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Efficient synthesis and resolution of (±)-1-[2-carboxy-6-(trifluoromethyl)phenyl]pyrrole-2-carboxylic acid

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Abstract

A novel, efficient synthesis and resolution of (±)-1-[2-carboxy-6-(trifluoromethyl)-phenyl]pyrrole-2-carboxylic acid has been developed for the preparation of new members of optically active atropisomers. The e.e. values were determined by a highly sensitive ^{19}F NMR spectroscopic method using β-cyclodextrin as chiral complexing agent. Single-crystal X-ray structures of the two diastereoisomeric salts and consequently, the absolute configurations of the enantiomers are also reported. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

In recent years C_2-symmetric optically active compounds have been recognized as efficient inducers for asymmetric synthesis.[1,2] The derivatives of (*R,R)*-tartaric acid (e.g. TADDOL[3]) and 2,2′-binaphthol[4] are among the widely used chiral ligands. The 2,2′-binaphthol derivatives are the well known members of C_2-symmetric atropisomers. Recently, we have published the preparation and the structure of (±)-1-[2-carboxy-6-(trifluoromethyl)phenyl]pyrrole-2-carboxylic acid **1**, a new asymmetric representative of atropisomeric compounds.[5] Single-crystal X-ray diffraction measurements confirmed that **1** exists as a racemate (a one to one molecular compound of the two enantiomeric conformers) in the crystals. The activation energy of isomerization is about 290 kJ/mol according to molecular modeling calculations.[5] Consequently, the enantiomers should be stable in solution at ordinary temperatures and the optically active

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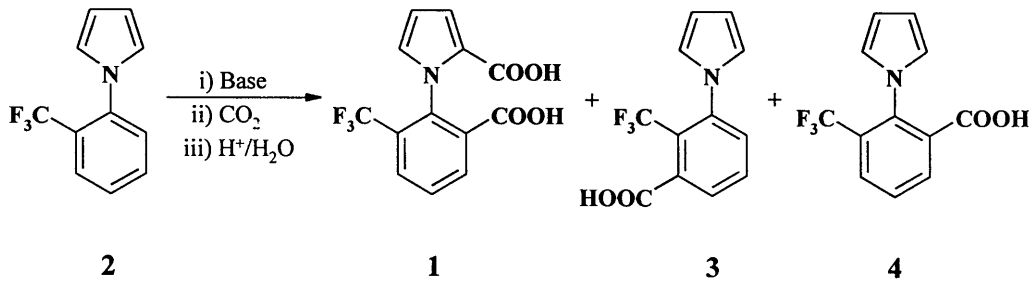
isomers of **1** could be used as new resolving agents or key intermediates for novel chiral ligands if we found a suitable method for resolution of the racemate. On the other hand, the efficiency of the synthesis of (±)-**1** should also be improved. Dilithiation of 1-[2-(trifluoromethyl)phenyl]pyrrole **2** with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) activated butyllithium (LiC) followed by dry ice quenching provided us an approximately one to one mixture of the dicarboxylic acid **1** and a monocarboxylic acid **3**.[5] Separation and purification of the products could not be carried out without significant waste of **1**.

In order to find more efficient methods for selective synthesis and resolution of (±)-**1**, a systematic investigation of the dimetallation as well as trials for the enantiomer separation were accomplished in our laboratory.

2. Results and discussion

*2.1. Selective method for the preparation of (±)-**1***

Changes on the solvent compositions from diethyl ether to neat hexane during metallation of **2** with LiC-TMEDA reagent at 0°C did not result in a better product ratio than the original synthesis.[5] A 52:48 mixture of the two acids (**1** and **3**) was isolated after dry ice quenching (Scheme 1., Table 1).



Scheme 1.

In the next run we looked for other metallating agents such as potassium *tert*-butoxide (KOR) activated lithium 2,2,6,6-tetramethylpiperidide (LiTMP-KOR reagent) and butyllithium (LiC-KOR, Schlosser's base[6]), respectively. The reaction conditions and results are summarized in Table 1. The LiTMP-KOR reagent improves the selectivity of dimetallation: even in tetrahydrofuran at −75°C; a 78:22 mixture of **1** and **3** could be obtained (Table 1, line 2). Metallations with LiC-KOR superbase and consecutive reactions with dry ice yielded mixtures of three acids **1**, **3** and **4**. The product distribution strongly depended on the reaction temperature and the type of solvent. The organometallic intermediate of **4** might be a precursor of the intermediate of **1** because the relative amount of **1** increased at the expense of **4** when a larger amount of LiC-KOR was used (Table 1, lines 3 versus 4 and 9 versus 10). In a series of experiments in diethyl ether the same concentrations of the reagents and 1 hour reaction time were used, but the temperature was systematically changed from −75 to 0°C, thus the optimum temperature of the metallation was determined (at about −40°C, lines 5–11). The fine tuning of

