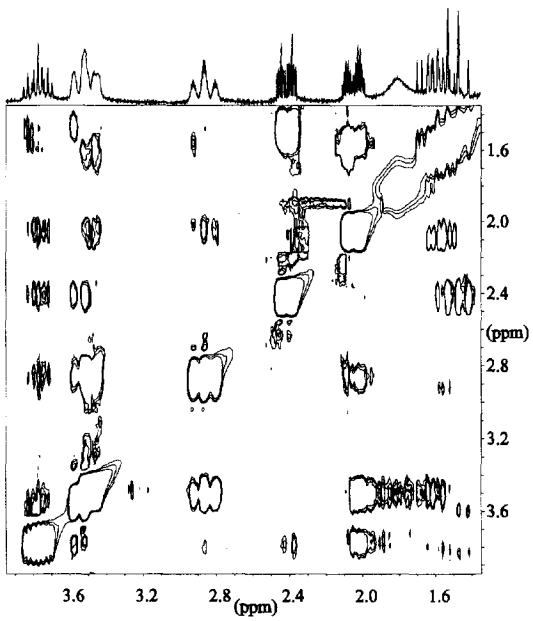
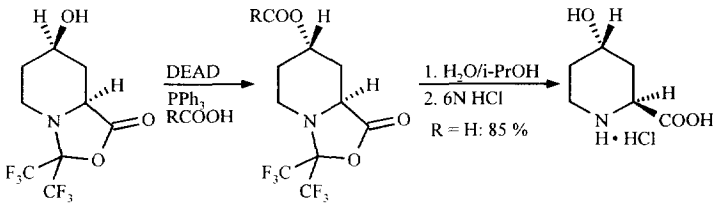


Fig. 2a: Phase sensitive DQF-COSY spectrum of **12** Fig. 2b: Phase sensitive NOESY spectrum of **12**

The signals in the ^{1}H NMR spectrum of **12** can be fully assigned by a DQF-COSY spectrum (Fig. 2a). The complete assignment of the diastereotopic protons (axial vs. equatorial) and of the relative configuration at C-7 with respect to the known configuration at C-5 is possible by a NOESY spectrum (Fig. 2b). The crosspeak between H-5 and H-7 directly provides the information that the absolute configuration of **12** is (5S,7R). This finding is further supported by the accordance of the spectral and physical data of compound **14** (obtained on deprotection of **12**, Scheme 5) with the data of the known *cis*-4-hydroxy-L-pipecolic acid[30] giving proof of the *cis*-stereochemistry in **12** and **14**. Additional proof is given by compound **13**, the product of the treatment of **12** with benzoyl chloride in the presence of pyridine at 0°C. The NMR spectrum of **13** is also in full accordance with *cis*-stereochemistry (the axial position of the H-7 proton adjacent to the benzoyloxy function and the axial position of the angular H-5 proton as derived from the value of the coupling constants).[31,32]

The stereochemistry at C-7 of compound **12** can be inverted by Mitsunobu reaction[33] (Scheme 6). Both formic and benzoic acid give the corresponding compounds **15a,b** in good yields. The Mitsunobu reaction with formic acid is favourable with respect to the following deprotection. In the case of **15a** it can be

accomplished in two steps: cleavage of the 1,3-oxazolidin-4-one ring with H_2O/*i*-PrOH followed by treatment with 6N HCl for deblocking the hydroxy function to provide *trans*-4-hydroxy-L-pipecolic acid as its hydrochloride **16**.[34]



12 **15a** (R = H): 78 %
15b (R = Ph): 67 % **16**

Scheme 6

Conclusions

We developed new methodology for the synthesis of γ-oxo α-amino acids starting from aspartic acid using hexafluoroacetone as protecting and activating agent. Since the reaction sequences described proceed in a stereoconservative manner, both the L- and D-series of the amino acids can be obtained.

Acknowledgement. We are grateful to DAAD, Deutsche Forschungsgemeinschaft and Volkswagen-Stiftung for grants and Hoechst AG, Frankfurt/Main for generous supply of chemicals.

Experimental Part

^{1}H NMR spectra were recorded at 200 MHz and 360 MHz with Me_4Si as internal standard. ^{13}C NMR spectroscopy was performed at 50 MHz and 90 MHz. ^{19}F NMR spectra were obtained at 235 MHz with trifluoroacetic acid as external standard, downfield shifts being designated as positive. Melting points were determined on a BÜCHI SMP-20 apparatus according to Tottoli and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 or a Perkin-Elmer 1600 spectrometer. Optical rotation indices were measured using Perkin-Elmer 241 MC or Schmidt & Haensch Polartronic-D polarimeters. Microanalyses were performed on Heraeus EA 415/0, Monar System or Heraeus CHNO-Rapid-Elemental-Analyser. All reactions were routinely monitored with the aid of ^{19}F NMR spectroscopy or TLC. Analytical TLC was performed using Merck precoated silica gel $60F_{254}$ plates. Merck silica gel 60 (63-200 μm) was used for column chromatography with hexanes/ethyl acetate solvent systems. Organic solvents were dried and distilled prior to use.

Catalysts. $Pd_2(DBA)_3 \cdot CHCl_3$,[35a] $Pd(PPh_3)_4$,[35b] $PhCH_2Pd(PPh_3)_2Cl$[35c] were prepared according to published procedures.

Tin compounds. (*o*-Nitrophenyl)tributyltin,[36a] (*t*-butyldimethylsilyloxymethyl)tributyltin,[36b] (*Z*)-1-propenyltributyltin,[14a] (*E*)-β-styryltributyltin,[14b] (phenylethynyl)tributyltin,[36c] isobutenyltrimethyltin[14a] were prepared according to published procedures. Phenyltrimethyltin, (4-fluorophenyl)trimethyltin, (4-methoxyphenyl)-trimethyltin, (pentafluorophenyl)trimethyltin, (3-trifluoromethylphenyl)trimethyltin, (2-thienyl)trimethyltin were prepared from the corresponding Grignard reagent and trimethyltin chloride according to ref.[36d] (3,4-Dimethoxyphenyl)trimethyltin and (2-furyl)trimethyltin were prepared from the corresponding lithium derivative and trimethyltin chloride according to ref.[36e]

Method 1. 1.5 g (5.0 mmol) of acyl chloride **1** was dissolved in dry toluene, the solution was degassed with argon, and then the tin derivative (5.0 mmol) was added with a syringe. A solution of 80 mg of $Pd_2(DBA)_3 \cdot CHCl_3$ (77 μmol) in toluene was added portionwise over a period of 36 h to the reaction mixture. a) Trimethyltin derivatives: After removal of the toluene in vacuo the residue was dissolved in ether (80 ml), washed twice with water, dried over $MgSO_4$, evaporated, and the residue purified by column chromatography. The final purification proceeded by recrystallization from hexanes (or a mixture of hexanes and $CHCl_3$) or by sublimation. b) Tributyltin derivatives: After removal of the toluene in vacuo the residue was dissolved in ether (80 ml), treated with a saturated aqueous solution of KF (50 ml) for 15 min. Precipitated n-Bu_3SnF was filtered off. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography followed by recrystallization or sublimation.

