Pergamon

Tetrahedron, Vol. 52, No. 1, pp. 279-290, 1996

0040-4020/96 $15.00 + 0.00

0040-4020(95)00895-0

Synthesis of (2*R*, 3*S*)- or (2*S*, 3*R*)-2-Amino-3-trifluoromethyl-3-hydroxy-alkanoic Acid Derivatives (Threonine and *allo*-Threonine Analogs) from Enantiopure 4,4,4-Trifluoro-3-hydroxybutanoic Acid

Andrea R. Sting[1] and Dieter Seebach*

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich, Switzerland.

Abstract: The title compounds are prepared from the readily available enantiopure 6-alkyl- or 6-aryl-2-*tert*-butyl-6-trifluoromethyl-1,3-dioxan-4-ones with *cis* disposition of the *tert*-butyl and trifluoromethyl groups. Lithium enolates of these dioxanones are added to di-*tert*-butyl-azo-dicarboxylate to give exclusively the hydrazino derivatives formed by electrophilic attack from the face opposite to the *tert*-butyl and trifluoromethyl groups. Methanolysis of the dioxanone ring, removal of the N-Boc groups, and hydrogenolysis of the hydrazine N, N bond give methyl esters of (2*R*, 3*S*)-2-amino-4,4,4-trifluoro-3-hydroxybutanoic, (2*R*, 3*S*)-2-amino-4,4,4-trifluoro-3-hydroxy-3-methyl-butanoic, (2*R*, 3*S*)-2-amino-3-trifluoromethyl-3-hydroxyheptanoic, and (2*R*, 3*S*)-2-amino-4,4,4-trifluoro-3-hydroxy-3-phenyl-butanoic acids in overall yields ranging from 10 to 50 %.

INTRODUCTION

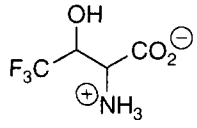
Fluorine containing analogs and derivatives of naturally occurring amino acids have proved to be of fundamental interest because of their intriguing chemical and biological properties[2]. A large number of fluoro amino acids have been synthesized, some of them exhibit high biological activities and are used as chemotherapeutic agents or in studies of the biosynthetic pathways of their corresponding proteinogenic counterparts[3]. Finally, they can be used as conformational modifiers in physiologically active proteins and enzymes[4].

In this context, the synthesis of trifluoromethyl substituted α-amino-β-hydroxy acids has attracted our attention not only because of their potential use in pharmaceuticals but also because of the challenge associated with their preparation in a stereoselective manner[5].

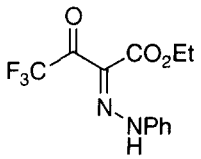
The first synthesis of racemic *threo* (*syn*) and *allo* (*anti*) 2-amino-4,4,4-trifluoro-3-hydroxybutanoic acids (**1**) was published in 1957 by *Walborsky* and *Baum*[6]. Their synthesis started from the readily available ethyl trifluoroacetoacetate which was diazotized with benzene diazonium chloride to give phenylhydrazone **2**. Reduction with $NaBH_4$, followed by saponification and catalytic hydrogenation gave the amino acids **1**.

A similar approach was chosen by *Scolastico* and his co-workers[7]. They nitrosated ethyl trifluoroacetoacetate with $NaNO_2$/AcOH to give the oxime which was O-methylated and reduced with $NaBH_4$ to give compound **3**. Reduction with zinc powder in formic acid produced a 1.5 : 1 mixture of *syn* and *anti* α-amino-β-hydroxy esters which could be separated by chromatography. Saponification of these esters led to the diastereoisomerically pure *syn*- and *anti*- amino acids **1**. In the same paper, the diastereoselective synthesis of *syn* 2-amino-4,4,4-trifluoro-3-hydroxybutanoic acid **1** is described, starting from dibenzylaminoacetate and ethyl trifluoroacetate to give the unstable β-ketoester by *Claisen* condensation followed by *in situ* reduction to the *syn* aminoester derivative **4**, which could readily be debenzylated with H_2/Pd(C).

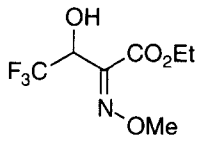
Chart 1. Different intermediates from the synthesis of fluorine containing α-amino-β-hydroxybutanoic acids



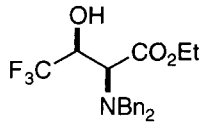
1



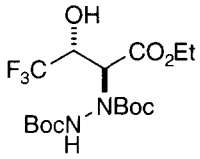
2
Walborsky, Baum [6]



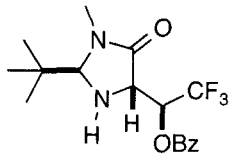
3
Scolastico [7]



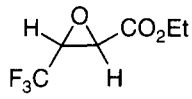
4
Scolastico [7]



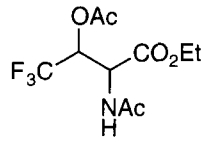
5
Guanti [8]



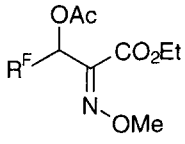
6
Seebach [9]



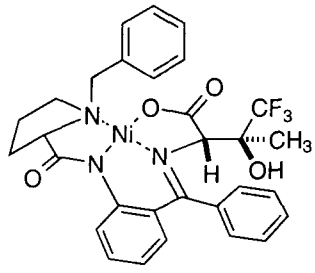
7
v.d.Bussche, Seebach [10]



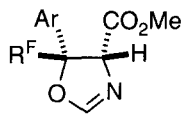
8
Kitazume [11]



9
Fujisawa [12]



10
Belokon, Soloshonok [13]



11
Hayashi [14]

In another diastereoselective synthesis furnishing *anti* -**1**, the electrophilic amination of β-hydroxy acids *via* the dianion with DBAD (di-*tert*-butyl-azodicarboxylate) was used by *Guanti* and coworkers[8]. The α-(*N*,*N*'-bis(*tert*-butoxycarbonyl)-hydrazino ester **5** was obtained in a 87 : 13 ratio of *anti* and *syn* product. Deblocking with TFA, saponification and hydrogenolysis of the hydrochloride gave the diastereoisomerically pure *anti*-**1**. In our group, an enantioselective synthesis of (2*S*, 3*S*)-trifluorothreonine was achieved using (*S*)-1-benzoyl-2-(*tert*-butyl)-3-methylimidazolidin-4-one[9]. The Li enolate of this heterocycle reacts diastereoselectively with aldehydes to form aldol adducts. The benzoate **6** thus obtained with trifluoroacetaldehyde was hydrolysed with 6N HCl at 100 °C in 24 h to give the enantiopure derivative (2*S*, 3*S*)-**1**. Enantiomerically pure *anti* ethyl 2-amino-4,4,4-trifluoro-3-hydroxybutanoate was also prepared in our group[10] starting from the glycidic ester **7**. The epoxide was treated with trimethylsilyl azide and the aminoester was obtained after hydrogenation with H_2 / Pd-C.

Another approach towards enantiomerically pure threonines **1** is the resolution of racemates *via* enzymatic transformations. *Kitazume* and coworkers[11] obtained a 1 : 1 mixture of *syn* and *anti* ethyl 2-amino-4,4,4-trifluoro-3-hydroxybutanoate by aldol addition of the *Schiff* base from glycin and benzaldehyde to trifluoroacetaldehyde. Acylation with acetylchloride gave an easily separable mixture of *syn* and *anti*-**8**. These racemates could be resolved by enantioselective hydrolysis of the acetate groups with lipase MY (*Candida Cylindracea*). A slightly different method was used by *Fujisawa* and his coworkers[12]. They prepared their

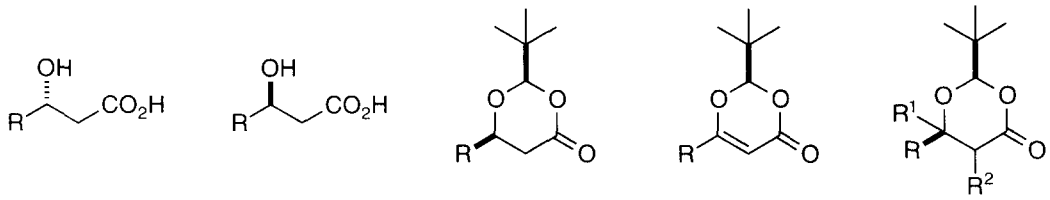
starting material **3** according to the method of *Scolastico*[7]. O-Acetylation led to the substrate **9** ($R^F = CF_3$) for enzymatic kinetic resolution by lipase-mediated hydrolysis (with *Amano* PS lipase). The resolved alcohols and acetates were readily transformed into the corresponding enantiopure threonines **1** using known procedures. Not only the derivatives **9** ($R^F = CF_3$) but also the ones having $R^F = CHF_2$, CH_2F and $CHCl_2$ could be resolved using this methodology.