Table 1
Reaction conditions and results of dimetallation and carboxylation of **2**

No.	Solvent[a]	Temperature (°C)	Base (molar ratio[b])	Products after carboxylation (ratio)	Total yield of the products[c] (%)
1	HEX	0	LiC-TMEDA (2.0)	**1**+**3** (52:48)	72
2	THF	−75	LiTMP-KOR (2.0)	**1**+**3** (78:22)	26
3	THF	−75	LiC-KOR (1.0)	**1**+**3**+**4** (28:22:50)	65
4	THF	−75	LiC-KOR (2.0)	**1**+**3**+**4** (57:19:24)	86
5	Et_2O	−75	LiC-KOR (2.0)	**1**+**3**+**4** (45:4:51)	64
6	Et_2O	−55	LiC-KOR (2.0)	**1**+**3**+**4** (73:4:23)	53
7	Et_2O	−40	LiC-KOR (2.0)	**1**+**3**+**4** (73:5:22)	83
8	Et_2O	−25	LiC-KOR (2.0)	**1**+**3**+**4** (72:15:13)	66
9	Et_2O	0	LiC-KOR (2.0)	**1**+**3**+**4** (75:13:13)	42
10	Et_2O	−40	LiC-KOR (2.5)	**1**+**3**+**4** (96:2:2)	74
11	Et_2O	−40	LiC-KOR (3.0)	**1**+**3**+**4** (94:3:3)	80

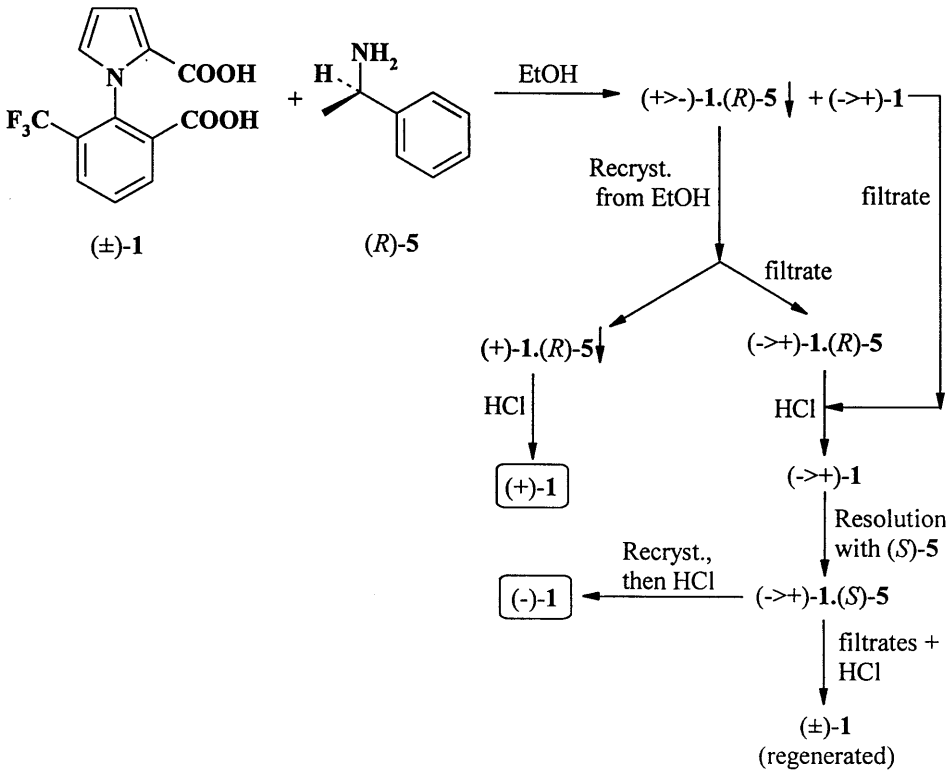
[a] HEX = hexane, THF = tetrahydrofuran, Et_2O = diethyl ether; butyllithium was added to the reaction mixtures as a 15% hexane solution in each case.
[b] Molar ratio is related to the substrate **2**.
[c] The reaction time of metallation was 1 hour in each case.

the reaction conditions finally let us prepare the target compound **1** with 94–96% selectivity (2–3% of **3** and **4** were present in the crude product; Table 1, lines 10 and 11).