Method 2. A solution of 10.0 g (33.4 mmol) of acyl chloride **1** and 10.58 g (33.4 mmol) of vinyltributyltin in 100 ml of dimethoxyethane was degassed with argon and 80 mg of $PhCH_2Pd(PPh_3)_2Cl$ (110 μmol) in 5 ml of DME was added. The reaction mixture was heated to 60°C for 8 h; additional 40 mg of the catalyst (55 μmol) were added every 2 h. After removal of the solvent the residue was distilled in vacuo to afford two fractions: 55-75°/0.01 Torr, 8.89 g (**2j**) and 110-115°/0.01 Torr (tributyltin chloride). The first fraction crystallized upon standing and was recrystallized from hexanes to give 6.68 g of pure **2j**. The mother liquor was evaporated, redissolved in ether (80 ml) and treated with a saturated aqueous solution of KF (50 ml) for 15 min. Precipitated n-Bu_3SnF was filtered off. The organic layer was dried over $MgSO_4$, and evaporated. The residue was recrystallized from hexanes to give additional 0.6 g of **2j**.

Method 3. 1.5 g (5.0 mmol) of acyl chloride **1** were dissolved in dry NMP, the solution was degassed with argon, 40 mg of tri(2-furyl)phosphine (170 μmmol) were added, followed by a stannane. A solution of 60 mg of $Pd_2(DBA)_3 \cdot CHCl_3$ (58 μmol) in 5 ml NMP was added over a period of 3 h. The reaction mixture was stirred for 12 h, diluted with ethyl acetate (100 ml), washed three times with water and once with brine. The solvent was evaporated, the residue redissolved in ether and treated with a saturated aqueous solution of KF (50 ml) for 15 min. Further manipulations proceeded as above, see Method 1b.

Spectral and physical data of compounds **2a-c,f,g** are identical to those given in ref.[11] However, the rotation index values of these compounds differ from those published previously, being always higher for our derivatives. We reproduced the syntheses of **2a-c,f,g** according to the Friedel-Crafts protocol given in ref.[11] The rotation index values of Friedel-Crafts products **2a-c,f,g** according to our measurements were higher than those given in ref.[11] and identical to the values of the Stille reaction products.

4-(Benzoylmethyl)-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (2a): $[\alpha]_D^{22}$ -43.4 (c 1.0; $CHCl_3$).

4-[(4-Methoxybenzoyl)methyl]-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (2b): $[\alpha]_D^{22}$ -32.0 (c 1.0; $CHCl_3$).

4-[(3,4-Dimethoxybenzoyl)methyl]-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (2c): $[\alpha]_D^{22}$ -39.7 (c 1.0; $CHCl_3$).

4-[(4-Fluorobenzoyl)methyl]-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (2d): m.p. 56-57°C (hexanes); $[\alpha]_D^{22}$ -39.2 (c 1.0; $CHCl_3$). ^{1}H NMR (360 MHz, $CDCl_3$): 7.98 (m, 2H); 7.17 (m, 2H); 4.57 (m, 1H); 3.87 (d, J = 6.7, 1H); 3.65 (dd, J = 1.9, J = 18.1, 1H); 3.31 (dd; J = 10.2, J = 18.1, 1H); ^{13}C NMR (90 MHz, $CDCl_3$): 194.81; 171.01; 166.51 (d, J = 256.9); 132.06 (d, J = 3.0); 131.05 (d, J = 9.5); 121.38 (q, J = 288.8 Hz, CF_3); 120.21 (q, J = 284.9 Hz, CF_3); 116.24 (d, J = 22.1); 88.51 (sept, J = 34.3 Hz); 50.95; 42.64; ^{19}F NMR (235 MHz, $CDCl_3$): -2.20 (q, J = 8.9 Hz, 3F, CF_3); -3.40 (q, J = 8.9 Hz, 3F, CF_3); -25.18 (m, 1F); IR (KBr, cm^{-1}) 3320 (NH); 1820 (C=O); 1670 (C=O). Anal. Calcd for $C_{13}H_8F_7NO_3$ [359.20]: C 43.47; H 2.24; N 3.90. Found: C 43.36; H 2.32; N 4.11.

4-[(3-Trifluoromethylbenzoyl)methyl]-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (2e): m.p. 35-36°C (hexanes); $[\alpha]_D^{22}$ -34.2 (c 1.0; $CHCl_3$). ^{1}H NMR (360 MHz, $CDCl_3$): 8.21 (s, 1H); 8.15 (m, 1H); 7.89 (m, 1H); 7.67 (m, 1H); 4.61 (m, 1H); 3.83 (d, J = 6.8, 1H); 3.71 (dd, J = 1.9, J = 18.2, 1H); 3.37 (dd; J = 10.1, J = 18.2, 1H); ^{13}C NMR (90 MHz, $CDCl_3$): 195.24; 170.77; 136.04; 131.83 (q, J = 33.4); 131.42; 130.69; 129.81; 125.16; 123.61 (q, J = 280.0 Hz, CF_3-Ar); 121.36 (q, J = 288.8 Hz, CF_3); 120.17 (q, J = 284.6 Hz, CF_3); 88.51 (sept, J = 34.0 Hz); 50.83; 42.92; ^{19}F NMR (235 MHz, $CDCl_3$): 14.78 (s, 3F; CF_3-Ar); -2.17 (q, J = 8.9 Hz, 3F, CF_3); -3.40 (q, J = 8.9 Hz, 3F, CF_3). Anal. Calcd for $C_{14}H_8F_9NO_3$ [409.21]: C 41.09; H 1.97; N 3.42. Found: C 41.22; H 2.00; N 3.46.