The chiral Ni^{II} complex of a *Schiff* base derived from (*S*)-ortho-[*N*-(*N*-benzylprolyl)amino]-benzophenone (BPB) was used for enantioselective synthesis of several fluorinated α-amino-β-hydroxy acids by the groups of *Belokon* and *Soloshonok* [13]. Aldol addition of this complex to several F-containing aldehydes led to either *syn* or *anti* products, depending on the exact reaction conditions and on the base used. Addition of 1,1,1-trifluoroacetone produced adduct **10** which could be readily cleaved to give (2*S*, 3*S*)-3-(trifluoromethyl)-threonine in good yield. Enantiopure (2*S*, 3*S*)-4,4,4-trifluorothreonine **1** was obtained from trifluoroacetaldehyde and the chiral Ni complex by the same method.

Finally, eight different oxazolines **11** derived from the aldol reaction between fluoro substituted aryl ketones and isocyanoacetic acid catalyzed by transition metals have been published recently by *Hayashi* and coworkers[14]. The *cis* products depicted in formula **11** are formed predominantly. These oxazolines can be cleaved with conc. HCl / MeOH to the corresponding *syn* threonine esters (see Chart 1).

In the course of our work on β-hydroxy acids **12**, we have shown that (*R*)-3-hydroxybutanoic acid (**12**, R = CH_3, from polyhydroxy butanoate[15]) and (*S*)-3-hydroxybutyric acid (*ent*-**12**, R = CH_3, from ethyl acetoacetate by yeast reduction[16] or BINAP-Ru hydrogenation[17]) and other analogs can be transformed to *cis*-dioxanones of type **13** (R = CH_3[18], C_2H_5[18,19], CCl_3[20], CF_3[21]). Bromination with NBS, followed by hydrogenolysis gives enantiopure dioxinones **14**. However, the trifluoro derivative **14** (R = CF_3) cannot be prepared in this way because of the lack of reactivity of **13** (R = CF_3) with NBS (see below).

Chart 2. 3-Hydroxycarboxylic acids and the derived dioxanones and dioxinones

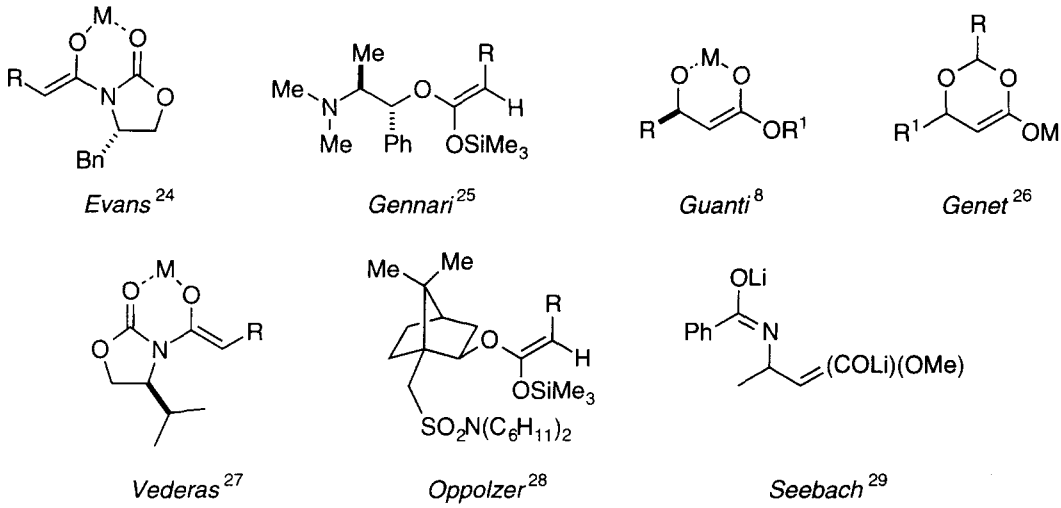


12 *ent* - **12** **13** **14** **15**

Several dioxanones of type **15** have been prepared from either compound **13** (leading to 2,5,6 trisubstituted dioxanones **15** having $R^1 = H$) or **14** (leading to 2,5,6,6 tetrasubstituted dioxanones **15**)[22], see Chart 2. The reaction sequence beginning with a chiral β-hydroxy acid **12** or ent-**12**, building up a second stereocenter diastereoselectively to give compounds of type **13**, followed by elimination of the original stereocenter with formation of **14** and then addition of a new substituent to this center in such a way, that the original orientation is regenerated as in dioxanones **15** ($R^2 = H$), is an application of the principle of "self-regeneration of stereogenic centers"[23]. The corresponding α- and/or β-branched β-hydroxy acids or esters can be obtained from these dioxanones by hydrolysis or alcoholysis under acidic conditions.

Inspired by the fact that chiral enolates (for some examples see Chart 3) can be converted stereoselectively to α-hydrazino derivatives with electrophilic aminating reagents such as DBAD[8, 24-29], we envisaged the synthesis of some 3-subtituted *allo*-threonines bearing a trifluoromethyl group by this method.

Chart 3. Some chiral enolates that have been diastereoselectively aminated with the azo-dicarboxylate DBAD

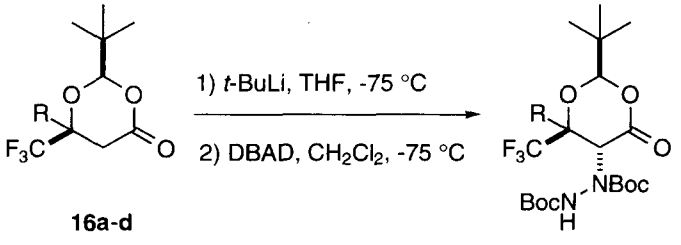


RESULTS

In this work, we chose the three trifluoro substituted dioxanones **16** (R = Me, Bu, Ph), which were prepared according to known procedures[30] by cuprate addition to the dioxinone **14** (R = CF_3). However, about a dozen of these compounds **16** are known, having R = CD_3, C_2H_5, C_3H_7, $CH(CH_3)_2$, $C(CH_3)_3$, CH_2-$CH{=}CH_2$, $CH_2C_6H_5$ and we believe that these could have been used analogously. Compound **14** (R = CF_3) can be prepared starting from the corresponding (*S*)-4,4,4-trifluoro-3-hydroxybutanoic acid (ent-**12**, R = CF_3) by acid catalyzed acetalization to the dioxanone **13** (R = CF_3)[21], which in turn is brominated in the 5-position, followed by dehydrohalogenation with DBU. Enantiopure acids **12** (R = CF_3) and ent-**12** (R = CF_3) are available on a 500 g scale from resolution of enantiomers by crystallization of the diastereoisomeric salts with (*R*)- and (*S*)-1-phenylethylamine[31].

Dioxanones **16a-d** were treated with *tert*-BuLi (other bases like LDA or LHMDS gave poorer results) at -75 °C, and then a cold (-75 °C) solution of DBAD in CH_2Cl_2 was added slowly to the enolate solution. Usually the reactions were complete after a few minutes and the hydrazino dioxanones **17a-d** were isolated in good yields and excellent diastereoselectivities (dr > 98 : 2), as outlined in Scheme 1.

Scheme 1.



Entry	Starting Material	R	Yield %
1	**16a**	H	97
2	**16b**	Me	86
3	**16c**	Bu	80
4	**16d**	Ph	71

The ^1H NMR spectra of compounds **17** obtained at room temperature in $CDCl_3$ were largely uninterpretable due to hindered rotation about the Boc groups. However, the corresponding spectra of **17a** and

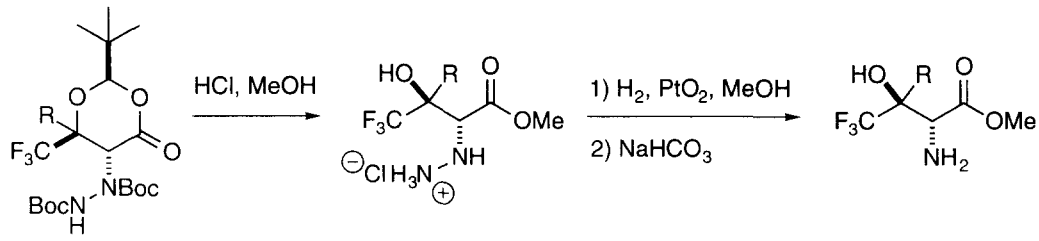
17b obtained in d_6-DMSO at 80 °C were dramatically simplified and could be readily analyzed. None of the other diastereoisomer could be detected either with ^1H- or ^{19}F-NMR spectroscopy. The relative configuration of the amination products could not be established at this stage. Compounds **17c** and **17d** were not isolated in analytically pure form, after flash chromatography (FC) there was still an impurity (a rotamer ?) present which could not be removed. Therefore, these two compounds were employed in the next step without further purification (see Experimental Part).

Treatment of **17a-d** with a saturated solution of HCl in methanol produced the α-hydrazino-β-hydroxy esters **18a-d** as the hydrochlorides. Depending upon the substituent R, this methanolysis had to be performed at elevated temperatures and with longer reaction times to achieve complete conversion. This led to the formation of significant amounts of by-products and lowered the yields of this step. The resulting hydrochlorides were directly hydrogenated with H_2/PtO_2 in methanol, without purification. Only small portions of these hydrochlorides were treated with saturated Na_2CO_3 solution and then purified by recrystallization, FC or sublimation to give the analytically pure α-hydrazino-β-hydroxy esters **18b-d** for full characterization.