4-[(2-Thienoyl)methyl]-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (2f): $[\alpha]_D^{22}$ -49.4 (c 1.0; $CHCl_3$).

4-[(2-Furoyl)methyl]-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (2g): $[\alpha]_D^{22}$ -28.5 (c 1.0; $CHCl_3$).

4-[(Pentafluorobenzoyl)methyl]-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (2h): m.p. 63-64°C (hexanes); $[\alpha]_D^{22}$ -20.2 (c 1.0; $CHCl_3$). ^{1}H NMR (360 MHz, $CDCl_3$): 4.59 (m, 1H); 3.74 (d, J = 6.8, 1H); 3.60 (dd, J = 1.0, J = 18.8, 1H); 3.26 (dd; J = 9.8, J = 18.8, 1H); ^{13}C NMR (90 MHz, $CDCl_3$): 190.58; 170.03; 145.45 (d, J = 253.3); 144.04 (d, J = 262.3); 137.98 (d, J = 251.2); 121.15 (q, J = 288.8 Hz, CF_3); 120.15 (q, J = 284.6 Hz, CF_3); 113.01; 88.51 (sept, J = 34.0 Hz); 50.56; 48.67; ^{19}F NMR (235 MHz, $CDCl_3$): -2.92 (q, J = 8.6 Hz, 3F, CF_3); -3.57 (q, J = 8.6 Hz, 3F, CF_3); -61.75 (m, 2F); -68.29 (m, 1F); -81.24 (m, 2F). Anal. Calcd for $C_{13}H_4F_{11}NO_3$ [431.16] : C 36.21; H 0.94; N 3.25. Found: C 36.24; H 1.00; N 3.30.

4-(2-Oxo-but-3-enyl)-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (2j): m.p. 43°C (hexanes); $[\alpha]_D^{22}$ -42.6 (c 1.0; $CHCl_3$). ^1H NMR (360 MHz, $CDCl_3$): 6.28-6.44 (m, 2H, CH_2= and CH=); 6.03 (dd, J = 9.73, J = 1.6 Hz, 1H, CH_2=); 4.44 (m, 1H, CH); 3.69 (d, J = 6.6, 1H); 3.30 (dd, J = 2.3, J = 18.2, 1H); 2.96 (dd, J = 18.2, J = 10.2, 1H); ^{13}C NMR (90 MHz, $CDCl_3$): 196.91; 170.97; 135.66; 130.76; 121.33 (q, J = 288.4 Hz, CF_3); 120.18 (q, J = 285.0 Hz, CF_3); 88.5 (sept, J = 33.8 Hz); 50.60; 42.99; ^{19}F NMR (235 MHz, $CDCl_3$): -2.15 (q, J = 8.0 Hz, 3F, CF_3); -3.36 (q, J = 8.0 Hz, 3F, CF_3); IR (KBr, cm^{-1}) 3335 (NH); 1816 (C=O); 1700; 1684 (C=O); 1622 (C=C). Anal. Calcd for $C_9H_7F_6NO_3$ [291.15]: C 37.13; H 2.42; N 4.81. Found: C 37.28; H 2.66; N 4.80.

4-(2-Oxo-4-methyl-3-pentenyl)-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (2k): m.p. 43-44°C (hexanes); $[\alpha]_D^{22}$ -47.1 (c 1.0; $CHCl_3$). ^1H NMR (360 MHz, $CDCl_3$): 6.09 (m, 1H, CH=); 4.39 (m, 1H, CH); 3.75 (d, J = 6.7 Hz; 1H); 3.11 (dd, J = 2.2, J = 18.0, 1H); 2.79 (dd, J = 10.1, J = 18.0, 1H); 2.18 (s, 3H); 1.94 (d; J = 0.7, 3H); ^{13}C NMR (90 MHz, $CDCl_3$): 195.97; 171.19; 159.32; 122.45; 121.40 (q, J = 288.5 Hz, CF_3); 120.23 (q, J = 285.1 Hz, CF_3); 88.46 (sept, J = 34.0 Hz); 50.87; 46.87; 27.92; 21.18; ^{19}F NMR (235 MHz, $CDCl_3$): -2.28 (q, J = 8.9 Hz, 3F, CF_3); -3.30 (q, J = 8.9 Hz, 3F, CF_3); IR (KBr, cm^{-1}) 3377 (NH); 1832 (C=O); 1686 (C=O); 1627 (C=C). Anal. Calcd for $C_{11}H_{11}F_6NO_3$ [319.20]: C 41.39; H 3.47; N 4.39. Found: C 41.31; H 3.51; N 4.42.

4-(*E*-2-Oxo-4-phenyl-3-butenyl)-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (2l): m.p. 87-88°C (hexanes); $[\alpha]_D^{22}$ -17.5 (c 1.0; $CHCl_3$). ^1H NMR (360 MHz, $CDCl_3$): 7.59 (d, J = 16.2, 1H); 7.50 (m, 5H); 6.74 (d, J = 16.2, 1H); 4.49 (m, 1H); 3.77 (d, J = 6.7, 1H); 3.37 (dd, J = 2.2, J = 18.0, 1H); 3.04 (dd; J = 9.9, J = 18.0, 1H); ^{13}C NMR (90 MHz, $CDCl_3$): 195.99; 170.94; 144.94; 133.75; 131.20; 129.09; 128.51; 124.95; 121.24 (q, J = 288.8 Hz, CF_3); 120.10 (q, J = 284.7 Hz, CF_3); 88.37 (sept, J = 35.3 Hz); 50.74; 43.73; ^{19}F NMR (235 MHz, $CDCl_3$): -2.09 (q, J = 8.9 Hz, 3F, CF_3); -3.25 (q, J = 8.9 Hz, 3F, CF_3); IR (KBr, cm^{-1}) 3330 (NH); 1835 (C=O); 1665 (C=O); 1635 (C=C). Anal. Calcd for $C_{15}H_{11}F_6NO_3$ [367.25]: C 49.06; H 3.02; N 3.81. Found: C 49.03; H 3.05; N 3.92.

Isomerization of (*Z*)-2m. 0.2 g of a mixture of (*E*)- and (*Z*)-enones **2m** (0.66 mmol), obtained by Stille cross-coupling reaction of acyl chloride **1** with (*Z*)-1-propenyltributyltin (Method 1b), was heated in toluene at 70°C in the presence of $BF_3{\cdot}OEt_2$ (2 drops) for 12 h. The solvent was evaporated, the residue dissolved in ether, washed with satd. $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated to give 0.18 g (90 %) of a liquid, which solidified upon standing. Recrystallization from hexanes gave pure *(E)*-**2m**.

4-(*E*-2-Oxo-3-pentenyl)-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one *(E)*-(2m): m.p. 38°C (hexanes); $[\alpha]_D^{22}$ -47.2 (c 1.0; $CHCl_3$). ^1H NMR (360 MHz, $CDCl_3$): 6.93 (dq, J = 15.7, J = 7.2, 1H, CH_3CH=); 6.15 (dq, J = 15.7, J = 1.8, 1H, CH=); 4.41 (m, 1H, CH); 3.65 (d, J = 6.3, 1H); 3.22 (dd, J = 2.2, J = 18.0, 1H); 2.89 (dd; J = 9.9, J = 18.0, 1H); 1.94 (dd, J = 1.8, J = 7.2, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): 195.45; 170.44; 145.13; 130.44; 120.65 (q, J = 287.5 Hz, CF_3); 119.48 (q, J = 285.1 Hz, CF_3); 87.73 (sept, J = 33.7 Hz); 50.04; 42.42; 17.86; ^{19}F NMR (235 MHz, $CDCl_3$): -2.17 (q, J = 8.5 Hz, 3F, CF_3); -3.35 (q, J = 8.5 Hz, 3F, CF_3); IR

(KBr, cm^{-1}) 3325 (NH); 2200; 1830 (C=O); 1660 (C=O). Anal. Calcd for $C_{10}H_9F_6NO_3$ [305.18]: C 39.36; H 2.97; N 4.59. Found: C 39.54; H 3.07; N 4.61.

4-(2-Oxo-4-phenyl-3-butynyl)-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (2n): m.p. 91-92°C (hexanes). ^1H NMR (200 MHz, $CDCl_3$): 7.41-7.61 (m, 5H); 4.63 (m, 1H); 3.63 (d, J = 6.7, 1H); 3.42 (dd, J = 3.6, J = 18.4, 1H); 3.22 (dd; J = 7.6, J = 18.4, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): 182.97; 170.01; 133.19; 131.36; 128.69; 121.08 (q, J = 287.5 Hz, CF_3); 119.94 (q, J = 285.1 Hz, CF_3); 118.97; 93.91; 88.23 (sept, J = 34.5 Hz); 86.70; 50.17; 48.54; ^{19}F NMR (235 MHz, $CDCl_3$): -2.11 (q, J = 9.2 Hz, 3F, CF_3); -3.28 (q, J = 9.2 Hz, 3F, CF_3). IR (KBr, cm^{-1}) 3330 (NH), 2200 (C≡C), 1835 (C=O), 1660 (C=O). Anal. Calcd for $C_{15}H_9F_6NO_3$ [365.23]: C 49.33; H 2.48; N 3.84. Found: C 49.43; H 2.52; N 3.75.

L-3-(Benzoyl)alanine (3a). Compound **2a** (1.0 g, 2.9 mmol) was dissolved in 200 ml of H_2O/*i*-PrOH (1:1, v/v) and the solution was stirred for 7 d at rt. The volatiles were evaporated in vacuo and the residue was treated with ethyl acetate (80 ml). The precipitate was filtered off to give 0.32 g (57 %) of **3a**. The mother liquor was evaporated to afford 0.4 g (≅ 60 % conversion) of starting **2a**. An analytical sample of **3a** was obtained by recrystallization from water. **3a**: m.p. 174-175°C; $[\alpha]_D^{22}$ +44.3 (c 0.1; 6N HCl); [lit.: m.p. 155-160°C (dec.);[16b] $[\alpha]_D^{22}$ +42.9 (c 0.105; 6N HCl); racemic 3-benzoylalanine: lit.: m.p. 179-181°C (dec.)[16c]]. ^1H NMR (200 MHz, D_2O): 7.86 (m, 2H); 7.53 (m, 1H); 7.42 (m, 2H); 4.04 (m, 1H); 3.61 (m, 2H); ^{13}C NMR (50 MHz, D_2O): 202.01; 175.48; 137.07; 136.28; 130.66; 129.96; 52.19; 40.43; IR (KBr, cm^{-1}) 3600-2500 (NH, OH); 1687 (C=O). Anal. Calcd for $C_{10}H_{11}NO_3$ [193.20]: C 62.17; H 5.74; N 7.25. Found: C 62.04; H 5.69; N 7.32.

Amino acids **3b-d** were obtained in the same manner from **2d**, **2f**, **2g**, resp.

L-3-(4-Fluorobenzoyl)-alanine (3b): m.p. 189-190°C (decomp.); $[\alpha]_D^{22}$ +42.2 (c 0.1; 6N HCl); yield 59 %; reaction time 7 d; conversion 60 %. ^1H NMR (200 MHz, D_2O): 7.95 (m, 2H); 7.16 (m, 2H); 4.06 (m, 1H); 3.63 (m, 2H); ^{13}C NMR (50 MHz, D_2O): 200.37; 175.42; 168.00 (d, J = 253.8); 133.91 (d, J = 3.2); 132.93 (d, J = 10.4); 117.65 (d, J = 22.5); 52.16; 40.30; ^{19}F NMR (235 MHz, D_2O): -26.23 (m, 1F). IR (KBr, cm^{-1}) 3500-2400 (NH, OH), 1685 (C=O). Anal. Calcd for $C_{10}H_{10}FNO_3$ [211.19]: C 56.87; H 4.77; N 6.63. Found: C 56.39; H 4.73; N 6.64.

L-3-(2-Furoyl)-alanine (3c): m.p. 150°C (decomp.); $[\alpha]_D^{22}$ +43.0 (c 1.0; 2N HCl); $[\alpha]_D^{22}$ +13.8 (c 0.7; H_2O) [ref.[5a]: m.p. >150°C; $[\alpha]_D^{23}$ +46.5 (c 1.1; 2N HCl); $[\alpha]_D^{23}$ +14.5 (c 1.3; H_2O)]; yield 52 %; reaction time 7 d, conversion 60 %. The IR, ^1H and ^{13}C NMR spectra are in good agreement with those reported in refs.[5a-c,11] Anal. Calcd for $C_8H_9NO_4 \cdot H_2O$ [201.18]: C 47.76; H 5.51; N 6.96. Found: C 47.21; H 5.42; N 6.69.