It is noteworthy that **18a** could not be obtained by this procedure: As soon as the hydrochloride was treated with Na_2CO_3, an inseparable mixture of products was formed. Therefore, this compound was recrystallized in the form of the hydrochloride **18a**·HCl for analytical purposes. Aminoesters **19a-d** were isolated with the yields indicated in Scheme 2, by treating the crude products with saturated $NaHCO_3$ solution.

The enantiomer of **19a**, (2*S*, 3*R*)-methyl 2-amino-4,4,4-trifluoro-3-hydroxybutanoate (ent-**19a**) was also synthesized starting with ent-**16a**.

Scheme 2.



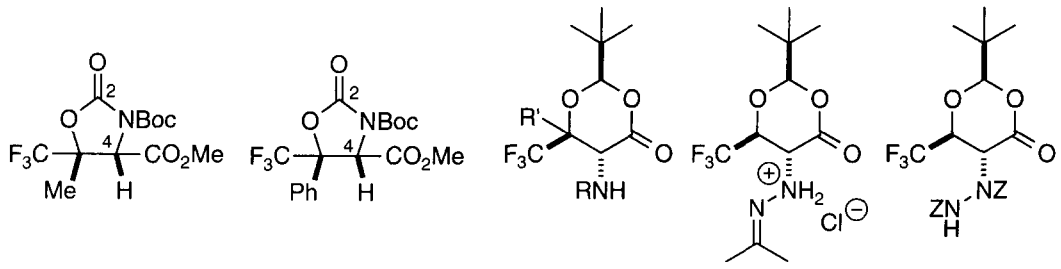
17a-d **18a-d** • HCl **19a-d**

Entry	Starting Material	R	Aminoester	Yield %	$[\alpha]_D^{RT}$ (EtOH)
1	**17a**	H	**19a**	37	- 25.0 (c: 1.15)
2	**17b**	Me	**19b**	47	- 25.5 (c: 1.46)
3	**17c**	Bu	**19c**	12	- 32.8 (c: 1.50)
4	**17d**	Ph	**19d**	11	- 28.5 (c: 0.94)

The relative configuration of aminoester **19a** was assigned by comparison of the coupling constant (J = 5.9 Hz) between H-C(2) and H-C(3) with that of the corresponding *anti* ethyl 2-amino-4,4,4-trifluoro-3-hydroxybutanoate (J = 5.7 Hz)[10]. The coupling constant of *syn* ethyl 2-amino-4,4,4-trifluoro-3-hydroxybutanoate is smaller (J = 3.1 Hz). This difference of coupling constants is qualitatively analogous to the situation in trifluoro-*allo*-threonine (J = 5.7 Hz) and trifluorothreonine (J = 1.8 Hz)[7, 9]. For the β-branched derivatives **19**, another configurational assignement had to be found. Serendipity came to our rescue: attempted protection of the NH_2 groups in **19b** and **19d** with excess di-*tert*-butyl-dicarbonate produced the N-Boc-oxazolidin-2-ones **20** and **21** in excellent yields (a manifestation of the Thorpe - Ingold[32] or "reactive-rotamer"

effect[33] !?). In these heterocycles **20** and **21** (Chart 4), there is a clear-cut positive nuclear-*Overhauser* effect (NOE) indicating *cis* position of Me / H and Ph / H. Irradiation with the resonance frequency of the CH_3-C(5) protons in **20** led to a positive NOE-effect on H-C(4) and irradiation with the resonance frequency of H-C(4) in **21** caused a positive NOE-effect on the ortho protons of the phenyl ring.

Chart 4. N-Boc-oxazolidin-2-ones from **19b** and **19d** and some dioxanones with N-subtituents in the 5-position.



20 **21** **22** **23** **24**

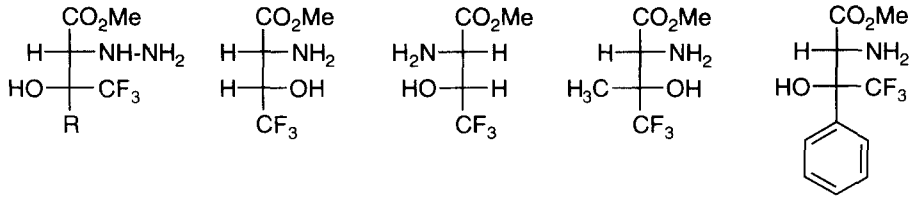
All attempts to prepare the 5-hydrazino- or 5-amino-substituted dioxanones **22** from the *N,N'*-di-Boc substituted hydrazino dioxanones **17** failed. Inseparable mixtures resulted from applications of the usual Boc deprotection procedure with compounds **17**. Experiments carried out to isolate the initially formed hydrazine **22** (R = NH_2, R' = H) and purify it by crystallization from acetone led to the hydrazone hydrochloride **23**, hydrogenation (H_2 / PtO_2) of which generated a product mixture from which no amino-dioxanone **22** (R, R' = H) could be isolated. In order to avoid acidic conditions, we also prepared the di-carbobenzyloxy-derivative **24** by *Michael* addition of the dioxanone **16a** to dibenzyl azodicarboxylate (61 % yield). However, hydrogenolytic deprotection (H_2 / Pd-C in EtOAc) again led to a terrible mixture of products. The recommended cleavage of hydrazine N, N bonds with SmI_2[34] also failed to afford the desired amino-dioxanone **22** (R = H) from **17a** or from **24**.

DISCUSSION

The reaction of the dioxanone enolates to give products **17** from attack of the azodicarboxylate trans to the CF_3 group exclusively is surprizing for two reasons. First of all, other 6,6-di-substituted dioxanone enolates of this type generally combine with electrophiles with poor diastereoselectivity[35,36]. Secondly, when going from R = H to R = CH_3 to R = Ph in **16**, there should be a decrease in selectivity with increasing *van der Waals* radius of these groups (1.2, 2.0 and *ca.* 5.3 Å) relative to CF_3 (2.7 Å)[37]. Since the conformation of the dioxanone enolate ring is presently unknown[35], it is difficult to interpret the effect observed.

From a synthetic point of view, we have described here simple methods for the preparation of new types of enantiopure amino- and hydrazino-hydroxy acid derivatives, see the *Fischer* projections in Chart 5. Both classes of derivatives should be interestingly incorporated into peptides to study their effects on the secondary structure and on physiological properties. So called aza-peptides containing a hydrazine unit in the backbone have been shown to be promising peptide analogs[38]. Also, the effect of the CF_3 group in the novel amino acids bearing a branched substituent, an OH and a CF_3 group in the 3-position will be important in peptides containing these residues: the OH group, embedded in a hydrophobic environment is a much stronger H-bond donor than in the non-fluorinated analogs (the pK_a values of CH_3CH_2OH and CF_3CH_2OH are 16[39] and 13[40], respectively).

Chart 5. *Fischer* projections of some of the prepared α-hydrazino- and α-amino-β-hydroxycarboxylic acid derivatives containing CF_3 groups.



18 **19a** ***ent*-19a** **19b** **19d**

Acknowledgements: We thank Dr. M. Gautschi for supervising some of the experiments described here. Generous supply of ethyl trifluoroacetoacetate from the *LONZA AG* (CH-Visp) and of pivalaldehyde from *BASF AG* (D-Ludwigshafen) as well as financial support from *SANDOZ PHARMA AG* (CH-Basel) are gratefully acknowledged. We thank J. Matthews and A. K. Beck for their help in preparing this manuscript.

EXPERIMENTAL

General. Abbreviations: THF (tetrahydrofuran), *t*-BuLi (*tert*-butyllithium), DBAD (di-*tert*-butyl-azodicarboxylate), DMAP (dimethylaminopyridine), rt (room temperature, *ca.* 22 °C), FC (flash chromatography). Solvents and reagents: ether was distilled over Na wire, THF was distilled over K under Ar, CH_2Cl_2 was dried over molecular sieves 4Å. The solution of *t*-BuLi (*ca.* 1.55M in pentane) was used as purchased and its content was titrated with *sec*-BuOH[41]. The solvents used for work-up and purification were distilled at normal pressure. Dioxanones **16** were prepared according to published procedures[30]. FC[42]: performed on silica gel (230 - 400 mesh, *Merck*). M.p.: *Büchi* 510, uncorrected. Optical rotations $[\alpha]_D^{RT}$: *Perkin-Elmer* 241 polarimeter, in 10 cm cells. ^{1}H NMR spectra: *Bruker WM* 300 (300 MHz) or *Varian XL* 300 (300 MHz), δ in ppm relative to TMS, *J* in Hz. ^{13}C NMR: *Bruker WM* 300 (75 MHz) or *Varian XL* 300 (75 MHz), δ in ppm relative to TMS, *J* in Hz.^{19}F NMR: *Varian XL* 300 (282.2 MHz) or *Varian Gemini* 300 (282.2 MHz), δ in ppm relative to $CFCl_3$, *J* in Hz. If not otherwise marked, the spectra were recorded at rt in $CDCl_3$. Mass spectra: *Hitachi-Elmer RMU-6M* or *VG Tribrid*, peak intensities are given as percentage of the base peak in parantheses. IR: *Perkin-Elmer 983* and *Perkin-Elmer 1600 FTIR*, absorptions are reported in cm^{-1}. Elemental analyses were performed by the Microanalytical Service Laboratory of ETH-Zürich.