L-3-(2-Thienoyl)-alanine (3d): 161-162°C (decomp.); $[\alpha]_D^{22}$ +38.5 (c 0.1; 6N HCl); yield 80 %; reaction time 14 d, conversion 85 %. ^1H NMR (200 MHz, D_2O): 7.79-7.85 (m, 2H); 7.12 (dd, J = 4.0, J = 4.5, 1H); 4.03 (m, 1H); 3.56 (m, 2H); IR (KBr, cm^{-1}) 3600-2500 (NH, OH); 1650 (C=O); 1557 (NH_3^+). Anal. Calcd for $C_8H_9NO_3S \cdot H_2O$ [217.24]: C 44.23; H 5.10; N 6.45. Found: C 43.97; H 5.04; N 6.43.

4-[3-(Formyloxy)-2-oxopropyl]-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (6). Diazoketone **4**[18] (4.2 g, 13.8 mmol) was added dropwise at rt to formic acid (1.26 g, 27.4 mmol). Slow gas evolution was observed during the addition. The reaction mixture was stirred for 24 h, evaporated in vacuo, the residue was dissolved in CH_2Cl_2 (80 ml), treated with satd. $NaHCO_3$ solution, then with brine. The organic layer was dried over $MgSO_4$ and evaporated. The residue was distilled („Kugelrohr" distillation, 0.1 Torr, 110°C) to give 2.48 g of **6** (57 %), which solidified upon standing. M.p. 66-67°C (hexanes); $[\alpha]_D^{22}$ -46.0 (c 1.0; $CHCl_3$). ^1H NMR (360 MHz, $CDCl_3$): 8.17 (s, 1H); 4.83 (d, J = 17.0, 1H); 4.78 (d, J = 17.0, 1H); 4.45 (m, 1H); 3.70 (d, J = 6.8, 1H); 3.17 (dd, J = 2.3, J = 18.3, 1H); 2.85 (dd; J = 10.0, J = 18.3, 1H); ^{13}C NMR (90 MHz, $CDCl_3$): 200.52; 170.53; 159.96; 121.22 (q, J = 288.3 Hz, CF_3); 120.15 (q, J = 285.1 Hz, CF_3); 88.55 (sept, J = 34.3 Hz); 67.10; 50.20; 42.76; ^{19}F NMR (235 MHz, $CDCl_3$): -2.31 (q, J = 8.5 Hz, 3F, CF_3); -3.47 (q, J = 8.5 Hz, 3F, CF_3). Anal. Calcd for $C_9H_7F_6NO_5$ [323.15]: C 33.45; H 2.18; N 4.33. Found: C 33.27; H 2.32; N 4.36.

5-Hydroxy-4-oxo-L-norvaline (-)-HON (7). Compound **6** (2.0 g, 6.2 mmol) was dissolved in 200 ml of H_2O/*i*-PrOH (1:1, v/v) and the solution was stirred for 7 d at rt. The volatiles were evaporated in vacuo to give 0.85 g of slightly brown crystals. They were triturated with ether several times and dried in vacuo (0.01 Torr) for 4 d over P_2O_5 at rt to give 0.82 g (80 %) of **7** as slightly yellow crystals. An analytically pure sample was obtained by twofold recrystallization from water-acetone. **7**: no definite m.p.; $[\alpha]_D^{22}$ -8.7 (c 2.1; H_2O). [Ref.[19c] reports no definite m.p.; $[\alpha]_D^{22}$ -8.2 (c 1.53; H_2O)]. ^1H NMR (360 MHz, D_2O): 4.22 (d, J = 19.1, 1H); 4.16 (d, J = 19.1, 1H); 3.86 (dd, J = 4.4, J = 7.0, 1H); 2.97 (dd, J = 4.4, J = 19.1, 1H); 2.89 (dd, J = 19.1, J = 7.0, 1H); ^{13}C NMR (90 MHz, D_2O): 212.33; 175.86; 69.60; 52.42; 40.63. Anal. Calcd for $C_5H_9NO_4 \cdot H_2O$ [165.15]: C 36.36; H 6.71; N 8.48. Found: C 36.64; H 6.85; N 8.52.

4-(3-Cyano-2-oxopropyl)-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (8). 2.05 ml of trimethylsilyl-cyanide was added dropwise to acyl chloride **1** (4.50 g, 15 mmol) at rt. The reaction mixture was heated slowly to 100°C and kept at this temperature for 2 h. After cooling to rt the volatiles were removed in vacuo. The residue was distilled to give 4.2 g of a liquid, which solidified upon standing. Recrystallization from hexanes/$CHCl_3$ gave 2.7 g (61 %) of **8**: m.p. 55-56°C. ^1H NMR (200 MHz, $CDCl_3$): 4.47 (m, 1H); 3.58 (d, J = 6.7, 1H); 3.47 (dd, J = 2.2, J = 19.3, 1H); 3.15 (dd; J = 9.4, J = 19.3, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): 173.25; 168.64; 120.85 (q, J = 288.2 Hz, CF_3); 119.78 (q, J = 284.2 Hz, CF_3); 112.36; 88.30 (sept, J = 35.3 Hz); 49.34; 48.40; ^{19}F NMR (235 MHz, $CDCl_3$): -2.19 (q, J = 7.6 Hz, 3F, CF_3); -3.41 (q, J = 7.6 Hz, 3F, CF_3); IR (KBr, cm^{-1}) 3388 (NH); 2232 (CN); 1827 (C=O); 1729 (C=O). Anal. Calcd for $C_8H_4F_6N_2O_3$ [290.12]: C 33.12; H 1.39; N 9.66. Found: C 33.13; H 1.48; N 9.45.

4-[3-(Acetylamino)-2-oxopropyl]-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (9). A solution of **8** (2.7 g; 9.3 mmol) in acetic acid (5 ml) and acetic anhydride (5 ml) was slowly added at 20°C to a slurry of zinc (6.6 g, 0.1 g-atom) in a mixture of 20 ml of acetic acid and 20 ml of acetic anhydride. After stirring at rt for 1 h, the zinc was filtered off and washed thoroughly with CH_2Cl_2. The filtrate and washings were combined and concentrated in vacuo. The residue was purified by chromatography (eluent: EE) to provide 1.35 g (43 %)

of **9**: m.p. 76-78°C. ^{1}H NMR (200 MHz, $CDCl_3$): 6.43 (br. s, 1H); 4.37 (m, 1H); 4.11 (m, 2H); 3.96 (d, J = 6.7, 1H); 3.10 (dd, J = 2.2, J = 17.8, 1H); 2.82 (dd, J = 9.0, J = 17.8, 1H); 2.02 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): 201.94; 170.33; 170.15; 120.54 (q, J = 290.8 Hz, CF_3); 119.44 (q, J = 284.3 Hz, CF_3); 87.93 (sept, J = 33.7 Hz); 49.93; 48.68; 42.36; 22.03; ^{19}F NMR (235 MHz, $CDCl_3$): -2.28 (q, J = 9.2 Hz, 3F, CF_3); -2.98 (q, J = 9.2 Hz, 3F, CF_3); IR (KBr, cm^{-1}) 3402 (NH); 3267 (NH); 1816 (C=O); 1725 (C=O); 1661 (C=O). Anal. Calcd for $C_{10}H_{10}F_6N_2O_4$ [336.19]: C 35.73; H 3.00; N 8.33. Found: C 36.00; H 3.08; N 8.48.

(5S)-2,2-Bis(trifluoromethyl)-1-aza-3-oxabicyclo[4.3.0]nonan-4,7-dione (10a). $BF_3{\cdot}Et_2O$ (0.1 g, 0.6 mmol) was added to a solution of **2j** (1.0 g; 3.4 mmol) in dry benzene. The reaction mixture was refluxed for 8 h, allowed to reach rt, diluted with 100 ml ether, washed twice with satd. $NaHCO_3$ solution, once with brine, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (EE/hexanes 1:4) and recrystallized from hexanes to give 0.6 g (60 %) of **10a**: m.p. 63°C; $[\alpha]_D^{22}$ -31.2 (c 1.0; $CHCl_3$). ^{1}H NMR (360 MHz, $CDCl_3$): 3.89 (dd, J = 11.8, 2.6 Hz, 1H, H-5); 3.74 (br. dd, J = 11.6, 7.4 Hz, 1H, H-9); 3.16 (m, 1H, H-9); 2.86 (ddd, J = 14.7, 3.4, 1.6 Hz, 1H, H-8); 2.48-2.68 (m, 3H, H-8, H-6); ^{13}C NMR (50 MHz, $CDCl_3$): 201.9 (C-7); 166.7 (C-4); 121.4 (q, J = 293.9 Hz, CF_3); 120.2 (q, J = 286.9 Hz, CF_3); 88.6 (sept, J = 33.5 Hz, C-2); 55.5 (C-5); 42.7; 42.3; 40.1 (C-6, C-8, C-9); ^{19}F NMR (235 MHz, $CDCl_3$): 3.07 (q, J = 8.4 Hz, 3F, CF_3); -0.30 (q, J = 8.4 Hz, 3F, CF_3); IR (KBr, cm^{-1}) 1847 (C=O); 1721 (C=O). Anal. Calcd for $C_9H_7F_6NO_3$ [291.15]: C 37.13; H 2.42; N 4.81. Found: C 37.30; H 2.39; N 4.87.

(5S,9R)-9-Methyl-2,2-bis(trifluoromethyl)-1-aza-3-oxabicyclo[4.3.0]nonan-4,7-dione (10b) was obtained in the same manner and purified by column chromatography (EE/hexanes/toluene 1:8:1.5). M.p. 48°C; $[\alpha]_D^{22}$ -35.2 (c 1.25; $CHCl_3$); yield 30 %, reaction time 40 h. ^{1}H NMR (360 MHz, acetone-d_6): 4.69 (dd, J = 8.2, 7.6 Hz, 1H, H-5); 4.27 (dq, J = 6.8, 6.5 Hz, 1H, H-9); 2.79 (dd, J = 14.1, 6.5 Hz, 1H, H-8); 2.64-2.68 (m, 2H, H-6); 2.27 (br. d, J = 14.1 Hz, 1H, H-8); 1.24 (d, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): 202.5 (C-7); 167.5 (C-4); 120.5 (q, J = 289.4 Hz, CF_3); 120.2 (q, J = 289.4 Hz, CF_3); 88.2 (q, J = 33.8 Hz, C-2); 50.2; 47.5; 46.7; 42.3 (C-5, C-6, C-8, C-9); 17.3 (CH_3); ^{19}F NMR (235 MHz, $CDCl_3$): 1.32 (q, J = 8.4 Hz, 3F, CF_3); -0.22 (q, J = 8.4 Hz, 3F, CF_3). Anal. Calcd for $C_{10}H_9F_6NO_3$ [305.18]: C 39.36; H 2.97; N 4.59. Found: C 39.20; H 2.97; N 4.55. DQF-COSY: acetone-d_6, 200 MHz, 64 scans, 2 dummy scans, 1K data blocks, 240 t_1 values, relaxation delay 1.6 s, spectral widths 1302.08 Hz, zero-filling to 2K*2K, apodization with shifted square sine bell window functions ($\pi/2$) in both dimensions. NOESY: acetone-d_6, 250 MHz, 48 scans, 2 dummy scans, 1K data blocks, 200 t_1 values, relaxation delay 2.0 s, mixing time 2.0 s, spectral widths 1501.50 Hz, zero-filling to 1K*1K, apodization with shifted square sine bell window functions ($\pi/2$) in both dimensions.

L-4-Oxo-pipecolic acid hydrochloride (11)·HCl. Compound **10a** (1.1 g, 3.8 mmol) was dissolved in 250 ml of H_2O/*i*-PrOH (1:1, v/v). The reaction was stirred for 3 d at rt. Then the volatiles were evaporated in vacuo. The residue was dissolved in 1N HCl and evaporated again to give 0.71 g (95 %) of **11·HCl**. An analytically

pure sample of **11·HCl** was obtained by crystallization after dilution of an aqueous solution with isopropanol. M.p. 190-191°C (dec.); $[\alpha]_D^{22}$ +4.1 (c 0.55; H_2O) [ref.[30b]: m.p. 204°C, $[\alpha]_D^{22}$ +3.8 (2 %, H_2O)]. The ^1H NMR spectrum (360 MHz, D_2O) consists of two sets of signals. The first set essentially coincides with the ^1H NMR spectra given for **11·HBr** (see ref.[37]) and corresponds to the geminal diol form **11·HCl** (97.4 % as estimated from the ^1H NMR spectrum); the second set of signals corresponds to the keto form **11·HCl** (2.6 %); ^{13}C NMR (50 MHz, D_2O): 172.6 (COOH); 92.4 (C-4); 56.5 (C-2); 42.5 (C-6); 38.7 (C-3); 35.2 (C-5) (geminal diol form); 206.7 (C-4); 171.7; 57.4; 42.8; 41.2; 37.9 (keto form). Anal. Calcd for $C_6H_9NO_3 \cdot HCl \cdot H_2O$ [197.62]: C 36.47; H 6.12; N 7.09. Found: C 36.75; H 5.92; N 7.42. Several examples of an equilibrium between the keto form and the geminal diol form in 4-oxo-2-amino acids have been described, see ref.[38]