General Procedure for the reaction of dioxanones 16[30] with DBAD: GP I. A solution of 20 mmol of the appropriate dioxanone in 50 ml THF was cooled to -75 °C under Ar. *t*-BuLi (14.2 ml, 22 mmol) was added slowly by syringe while keeping the temperature below -70 °C. The solution became yellow upon addition of the final drops. After stirring for 20 min at -75 °C, a cold (-75 °C) solution of DBAD (4.6 g, 20 mmol) in 125 ml CH_2Cl_2 was added *via* teflon cannula. The resulting solution was kept at -75 °C for a further 40 min and then quenched by the addition of 75 ml of saturated NH_4Cl solution. This mixture was allowed to warm to 0 °C, approximately 15 ml of water were added to dissolve the precipitated NH_4Cl and the aqueous layer was extracted twice with portions of 100 ml CH_2Cl_2, the combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure.

(2*R*,5*R*,6*S*)-2-(*tert*-Butyl)-5-(*N*,*N*'-bis-(*tert*-butyloxycarbonyl)-hydrazino)-6-trifluoromethyl-1,3-dioxan-4-one (17a). Following **GP I**, dioxanone **16a** (4.53 g, 20 mmol) was treated with *t*-BuLi (14.2 ml, 22 mmol) and DBAD (4.6 g, 20 mmol). After work-up, the yellow oil was carefully dried *in vacuo* (a sticky foam!) whereby a yellowish, glassy product (8.84 g, 97 %) was isolated, which, according to ^{1}H NMR, was essentially pure. Recrystallization (from pentane) of a small sample yielded the analytically pure compound. M.p.: 115.0-116.5 °C; $[\alpha]_D^{RT}$ = +19.3 (c = 0.90, EtOH); IR (KBr): 3380*w*, 3330*m*, 2980*m*, 2940*w*, 1740*s*, 1695*s*, 1480*m*, 1410*m*, 1395*m*, 1370*s*, 1355*m*, 1340*m*, 1305*m*, 1290*s*, 1275*s*, 1265*s*, 1245*s*, 1200*s*, 1155*s*, 1135*s*, 1095*m*, 990*s*; ^{1}H NMR (300 MHz, d_6-DMSO, 80 °C): 0.95 (*s*, 9H, *t*-Bu), 1.42 (*s*, 18H, *t*-Bu), 4.74-4.81 (*m*, H-C(6)), 4.87 (*d*, *J* = 9.1, H-C(5)), 5.30 (*s*, H-C(2)), 8.70 (*br.*, NH); ^{13}C NMR (75 MHz, d_6-DMSO, 80 °C): 23.34 (CH_3), 27.71 (CH_3), 27.95 (CH_3), 34.70 (C), 56.16 (CH), 73.40 (*q*, *J* (C,F) = 31.5), 80.41 (C), 82.28 (C), 105.96 (CH), 122.86 (*q*, *J* (C,F) = 281.0), 153.65 (C), 155.19 (C), 163.02 (C); MS: 457 (1, $[M+1]^+$), 345 (7), 300 (20), 243 (48), 199 (56), 87 (25), 71 (19), 69 (34), 59 (31), 58 (42), 57 (100), 56 (36), 55 (21), 43 (45), 41 (65), 39 (35), 29 (55), 28 (50). Anal. Calcd. for $C_{19}H_{31}F_3N_2O_7$ (456.45): C, 50.00; H, 6.85; N, 6.14; F, 12.49; Found: C, 50.12; H, 7.08; N, 6.13; F, 12.31.

(2*R*,5*R*,6*S*)-2-(*tert*-Butyl)-5-(*N*,*N*'-bis-(*tert*-butyloxycarbonyl)-hydrazino)-6-methyl-6-trifluoromethyl-1,3-dioxan-4-one (17b). Following **GP I**, dioxanone **16b** (1.60 g, 6.7 mmol) was treated with *t*-BuLi (4.9 ml, 7.4 mmol) and DBAD (1.53 g, 6.7 mmol) in 40 ml of CH_2Cl_2. After usual work-up, the resulting colorless oil was carefully dried *in vacuo* (a sticky foam!) whereby a yellowish, glassy product (3.31 g, 99 %) was isolated, which, according to ^1H NMR, was essentialy pure. FC (ether/pentane 1:3) yielded the analytically pure compound (2.71 g, 86 %). M.p.: 68.0-70.0 °C; $[\alpha]_D^{RT}$ = +18.8 (c = 1.04, EtOH); IR (KBr): 3380*w*, 3310*w*, 2980*m*, 2940*w*, 2880*w*, 1750*s*, 1730*s*, 1485*m*, 1460*m*, 1405*m*, 1395*m*, 1370*s*, 1350*m*, 1310*s*, 1280*s*, 1245*s*, 1170*s*, 1105*s*, 1035*m*, 1005*m*; ^1H NMR (300 MHz, d_6-DMSO, 80 °C): 0.93 (*s*, *t*-Bu), 1.41 (*s*, *t*-Bu), 1.43 (*s*, *t*-Bu), 1.63 (*s*, CH_3), 4.88 (*s*, H-C(5)), 5.28 (*s*, H-C(2)), 8.60-9.15 (*br.*, NH); ^{13}C NMR (75 MHz, d_6-DMSO, 80 °C): 13.19 (CH_3), 22.81 (CH_3), 27.16 (CH_3), 27.40 (CH_3), 33.75 (C), 58.35 (CH), 79.00 (*q*, *J* (C,F) = 30.0), 80.02 (C), 82.08 (C), 100.91 (CH), 123.98 (*q*, *J* (C,F) = 284.5), 154.45 (C), 161.77 (C); MS: 471 (2, $[M+1]^+$), 314 (42), 301 (30), 257 (95), 213 (90), 184 (22), 139 (33), 87 (31), 71 (18), 69 (23), 57 (100), 43 (18), 41 (60), 39 (15), 29 (14), 28 (21). Anal. Calcd. for $C_{20}H_{33}F_3N_2O_7$ (470.48): C, 51.06; H, 7.07; N 5.95; Found: C, 51.32; H, 7.26; N, 5.86.

(2*R*,5*R*,6*S*)-2-(*tert*-Butyl)-6-butyl-5-(*N*,*N*'-bis-(*tert*-butyloxycarbonyl)-hydrazino)-6-trifluoromethyl-1,3-dioxan-4-one (17c). Following **GP I**, dioxanone **16c** (3.05 g, 10.8 mmol) was treated with *t*-BuLi (7.7 ml, 11.9 mmol) and DBAD (2.56 g, 10.8 mmol) in 75 ml of CH_2Cl_2. After usual work-up, the resulting yellow solid was carefully dried *in vacuo* (a sticky foam!) whereby 6.0 g of a yellowish, glassy product was obtained, which was purified by FC (ether/pentane 1:9) to give a colorless, amorphous solid (4.45 g, 80.4 %). This material was used in the next step without further purification. ^1H NMR (300 MHz, d_6-DMSO, 80 °C): 0.83-0.93 (*m*, 3H), 0.97 (*s*, 9H), 1.22-1.55 (*m*, 6H), 1.43 (*s*, 9H), 1.45 (*s*, 9H), 5.02, 5.26, 5.57, 5.71, 5.80 (5*s*, 3H).

(2*R*,5*R*,6*S*)-2-(*tert*-Butyl)-5-(*N*,*N*'-bis-(*tert*-butyloxycarbonyl)-hydrazino)-6-trifluoromethyl-6-phenyl-1,3-dioxan-4-one (17d). Following **GP I**, dioxanone **16d** (2.57 g, 8.5 mmol) was treated with *t*-BuLi (6.9 ml, 9.4 mmol) and DBAD (1.96 g, 8.5 mmol) in 60 ml of CH_2Cl_2. After usual work-up, the resulting yellow oil was carefully dried *in vacuo* (a sticky foam!). This mixture was purified by FC (ether/pentane 1:3) to give of a colorless foam (3.20 g, 70.7 %). This material was used in the next step without further purification. ^1H NMR (300 MHz, d_6-DMSO, 80 °C): 1.06, 1.09 (2*s*, 9H), 1.36, 1.39. 1.47 (3*s*, 18H), 3.49, 3.58, 3.61, 3.70 (4*s*, 1H), 5.26, 5.68, 5.75, 5.80, 5.86 (5*s*, 2H), 7.40-7.62 (*m*, 5H).