(5S,7R)-7-Hydroxy-2,2-bis(trifluoromethyl)-1-aza-3-oxabicyclo[4.3.0]nonan-4-one (12). $NaBH_4$ (20 mg, 0.53 mmol) was added in three portions to a stirred solution of **10a** (0.3 g, 1.52 mmol) and pentafluorophenol (0.2 g, 1.09 mmol) in 5 ml of THF at -30°C. The clear solution was stirred for 2 h at the same temperature, allowed to reach 0°C, treated with 10 ml of 1N HCl, and extracted with ether (80 ml). The organic layer was washed with brine, separated, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (EE/hexanes 1:1) to give 0.24 g (80 %) of **12** as an oil: $[\alpha]_D^{22}$ +4.1 (c 2.0; $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): 3.74 (tt, J = 11.3, J = 4.5 Hz, 1H, H-7^{ax}); 3.52 (dm, J = 11.3, 1H, H-5^{ax}); 3.46 (ddm; J = 12.2, J = 4.5, 1H, H-9^{eq}); 2.83 (ddm, J = 12.2, J = 11.3, 1H, H-9^{ax}); 2.39 (dddd; J = 11.8, J = 4.5, J = 2.7, J = 1.8, 1H, H-6^{eq}); 2.03 (dddd, J = 12.3, J = 4.5, J = 4.5, J = 2.7, 1H, H-8^{eq}); 1.80 (s, 1H, OH); 1.58 (dddd, J = 12.5, J = 12.3, J = 11.3, J = 5.2, 1H, H-8^{ax}); 1.47 (q, J = 11.3, 1H, H-6^{ax}); ^{13}C NMR (50 MHz, $CDCl_3$): 167.62; 121.29 (q, J = 294.7 Hz, CF_3); 119.90 (q, J = 286.7 Hz, CF_3); 87.60 (sept, J = 33.5 Hz); 67.82; 54.73; 41.98; 35.37; 33.42; ^{19}F NMR (235 MHz, $CDCl_3$): 3.09 (q, J = 9.2 Hz, 3F, CF_3); -0.30 (q, J = 9.2 Hz, 3F, CF_3). Anal. Calcd for $C_9H_9F_6NO_3$ [293.17]: C 36.87; H 3.09; N 4.78. Found: C 36.75; H 3.27; N 4.62. DQF-COSY: $CDCl_3$, 200 MHz, 64 scans, 2 dummy scans, 1K data blocks, 128 t_1 values, relaxation delay 2.0 s, spectral widths 1000.00 Hz, zero-filling to 1K*1K, apodization with shifted square sine bell window functions ($\pi/2$) in both dimensions. NOESY: $CDCl_3$, 250 MHz, 64 scans, 2 dummy scans, 1K data blocks, 256 t_1 values, relaxation delay 2.0 s, mixing time 2.0 s, spectral widths 1501.50 Hz, zero-filling to 2K*2K, apodization with shifted square sine bell window functions ($\pi/2$) in both dimensions.

(5S,7R)-7-Benzoyloxy-2,2-bis(trifluoromethyl)-1-aza-3-oxabicyclo[4.3.0]nonan-4-one (13). To a solution of compound **12** (0.3 g, 1.0 mmol) and benzoyl chloride (0.28 g, 2.0 mmol) in CH_2Cl_2 (50 ml) at 0°C pyridine (0.16 g, 2.0 mmol) and DMAP (20 mg) were added. The reaction mixture was stirred for 12 h at this temperature, allowed to reach rt and treated with 1N HCl. The organic layer was separated, washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (EE/hexanes 1:15) to afford 0.35 g (86 %) of (**13**). M.p. 61-62°C; $[\alpha]_D^{22}$ +1.6 (c 1.0; $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): 8.01 (m, 2H); 7.39-7.61 (m, 3H); 5.05 (tt, J = 11.6, J = 4.6 Hz, 1H, H-7^{ax}); 3.66 (d, J = 11.6, 1H, H-5^{ax}); 3.52 (dd; J =

12.1, J = 4.0, 1H, H-9^{eq}); 2.97 (dd, J = 12.1, J = 11.6, 1H, H-9^{ax}); 2.58 (m, 1H, H-6^{eq}); 2.21 (m, 1H, H-8^{eq}); 1.81 (ddd, J = 12.1, J = 11.6, J = 4.9, 1H, H-8^{ax}); 1.72 (q, J = 11.6, 1H, H-6^{ax}); ^{13}C NMR (50 MHz, $CDCl_3$): 167.41; 165.54; 133.32; 130.07; 129.63; 128.44; 121.29 (q, J = 294.8 Hz, CF_3); 120.35 (q, J = 287.6 Hz, CF_3); 88.58 (sept, J = 32.9 Hz); 70.04; 54.94; 42.41; 32.57; 30.45; ^{19}F NMR (235 MHz, $CDCl_3$): 3.13 (q, J = 9.2 Hz, 3F, CF_3); -0.29 (q, J = 9.2 Hz, 3F, CF_3). Anal. Calcd for $C_{16}H_{13}F_6NO_4$ [397.27]: C 48.37; H 3.30; N 3.53. Found: C 48.40; H 3.34; N 3.53.