(2*R*, 3*S*)-Methyl 4,4,4-trifluoro-2-hydrazino-3-hydroxybutanoate hydrochloride (18a·HCl). Dioxanone **17a** (6.85 g, 15 mmol) was placed in a 250 ml flask and treated with 150 ml of a cold saturated solution of HCl in methanol. The suspension was stirred at 0 °C for 3 h (monitored by TLC) and after this time, a clear solution was obtained. After removing the solvent under reduced pressure **18a**·HCl (3.54 g, 98 %) was obtained as a yellow powder. A small portion was recrystallized from ethyl acetate/methanol (95:5) to give a colorless powder. M.p.: 161.0 °C (decomp.); $[\alpha]_D^{RT}$ = +13.3 (c = 1.09, EtOH); IR (KBr): 3230*br.*, 3120*br.*, 2960*m*, 2940*m*, 1730*s*, 1585*m*, 1510*m*, 1440*m*, 1375*m*, 1350*m*, 1325*m*, 1290*s*, 1260*m*, 1240*s*, 1210*m*, 1170*s*, 1130*s*, 1115*s*, 1080*m*, 950*m*; ^1H NMR (300 MHz, CD_3OD): 3.83 (*s*, CH_3), 4.05 (*d*, *J* = 4.9, H-C(2)), 4.42 (*qd*, *J* = 7.0, 4.9, H-C(3)), 4.88 (*br.*, OH, NH); ^{13}C NMR (75 MHz, CD_3OD): 53.41 (CH_3), 62.61 (CH), 71.00 (*q*, *J* (C,F) = 31.5), 125.60 (*q*, *J* (C,F) = 283.5), 170.23 (C); ^{19}F NMR (282.2 MHz, CD_3OD): -76.36 (*d*, *J* = 7.0); MS: 202 (14), 143 (68), 125 (78), 105 (55), 103 (100), 78 (34), 71 (94), 69 (24), 59 (20), 51 (32), 43 (71), 36 (66), 31 (59), 29 (27), 28 (99); Anal. Calcd. for $C_5H_{10}ClF_3N_2O_3$ (238.59): C, 25.17; H, 4.22; N, 11.74; Found: C, 25.28; H, 4.24; N, 11.70.

(2*R*, 3*S*)-Methyl 4,4,4-trifluoro-2-hydrazino-3-hydroxy-3-methylbutanoate (18b). Dioxanone **17b** (7.70 g, 16.4 mmol) was placed in a 250 ml flask and treated with 160 ml of a cold saturated solution of HCl in methanol. The suspension was stirred at rt for 8 h (monitored by TLC) and after this time, a clear solution was obtained. After removing the solvent under reduced pressure, the hydrochloride **18b**·HCl (5.50 g) was obtained as a yellow powder. This product was used in the hydrogenation step without further purification. A small amount (200 mg) was dissolved in 15 ml of saturated Na_2CO_3 solution and 15 ml ether and the aqueous layer was extracted twice with 30 ml portions of ether. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. Recrystallization from ethyl acetate/ether (95:5) yielded a colorless solid **18b**. M.p.: 121.0-122.0 °C (decomp.); $[\alpha]_D^{RT}$ = -20.5 (c = 1.15, EtOH); IR (KBr): 3330*s*, 3290*m*, 2960*m*, 1730*s*, 1610*w*, 1440*m*, 1385*w*, 1350*m*, 1325*m*, 1275*s*, 1220*s*, 1200*s*, 1190*s*, 1155*s*, 1115*s*, 1080*s*, 960*m*; ^1H NMR (300 MHz, CD_3OD): 1.46 (*d*, *J* = 1.0, CH_3), 3.64 (*s*, H-C(2)), 3.77 (*s*, OCH_3), 4.85 (*br.*, OH, NH); ^{13}C NMR (75 MHz, CD_3OD): 19.28 (CH_3), 52.65 (CH), 70.60 (CH_3), 74.76 (*q*, *J* (C,F) = 29.5), 127.14 (*q*, *J* (C,F) = 285.5), 173.02 (C); ^{19}F NMR (282.2 MHz, CD_3OD): -80.47 (*s*); MS: 217 (5, $[M+1]^+$), 157 (12), 139 (24), 119 (17), 103 (94), 71 (100), 69 (12), 59 (11), 43 (95), 42 (12), 31 (19), 29 (12); Anal. Calcd. for $C_6H_{11}F_3N_2O_3$ (216.15): C, 33.34; H, 5.13; N, 12.96; Found: C, 33.31; H, 5.24; N, 13.00.

(2*R*, 3*S*)-Methyl 2-hydrazino-3-hydroxy-3-trifluoromethylheptanoate (18c). Dioxanone **17c** (4.25 g, 8.3 mmol) was placed in a 250 ml flask and treated with 100 ml of a cold saturated solution of HCl in methanol. The suspension was heated to reflux, whereby a clear solution was formed, and heating was

continued for 12 h (monitored by TLC). After this time a yellow supension was obtained. Filtration trough celite, followed by removal of the solvent under reduced pressure furnished the hydrochloride **18c**·HCl (1.96 g) as a yellow powder. This product was used in the hydrogenation step without further purification. A small portion (230 mg) was dissolved in 10 ml of saturated Na_2CO_3 solution and 20 ml ether, the aqueous layer was extracted three times with 20 ml portions of ether. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. FC (pentane/ether 1:3) and subsequent sublimation (0.02 Torr/50 °C) gave the colorless solid **18c**. M.p.: 71.5-72.5 °C; $[\alpha]_D^{RT}$ = -6.8 (c = 1.00, EtOH); IR (KBr): 3430*br.*, 3335*s*, 3295*m*, 2960*m*, 2880*m*, 1725*s*, 1615*w*, 1465*m*, 1435*m*, 1345*m*, 1320*m*, 1305*m*, 1260*m*, 1220*s*, 1210*s*, 1185*s*, 1145*s*, 1110*m*, 990*m*, 970*m*; ^{1}H NMR (300 MHz): 0.95 (*t*, *J* = 7.2, CH_3), 1.24-1.70 (*m*, 4H), 1.78-1.98 (*m*, 2H), 2.80-4.94 (*br.*, 4H, OH, NH), 3.71 (*s*, H-C(2)), 3.81 (*s*, OCH_3); ^{13}C NMR (75 MHz): 13.92 (CH_3), 22.89 (CH_2), 24.41 (CH_2), 31.02 (CH_2), 52.64 (CH_3), 68.23 (CH), 74.92 (*q*, *J* (C,F) = 27.0), 125.79 (*q*, *J* (C,F) = 288.0), 170.79 (C); ^{19}F NMR (282.2 MHz): -78.16 (*s*); MS: 259 (0.4, $[M+1]^+$), 199 (3), 181 (4), 171 (2), 159 (2), 139 (1), 126 (1), 103 (100), 88 (4), 71 (64), 69 (3), 43 (13), 28 (16); Anal. Calcd. for $C_9H_{17}F_3N_2O_3$ (258.23): C, 41.86; H, 6.64; N, 10.85; Found: C, 42.17; H, 6.85; N, 10.43.

(2*R*, 3*S*)-Methyl 4,4,4-trifluoro-2-hydrazino-3-hydroxy-3-phenylbutanoate (18d). Dioxanone **17d** (3.20 g, 6 mmol) was placed in a 250 ml flask and treated with 100 ml of a cold saturated solution of HCl in methanol. The suspension was stirred at rt for 24 h (monitored by TLC) and the solvent was removed under reduced pressure to give the hydrochloride **18d**·HCl (1.80 g) as a yellow powder. This product was used in the hydrogenation step without further purification. A small portion (180 mg) was dissolved in 10 ml of saturated Na_2CO_3 solution and 20 ml ether, the aqueous layer extracted three times with 20 ml portions of ether. The combined organic layers were dried over $MgSO_4$ and the solvent evaporated. FC (pentane/ether 1:2) and subsequent sublimation (0.03 Torr/90 °C) gave the hydrazinoester **18d** as colorless needles. M.p.: 100.0-101.2 °C; $[\alpha]_D^{RT}$ = -13.9 (c = 1.44, EtOH); IR (KBr): 3430*br.*, 3350*m*, 3320*m*, 2955*w*, 1745*s*, 1735*s*, 1615*w*, 1495*w*, 1450*m*, 1435*m*, 1360*m*, 1310*m*, 1265*s*, 1220*s*, 1175*s*, 1075*m*, 1045*m*, 965*m*, 950*w*; ^{1}H NMR (300 MHz): 2.70-5.10 (*br.*, 4H, OH, NH), 3.84 (*s*, OCH_3), 4.14 (*s*, H-C(2)), 7.36-7.46 (*m*, 3 *arom.* H), 7.59-7.72 (*m*, 2 *arom.* H); ^{13}C NMR (75 MHz): 52.73 (CH_3), 66.87 (CH), 77.94 (*q*, *J* (C,F) = 28.0), 122.52 (C), 126.27 (CH), 128.00 (*q*, *J* (C,F) = 281.0), 128.46 (CH), 128.97 (CH), 135.25 (C), 172.95 (C); ^{19}F NMR (282.2 MHz): -76.84 (*s*); MS: 279 (0.5, $[M+1]^+$), 219 (3), 201 (4), 184 (3), 174 (2), 132 (2), 127 (2), 105 (28), 103 (100), 88 (3), 77 (26), 71 (72), 69 (5), 43 (15), 28 (23); Anal. Calcd. for $C_{11}H_{13}F_3N_2O_3$ (278.23): C, 47.49; H, 4.71; N, 10.07; Found: C, 47.45; H, 4.71; N, 9.85.

General Procedure for the hydrogenation of the hydrazinoesters GP II. A mixture of 5 mmol of the appropriate hydrazinoester hydrochloride and a catalytic amount (1 mmol) of $PtO_2 \cdot H_2O$ in 15 ml of methanol was placed in a 50 ml flask, equipped with a magnetic stirrer and a balloon filled with H_2. The reaction was usually complete after 2-5 d (TLC). After filtration (celite), the solvent was removed under reduced pressure to give the crude aminoester hydrochlorides as brownish powders.

(2*R*, 3*S*)-Methyl 2-amino-4,4,4-trifluoro-3-hydroxybutanoate (19a). Using the general procedure **GP II**, the hydrazinoester hydrochloride **18a**·HCl (1.19 g, 5 mmol) was hydrogenated with 100 mg of $PtO_2 \cdot H_2O$ over 5 d. After evaporation of the solvent, the resulting powder was dissolved in a mixture of 50 ml saturated $NaHCO_3$ solution /50 ml ether. The aqueous layer was extracted twice with 50 ml portions of ether, the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. FC (ethyl acetate/ether 1:1) of the colorless, amorphous product gave the aminoester **19a** (578 mg, 62 %) as fine needles. M.p.: 116.0-117.0 °C; $[\alpha]_D^{RT}$ = -25.0 (c = 1.15, EtOH); IR (KBr): 3390*m*, 3320*w*, 3080*br.*, 2960*w*, 2930*w*, 2820*br.*, 2720*br.*, 1730*s*, 1725*s*, 1585*m*, 1440*m*, 1390*w*, 1375*m*, 1340*m*, 1290*s*, 1265*m*, 1235*s*, 1200*s*, 1180*s*, 1165*s*, 1155*s*, 1125*s*, 1090*s*, 1025*s*; ^{1}H NMR (300 MHz, CD_3OD): 3.72 (*d*, *J* = 5.9, H-C(2)), 3.74 (*s*, CH_3), 4.19 (*qd*, *J* = 7.2, 5.9, H-C(3)), 4.86 (*br.*, OH, NH); ^{13}C NMR (75 MHz, CD_3OD): 52.70 (CH_3), 56.54 (CH), 72.52 (*q*, *J* (C,F) = 30.0), 126.24 (*q*, *J* (C,F) = 283.0), 173.51 (C); ^{19}F NMR (282.2 MHz, CD_3OD): -76.24 (*d*, *J* = 7.2); MS: 188 (35, $[M+1]^+$), 128 (100), 118 (11), 88 (93), 80 (56), 69 (9), 60 (21), 59 (65), 58 (17), 48 (14), 42 (12), 33 (61), 30 (35), 29 (34), 28 (67); Anal. Calcd. for $C_5H_8F_3NO_3$ (187.11): C, 32.10; H, 4.31; N, 7.49; F, 30.46; Found: C, 32.11; H, 4.40; N, 7.56; F, 30.42.

(2*S*, 3*R*)-Methyl 2-amino-4,4,4-trifluoro-3-hydroxybutanoate (ent-19a). Following **GP I**, dioxanone *ent*-**16a** (4.53 g, 20 mmol) was treated with *t*-BuLi (14.2 ml, 22 mmol) and DBAD (4.6 g, 20 mmol). After work-up the yellow oil was carefully dried *in vacuo* (a sticky foam!) whereby a yellowish, glassy product (9.25 g, 97%) was isolated which, according to ^{1}H NMR, was essentialy pure. This product was treated with 100 ml of a cold saturated solution of HCl in methanol. The solution was held at 0 °C for 5 h (monitored by TLC), the solvent was removed under reduced pressure and the hydrochloride (5.52 g) was obtained as a yellow powder. Using **GP II**, this material was hydrogenated in 60 ml of methanol with 1.2 g of $PtO_2 \cdot H_2O$ over 24 h. After evaporation of the solvent, the resulting powder was dissolved in a mixture of 50 ml saturated $NaHCO_3$ solution /50 ml ether. The aqueous layer was extracted three times with 50 ml portions of ether, the combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. FC (ether) of the yellow oil afforded the aminoester *ent*-**19a** (1.39 g, 37 %) as a colorless solid. M.p.: 32.5-33.7 °C; $[\alpha]_D^{RT}$ = +25.5 (c = 1.02, EtOH).

(2*R*, 3*S*)-Methyl 2-amino-4,4,4-trifluoro-3-hydroxy-3-methylbutanoate (19b). Using the general procedure **GP II**, the hydrazinoester hydrochloride **18b**·HCl (5.6 g, ca. 16 mmol) was hydrogenated in 50 ml of methanol with 273 mg of $PtO_2 \cdot H_2O$ over 3 d. After evaporation of the solvent, the resulting powder was dissolved in a mixture of 50 ml saturated $NaHCO_3$ solution /50 ml ether. The aqueous layer was extracted twice with 50 ml portions of ether, the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Bulb-to-bulb distillation (0.01 Torr/50 °C) of the yellow oil gave the aminoester **19b** (1.62 g, 50.3 %) as a colorless solid. M.p.: 32.0-33.2 °C; $[\alpha]_D^{RT}$ = -25.5 (c = 1.46, EtOH); IR ($CHCl_3$): 3420*m*, 3345*w*, 2955*m*, 1745*s*, 1605*w*, 1460*m*, 1450*m*, 1440*m*, 1405*m*, 1380*m*, 1345*m*, 1275*s*, 1180*s*, 1155*s*, 1090*s*, 1020*w*, 995*m*, 945*w*; ^{1}H NMR (300 MHz): 1.54 (*q*, *J* = 1.0, CH_3), 2.10-3.60 (*br.*, 3H, OH, NH_2), 3.45 (*d*, *J* = 1.0, H-C(2)), 3.79 (*s*, OCH_3); ^{13}C NMR (75 MHz): 19.91 (CH_3), 52.67 (CH_3), 59.21 (CH), 72.90 (*q*, *J* (C,F) = 27.5), 125.79 (*q*, *J* (C,F) = 288.0), 172.25 (C); ^{19}F NMR (282.2 MHz): -79.18 (*t*, *J* = 1.0); MS: 202 (2, $[M+1]^+$), 142 (45), 89 (10), 88 (100), 74 (11), 69 (4), 43 (19), 33 (25), 28 (28), 15 (8); Anal. Calcd. for $C_6H_{10}F_3NO_3$ (201.14): C, 35.83; H, 5.01; N, 6.96; Found: C, 35.54; H, 4.70; N, 6.50.

(2*R*, 3*S*)-Methyl 2-amino-3-trifluoromethyl-3-hydroxyheptanoate (19c). Using the general procedure **GP II**, the hydrazinoester hydrochloride **18c**·HCl (1.73 g, ca. 5.8 mmol) was hydrogenated in 30 ml of methanol with 120 mg of $PtO_2 \cdot H_2O$ over 3 d. After evaporation of the solvent, the resulting powder was dissolved in a mixture of 50 ml saturated $NaHCO_3$ solution /50 ml ether. The aqueous layer was extracted three times with 50 ml portions of ether, the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. FC (ether/pentane 1:2) followed by bulb-to-bulb distillation (0.01 Torr/50 °C) of the oil gave the aminoester **19c** (160.7 mg, 11.4 %) as a colorless oil. $[\alpha]_D^{RT}$ = -32.8 (c = 1.50, EtOH); IR ($CHCl_3$): 3415*w*, 3345*br.*, 2960*m*, 2935*m*, 2875*w*, 1745*s*, 1615*w*, 1455*w*, 1435*m*, 1410*m*, 1320*m*, 1275*s*, 1260*s*, 1180*s*, 1150*s*, 1110*m*, 1095*m*, 1015*m*; ^{1}H NMR (300 MHz): 0.95 (*t*, *J* = 7.2, CH_3), 1.28-1.65 (*m*, 4H), 1.83-1.92 (*m*, 2H), 1.20-2.20 (*br.*, 2H, NH_2), 3.60 (*s*, H-C(2)), 3.78 (*s*, OCH_3), 5.01-5.62 (*br.*, 1H, OH); ^{13}C NMR (75 MHz): 13.95 (CH_3), 22.98 (CH_2), 24.47 (CH_2), 30.91 (CH_2), 52.63 (CH_3), 55.91 (CH), 74.69 (*q*, *J* (C,F) = 26.0), 126.09 (*q*, *J* (C,F) = 288.0), 172.08 (C); ^{19}F NMR (282.2 MHz): -78.07 (*s*); MS: 244 (4, $[M+1]^+$), 184 (15), 174 (4), 127 (4), 88 (100), 74 (14), 69 (3), 57 (16), 41 (12), 33 (19), 29 (19), 28 (25), 27 (10); Anal. Calcd. for $C_9H_{16}F_3NO_3$ (243.22): C, 44.44; H, 6.63; N, 5.76; Found: C, 44.55; H, 6.94; N, 5.69.