***cis*-4-Hydroxy-L-pipecolic acid (14).** Compound **12** (0.33 g, 1.1 mmol) was stirred in 100 ml of H_2O/*i*-PrOH (1:1, v/v) for 2 d at rt. The volatiles were evaporated in vacuo. The residue was dried in vacuo (0.01 Torr) for 4 d over P_2O_5 at rt to give 0.14 g (77 %) of **14**: $[\alpha]_D^{22}$ -16.8 (c 2.0; H_2O) [ref.[30b] $[\alpha]_D^{22}$ -17.0 (1.1 %, H_2O); ref.[24a] $[\alpha]_D^{22}$ -21.0 (1.1 %, H_2O)]. ^{1}H and ^{13}C NMR spectra are in good agreement with those reported in ref.[30a]

(5S,7S)-7-Formyloxy-2,2-bis(trifluoromethyl)-1-aza-3-oxabicyclo[4.3.0]nonan-4-one (15a). A solution of **12** (0.5 g, 1.7 mmol), PPh_3 (0.89 g, 3.4 mmol) and formic acid (0.14 ml, 3.4 mmol) in dry THF (30 ml) was stirred at 20°C. A solution of DEAD (0.59 g, 3.4 mmol) in THF (5 ml) was added dropwise and a moderately exothermic reaction took place. The reaction was stirred for 16 h. Evaporation of the solvent in vacuo afforded a syrupy product, which was chromatographed over silica gel (EE/hexanes 1:1) to give 0.43 g (78 %) of **15a** as an oil: $[\alpha]_D^{22}$ -1.2 (c 1.0; $CHCl_3$). ^{1}H NMR (360 MHz, $CDCl_3$): 8.07 (s, 1H); 5.42 (m, 1H, H-7^{eq}); 3.92 (d, J = 11.7, 1H, H-5^{ax}); 3.34 (dd; J = 12.1, J = 4.5, 1H, H-9^{eq}); 3.12 (dd, J = 12.1, J = 11.2, 1H, H-9^{ax}); 2.32 (dq, J = 13.5, J = 1.8, 1H, H-6^{eq}); 1.72-2.03 (m, 3H, H-6^{ax}, H-8^{eq}, H-8^{ax}); ^{13}C NMR (50 MHz, $CDCl_3$): 168.57; 159.52; 121.70 (q, J = 294.8 Hz, CF_3); 120.36 (q, J = 286.7 Hz, CF_3); 88.83 (sept, J = 32.1 Hz); 65.87; 51.70; 40.50; 31.75; 29.50; ^{19}F NMR (235 MHz, $CDCl_3$): 3.53 (q, J = 8.4 Hz, 3F, CF_3); -0.51 (q, J = 8.4 Hz, 3F, CF_3). Anal. Calcd for $C_{10}H_9F_6NO_4$ [321.18]: C 37.40; H 2.82; N 4.36. Found: C 37.64; H 2.88; N 4.38.

(5S,7S)-7-Benzoyloxy-2,2-bis(trifluoromethyl)-1-aza-3-oxabicyclo[4.3.0]nonan-4-one (15b) was obtained in the same manner in 67 % yield using benzoic acid. M.p. 81-82°C; $[\alpha]_D^{22}$ +15.6 (c 1.0; $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): 8.00 (m, 2H); 7.41-7.62 (m, 3H); 5.50 (quin, J = 3.0, 1H, H-7^{eq}); 3.92 (d, J = 11.7, 1H, H-5^{ax}); 3.39 (dd; J = 12.1, J = 5.4, 1H, H-9^{eq}); 3.19 (dd, J = 12.1, J = 11.2, 1H, H-9^{ax}); 2.43 (dq, J = 13.5, J = 1.8, 1H, H-6^{eq}); 1.78-2.11 (m, 3H, H-6^{ax}, H-8^{eq}, H-8^{ax}); ^{13}C NMR (50 MHz, $CDCl_3$): 168.70; 165.06; 133.44; 129.72; 129.48; 128.57; 121.79 (q, J = 294.0 Hz, CF_3); 120.39 (q, J = 284.3 Hz, CF_3); 88.88 (sept, J = 31.3 Hz); 66.55; 52.07; 40.83; 31.75; 29.50; ^{19}F NMR (235 MHz, $CDCl_3$): 3.61 (q, J = 9.2 Hz, 3F, CF_3); -0.46 (q, J = 9.2 Hz, 3F, CF_3); IR (KBr, cm^{-1}) 1843 (C=O); 1720 (C=O). Anal. Calcd for $C_{16}H_{13}F_6NO_4$ [397.27]: C 48.37; H 3.30; N 3.53. Found: C 48.13; H 3.25; N 3.69.

***trans*-4-Hydroxy-L-pipecolic acid hydrochloride (16).** Compound **15a** (0.32 g, 1 mmol) was stirred in 100 ml of H_2O/*i*-PrOH (1:1, v/v) for 2 d at rt. The volatiles were evaporated in vacuo. ^{1}H NMR spectrum of the residue showed that the formyl group was still present. The residue was dissolved in 6N HCl and stirred at rt for 5 d. The solvent was evaporated in vacuo and the residue dried in vacuo (0.01 Torr) for 4 d over P_2O_5 at rt

to give 0.16 g (85 %) of **16**: $[\alpha]_D^{22}$ +3.5 (c 1.4; 6N HCl) [ref.[30b] $[\alpha]_D$ +2.7 (2 %, 6N HCl)]. ^1H and ^{13}C NMR spectra are in good agreement with those reported in ref.[34]

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32. In contrast to our results the $NaBH_4$ reduction of Boc-protected ethyl 4-oxo-L-pipecolate (Boc-4Kps-OEt) gave a mixture of diastereoisomeric alcohols (*cis*, *trans* 1.5:1).[24b] The authors postulated that the ethoxycarbonyl group in Boc-4Kps-OEt assumed an axial orientation to reduce allylic 1,3-strain. Using the bulky reducing agent L-selectride they were able to obtain selectively *cis*-4-hydroxy-L-pipecolic acid. We assume the five-membered ring junction at C-5 in bicycle **10a** to be equatorial. The magnitude of the coupling constant between H-5 and H-6^{ax} (^3J = 11.8 Hz) indicates, that H-5 occupies an axial orientation, assuming a chair-like conformation of piperidone ring. Then $NaBH_4$ reduction of the keto group in **10a** proceeds in the same manner, as in 4-oxo-pipecolic acid hydrobromide. Namely, treatment of the latter with $NaBH_4$ furnished *cis*-4-hydroxy pipecolic acid in a cis/trans ratio of >95/5 see ref.[37] This transformation of 4-oxo-L-pipecolic acid was accomplished selectively using K-selectride see ref.[24a] Noteworthy, it was suggested, that 4-oxo-pipecolic residue in cyclic hexapeptides *virginiamycins* represents a distorted twist-boat form; see Anteunis, M.J.O.; Callens, R.E.A.; Tavernier, D.K. *Eur. J. Biochem.* **1975**, *58*, 259-268.

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