(2*R*, 3*S*)-Methyl 2-amino-4,4,4-trifluoro-3-hydroxy-3-phenylbutanoate (19d). Using the general procedure **GP II**, the hydrazinoester hydrochloride **18d**·HCl (347 mg, 1 mmol) was hydrogenated in 20 ml of methanol with 50 mg of $PtO_2 \cdot H_2O$ over 4 d. After evaporation of the solvent, the resulting powder was dissolved in a mixture of 20 ml saturated $NaHCO_3$ solution /20 ml ether. The aqueous layer was extracted three times with 30 ml portions of ether, the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The resulting colorless oil (273 mg, according to ^{1}H NMR analysis a mixture of the desired aminoester **19d** and the corresponding cyclohexyl derivative) was purified by FC (ether/pentane 1:1) followed by bulb-to-bulb distillation (0.01 Torr/40 °C) to give the aminoester **19d** (112.0 mg, 38.8 %) as a colorless solid. M.p.: 83.5-84.5 °C; $[\alpha]_D^{RT}$ = -28.5 (c = 0.94, EtOH); IR (KBr): 3440*m*, 3395*m*, 3325*m*, 2950*w*, 1730*s*, 1715*s*, 1600*w*, 1455*m*, 1440*m*, 1335*m*, 1385*m*, 1270*m*, 1210*s*, 1180*s*, 1060*s*, 1075*m*, 970*m*; ^{1}H NMR (300 MHz): 1.05-1.80 (*br.*, 2H, NH_2), 3.83 (*s*, OCH_3), 4.06 (*s*, H-C(2)), 4.60-5.40 (*br.*, OH), 7.36-7.50 (*m*, 3 *arom.* H), 7.58-7.68 (*m*, 2 *arom.* H); ^{13}C NMR (75 MHz): 52.89 (CH_3), 56.61 (CH), 78.53 (*q*, *J* (C,F) = 28.5), 124.92 (*q*, *J* (C,F) = 288.0), 126.48 (CH), 128.64 (CH), 129.03 (CH), 134.76 (C), 173.64 (C); ^{19}F NMR (282.2 MHz): -76.41 (*s*); MS: 264 (0.4, $[M+1]^+$), 204 (8), 186 (4), 166 (3), 117 (5), 105 (18), 89 (48), 88 (100), 77 (15), 74 (14), 69 (3), 57 (11), 33 (16), 28 (21); Anal. Calcd. for $C_{11}H_{12}F_3NO_3$ (263.21): C, 50.20; H, 4.60; N, 5.32; Found: C, 50.26; H, 4.79; N, 5.15.

(4*R*, 5*S*)-3-(*tert*-Butyloxycarbonyl)-5-methyl-5-trifluoromethyl-4-(methoxycarbonyl)-oxazolidin-2-one (20). The aminoester **19b** (1.0 g, 5 mmol) was dissolved in 15 ml of CH_2Cl_2 and DMAP[43] (61 mg) and di-*tert*-butyldicarbonate (2.4 g, 11 mmol) were added. After 30 min at rt, the clear yellow solution was evaporated under reduced pressure. FC (ether/pentane 1:3) of the resulting yellow solid gave **20** (1.1 g, 73 %), wich was sublimed (0.01 Torr/80 °C) for analytical purposes. M.p.: 128.5-129.5 °C; $[\alpha]_D^{RT}$ = +29.0 (c = 0.99, EtOH); IR (KBr): 2980*w*, 1845*s*, 1820*s*, 1770*s*, 1735*m*, 1455*w*, 1430*m*, 1395*m*, 1370*s*, 1315*s*, 1260*s*, 1220*s*, 1210*s*, 1160*s*, 1110*s*, 1070*s*, 1020*m*, 975*m*, 960*m*; ^{1}H NMR (300 MHz): 1.52 (*s*, *t*-Bu), 1.79 (*d*, *J* = 1.0, CH_3), 3.83 (*s*, OCH_3), 4.61 (*s*, H-C(4)); ^{13}C NMR (75 MHz): 21.48 (CH_3), 27.81 (CH_3), 53.35 (CH_3), 63.42 (CH), 78.53 (*q*, *J* (C,F) = 32.5), 85.75 (C), 122.54 (*q*, *J* (C,F) = 284.0), 148.03 (C), 148.52 (C), 165.42 (C); ^{19}F NMR (282.2 MHz): -78.46 (*s*); MS: 312 (0.9), 268 (1), 254 (4), 228 (14), 168 (11), 104 (5), 86 (3), 69 (1), 59 (18), 57 (100), 43 (6), 41 (15), 28 (13); Anal. Calcd. for $C_{12}H_{16}F_3NO_6$ (327.26): C, 44.04; H, 4.93; N, 4.28; Found: C, 44.00; H, 4.85; N, 4.13.

(4*R*, 5*S*)-3-(*tert*-Butyloxycarbonyl)-5-trifluoromethyl-5-phenyl-4-(methoxycarbonyl)-oxazolidin-2-one (21). The aminoester **19d** (30 mg, 0.11 mmol) was dissolved in 1 ml of CH_2Cl_2 and DMAP[43] (2.5 mg) and di-*tert*-butyldicarbonate (52 mg, 0.24 mmol) were added. After 1 h at rt, the clear colorless solution was evaporated under reduced pressure. FC (ether/pentane 1:4) of the resulting oil gave **21**

(39.7 mg, 95 %) as a colorless liquid. ^{1}H NMR (300 MHz): 1.49 (*s*, *t*-Bu), 3.94 (*s*, OCH_3), 5.08 (*s*, H-C(4)), 7.49-7.52 (*m*, 3 *arom.* H), 7.69-7.72 (*m*, 2 *arom.* H); ^{13}C NMR (75 MHz): 27.76 (CH_3), 53.60 (CH_3), 64.71 (CH), 77.20 (*q*, *J* (C,F) = 32.0), 85.84 (C), 121.89 (*q*, *J* (C,F) = 284.5), 126.02 (CH), 129.11 (CH), 130.54 (CH), 133.50 (C), 147.80 (C), 148.17 (C), 165.72 (C); ^{19}F NMR (282.2 MHz): -75.78 (*s*).

(2*R*, 5*R*, 6*S*)-5-(Isopropylidene-hydrazino)-6-trifluoromethyl-1,3-dioxan-4-one hydrochloride (23). In a 50 ml, two necked flask, a solution of hydrazino dioxanone **17a** (2.28 g, 5 mmol) and *tert*-butanol (1.12 g) in 20 ml CH_2Cl_2 was cooled to 0 °C. HCl gas was bubbled into the solution for 1 h. The resulting yellow supension was evaporated and the residue (1.36 g) was dissolved in a small amount of ether. A white solid was precipitated by the addition of pentane. After filtration, the white residue (800 mg) was dissolved in 50 ml acetone, heated to reflux and then cooled in an ice bath. The white crystals were filtered and dried *in vacuo* to give **23** (450 mg, 27 %). M.p.: 165.0-167.0 °C (decomp.); $[\alpha]_D^{RT}$ = +24.5 (c = 0.96, EtOH); IR (KBr): 3420*br.*, 3140*m*, 2965*m*, 2620*br.*, 1755*s*, 1690*w*, 1485*m*, 1430*m*, 1400*m*, 1370*m*, 1360*m*, 1280*s*, 1240*s*, 1225*s*, 1200*s*, 1155*s*, 1085*s*, 1040*m*, 995*s*, 955*m*; ^{1}H NMR (300 MHz, d_6-DMSO): 0.95 (*s*, *t*-Bu), 2.02 (*s*, CH_3), 2.13 (*s*, CH_3), 4.43 (*d*, *J* = 9.9, H-C(5)), 5.04 (*dq*, *J* = 9.9, 6.0, H-C(6)), 5.48 (*s*, H-C(2)), 8.20-11.00 (*br.*, 1H, NH); ^{13}C NMR (75 MHz, d_6-DMSO): 17.64 (CH_3), 23.21 (CH_3), 23.32 (CH_3), 34.51 (C), 54.35 (CH), 73.29 (*q*, *J* (C,F) = 30.5), 105.89 (CH), 122.94 (*q*, *J* (C,F) = 281.0), 157.95 (C), 167.19 (C); ^{19}F NMR (282.2 MHz, d_6-DMSO): -74.93 (*d*, *J* = 6.0); MS: 298 (24), 297 (100), 239 (13), 211 (14), 166 (15), 165 (7), 154 (5), 123 (6), 71 (14), 69 (3), 57 (12), 56 (21); Anal. Calcd. for $C_{12}H_{20}ClF_3N_2O_3$ (332.74): C, 43.32; H, 6.06; N, 8.42; Found: C, 43.31; H, 5.92; N, 8.36.

(2*R*, 5*R*, 6*S*)-2-(*tert*-Butyl)-5-(*N*,*N*'-bis-(benzyloxycarbonyl)-hydrazino)-6-trifluoromethyl-1,3-dioxan-4-one (24). Following **GP I**, dioxanone **16a** (4.53 g, 20 mmol) was treated with *t*-BuLi (14.2 ml, 22 mmol) and dibenzyl azodicarboxylate (8.36 g, 28 mmol) in 100 ml of CH_2Cl_2. After work-up, the viscous oil was carefully dried for 12 h *in vacuo* whereby a yellowish oil (12.0 g) was isolated. FC (ether/pentane 1:3) gave 4.81 g (61% yield) of an amorphous compound. Recrystallization (from pentane/ether 1:1) of a small sample yielded the analytically pure compound **24** as colorless crystalls. M.p.: 123.5-124.0 °C; $[\alpha]_D^{RT}$ = +30.2 (c = 1.03, EtOH); IR (KBr): 3290*br.*, 2960*m*, 1755*s*, 1585*w*, 1495*m*, 1485*m*, 1455*m*, 1405*m*, 1370*m*, 1340*s*, 1275*s*, 1240*s*, 1220*s*, 1195*s*, 1145*s*, 995*s*, 695*s*; ^{1}H NMR (300 MHz, d_6-DMSO, 80 °C): 0.93 (*s*, *t*-Bu), 4.88 (*dq*, *J* = 9.4, 5.5, H-C(6)), 4.95-5.17 (*m*, 5H, -CH_2-Ph, H-C(5)), 5.31 (*s*, H-C(2)), 7.27-7.33 (*m*, 10 *arom.* H), 9.50-9.80 (*br.*, NH); ^{13}C NMR (75 MHz, d_6-DMSO, 80 °C): 23.28 (CH_3), 34.60 (C), 56.30 (CH), 66.68 (CH_2), 68.20 (CH_2), 72.86 (*q*, *J* (C,F) = 31.0), 106.12 (CH), 122.70 (*q*, *J* (C,F) = 281.0), 127.18-128.44 (*arom.* CH), 135.51 (C), 136.12 (C), 154.73 (C), 156.25 (C), 163.02 (C); MS: 525 (8, $[M+1]^+$), 424 (22), 423 (80), 271 (14), 215 (29), 182 (11), 181 (64), 107 (13), 92 (70), 91 (100), 77 (11), 69 (7), 65 (35), 57 (28), 41 (17), 39 (12); Anal. Calcd. for $C_{25}H_{27}F_3N_2O_7$ (524.49): C, 57.25; H, 5.19; N, 5.34; Found: C, 57.12; H, 5.27; N, 5.25.

REFERENCES AND NOTES

1. Part of the Master Thesis (Diplomarbeit) of A. R. Sting, ETH Zürich, 1992. Some of the results described here were mentioned in previous papers on the chemistry of trifluoro-hydroxybutanoic acid, see ref. [30].
2. *Fluorine-containing Amino Acids, Synthesis and Properties*; Kukhar, V. P.; Soloshonok, V. A., Eds.; J. Wiley and Sons: New York, 1995; *Biomedical Aspects of Fluorine Chemistry*; Filler, R.; Kobayashi, Y., Eds.; Kodansha Ltd.: Tokyo and Elsevier Biomedical: Amsterdam, 1982.
3. *Fluorine in Bioorganic Chemistry*; Welch, J. T.; Eswarakrishnan, S. Eds.; J. Wiley and Sons: New York, 1991; *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. Eds.; Elsevier: Amsterdam, 1993.
4. Ojima, I.; Kato, K.; Nakahashi, K.; Fuchikami, T.; Fujita, M. *J. Org. Chem.* **1989**, *54*, 4511-4522, see ref. 5 therein.
5. Welch, J. T. *Tetrahedron* **1987**, *43*, 3123-3197.
6. Walborsky, H. M.; Baum, M. E. *J. Am. Chem. Soc.* **1958**, *80*, 187-192.
7. Scolastico, C.; Conca, E.; Prati, L.; Guanti, G.; Banfi, L.; Berti, A.; Farina, P.; Valcavi, U. *Synthesis* **1985**, 850-855.
8. Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron* **1988**, *44*, 5553-5562.
9. Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237-261.
10. von dem Bussche-Hühnefeld, C.; Seebach, D. *Chem. Ber.* **1992**, *125*, 1273-1281.
11. Kitazume, T.; Tain Lin, J.; Yamazaki, T. *Tetrahedron: Asymmetry* **1991**, *2*, 235-238.
12. Shimizu, M.; Yokota, T.; Fujimori, K; Fujisawa, T. *Tetrahedron: Asymmetry* **1993**, *4*, 835-838.
13. Soloshonok, V. A.; Kukhar, V. P.; Gaiushko, S. V.; Svistunova, N. Y.; Avilov, D. V.; Kuz'mina, N. A.; Raevski, N. I.; Struchkov, Y. T.; Pyrsarevsky, A. P.; Belokon, Y. N. *J. Chem. Soc. Perkin Trans.I.* **1993**, 3143-3155.
14. Soloshonok, V. A.; Hayashi, T.; Ishikawa, K.; Nagashima, N. *Tetrahedron Lett.* **1994**, *35*, 1055-1058.

15. Müller, H. M.; Seebach, D. *Angew. Chem.* **1993**, *105*, 483-509; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 477-502; Seebach, D.; Beck, A. K.; Breitschuh, R.; Job, K. *Org. Synth.* **1992**, *71*, 39-47.
16. Seebach, D.; Roggo, S.; Zimmermann, J. in *Stereochemistry of Organic and Bioorganic Transformations*; Bartmann, W.; Sharpless, K.B. Eds.; Workshop Conferences Hoechst, VCH Verlagsgesellschaft: Weinheim, 1987, Vol 17, pp. 85-126; Seebach, D.; Sutter, M. A.; Weber; R. H.; Züger, M. F. *Org. Synth.* **1984**, *63*, 1-9, ibid **1990**, Collective Vol. VII, 215-220.
17. Noyori, R.; Okhuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856-5858.
18. Seebach, D.; Zimmermann, J. *Helv. Chim. Acta* **1986**, *69*, 1147-1152.
19. Seebach, D.; Misslitz, U.; Uhlmann, P. *Angew. Chem.* **1989**, *101*, 484-485; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 472-473; Seebach, D.; Misslitz, U.; Uhlmann, P. *Chem. Ber.* **1991**, *124*, 1845-1852.
20. Beck, A. K.; Brunner, A.; Montanari, V.; Seebach, D. *Chimia* **1991**, *45*, 379-382.
21. Beck, A. K.; Gautschi, M.; Seebach, D. *Chimia* **1990**, *44*, 291-295.
22. For a short review, see: Beck, A. K.; Seebach, D. in *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L.A. Ed.-in-Chief; J. Wiley and Sons: Chichester, in press.
23. Seebach, D.; Imwinkelried, R.; Weber, T. in *Modern Synthetic Methods 1986*; Scheffold, R. Ed.; Springer Verlag: Berlin, 1986, Vol. 4, pp. 125-259.; Sting, A. R.; Seebach, D. *Angew. Chem.*, in preparation.
24. Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria Jr., J. F. *Tetrahedron* **1988**, *44*, 5525-5540.
25. Gennari, G.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394-6395.
26. Genet, J. P.; Juge, S.; Mallart, S. *Tetrahedron Lett.* **1988**, *29*, 6765-6768; Greck, C.; Bischoff, L.; Ferreira, F.; Pinel, C.; Piveteau, E.; Genet, J. P. *Synlett* **1993**, 475-477.
27. Trimble, L. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 6397-6399.
28. Oppolzer, W.; Moretti, R. *Tetrahedron* **1988**, *44*, 5541-5552.
29. Estermann, H.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1824-1839.
30. Gautschi, M.; Seebach, D. *Angew. Chem.* **1992**, *104*, 1061-1062; *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1083-1085; Gautschi, M.; Schweizer, W. B.; Seebach, D. *Chem. Ber.* **1994**, *127*, 565-579.
31. Acs, M.; von dem Bussche, C.; Seebach, D. *Chimia* **1990**, *44*, 90-92.
32. Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc. Trans.* **1915**, *107*, 1080-1106.
33. Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224-232.
34. Souppe, J.; Danon, L.; Namy, J. L.; Kagan, H. B. *J. Organomet. Chem.* **1983**, *250*, 227-236; Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266-6267..
35. Zimmermann, J.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1143-1155.
36. Amberg, W.; Seebach, D. *Chem. Ber.* **1990**, *123*, 2429-2438.
37. Seebach, D. *Angew. Chem.***1990**, *102*, 1362-1409; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1320-1367.
38. For instance, when built into the decapeptide LH-RH ("luteinizing hormone-releasing hormone"): Dutta, A. S.; Morley, J. S. *J. Chem. Soc. Perkin Trans.I.* **1975**, 1712-1720; Gante, J. *Chem. Ber.* **1965**, *98*, 3340-3344; Gante, J. *Synthesis* **1989**, 405-413; Dutta, A. S.; Furr, B. J. A.; Giles, M. B.; Valcaccia, B. *J. Med. Chem.* **1978**, *21*, 1018-1024; Dutta, A. S.; Furr, B. J. A.; Giles, M. B. in *Peptides, Proceedings of the Fifth American Peptide Symposium*, Goodman, M.; Meienhofer, J., Eds.; J. Wiley and Sons: New York, 1977; pp.189-192; *Specialist Periodical Reports, Amino Acids, Peptides and Proteins*; Sheppard, R. C., Ed.; Vol. I-XII, Chemical Society: London, 1969-1981.
39. March, J. *Advanced Organic Chemistry*; 3rd. Ed., J. Wiley & Sons: New York, 1985; p. 221.
40. Chambers, R. D. *Fluorine in Organic Chemistry*; Wiley Interscience Publication: New York, 1973, p. 66.
41. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R., in *Vogel's Textbook of Practical Organic Chemistry*; 5th Ed., Longman Scientific & Technical: Burnt Mill, Harlow, Essex, 1989, pp. 442-444.
42. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.
43. Grehn, L.; Ragnarsson, K. *Angew. Chem.* **1985**, *97*, 519-520; *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 510-511.

(*Received* 30 *June* 1995)