2.2. Resolution of (±)-*1*

One of the simplest methods for the separation of carboxylic acid enantiomers is diastereoisomeric salt formation with an optically active amine. Selection of the best resolving agent among the commercially available chiral amines could easily be carried out by thermoanalytical investigations of the diastereoisomeric salt mixtures,[7,8] if we could observe the separate melting peaks of the euthectic mixture and the residue of the salt having the higher melting point. Unfortunately, every diastereoisomeric salt mixture of (±)-**1** with (*R*)-α-methylbenzylamine **5**, (*S*)-α-naphthylethylamine, (*S*)-α-hydroxymethylbenzylamine and (*R*,*R*)-2-amino-1-phenyl-1,3-propanediol decomposed before the melting temperature, therefore we could not determine the euthectic compositions by differential scanning calorimetry. On the other hand, the crystallization trials were successful when the ethanol solutions of (±)-**1** and (*R*)-**5** were mixed with each other. We achieved the best separation with a half molar equivalent amount of (*R*)-**5**. In this case the other half of the free acid **1** remained in the ethanol solution (Scheme 2).

The precipitated diastereomeric salt contained the (+)-**1** enantiomer in excess. The salt was recrystallized from ethanol, then the optically active acid was liberated in ethyl acetate with aqueous hydrochloric acid. The (−)-**1** isomer was obtained by the resolution of (->+)-**1** (which was regenerated from the filtrates of the first salt formation reaction and of the recrystallization). The salt formation and recrystallization conditions were the same as above, but (*S*)-**5** was used as resolving agent (Scheme 2). The results of two resolution processes are summarized in Table 2. The efficiency[9] ('*S*') of these separations ('*S*' = yield×e.e.) is about 28% and the unresolved acid **1** could be regenerated with 80% yield.



Scheme 2.

Table 2
Resolution of **1** with (*R*)- and (*S*)-α-methylbenzylamine **5**

Starting material **1**			Resolving agent **5**		Product **1**			Efficiency
(mmol)	Config.	E.e. (%)	(mmol)	Config.	Yield (%)	Config.	E.e. (%)	(*S*) (%)
10.7	*R,S*	0	5.3	*R*	22	*S*	99	22
7.9	*R>S*	32	4.6	*S*	33	*R*	93	31
26.8	*R,S*	0	13.4	*R*	32	*S*	99	32
20.4	*R>S*	22	13.0	*S*	30	*R*	98	29

2.3. Determination of the enantiomeric excess values of (+)-1 and (–)-1

The enantiomeric purity of compound **1** was determined by solution state ^{19}F NMR spectroscopy using a more recent technique which uses β-cyclodextrin as chiral complexing agent instead of lanthanide shift reagents. Cyclodextrins (cyclic oligomers of 1-4 linked α-D-glu copyranoses) are available in the so called α-, β- and γ-forms depending on the number of glucopyranose units 6, 7 and 8 linked together, respectively. When dissolved in water they adopt a conical shaped conformation and form a hydrophobic internal cavity which traps hydrophobic moieties of the guest molecules.[10] Formation of inclusion complexes with the analyte results in the formation of transient diastereomeric complexes, which is a fast process on the chemical

shift time scale. This leads to the discrimination of enantiomers according to their inherently different chemical shifts in their complexes, which affects the observed chemical shifts under fast exchange conditions.[11]

Since cyclodextrins do not contain fluorine atoms due to practical considerations concerning selectivity and sensitivity of the NMR measurements, it was reasonable to find a cyclodextrin–analyte system that resolves the CF_3 groups of the enantiomers. However, the internal diameter of the cyclodextrin-cavity that increases in the $\alpha<\beta<\gamma$ order influences the statistical distribution of the possible orientations of the enantiomers relative to the cyclodextrin, hence the average chemical shift of the resonances of the guest molecules. For compound **1** β-cyclodextrin has induced a shift difference (called shift non-equivalence) large enough to achieve baseline separation of the CF_3 resonances of the optical isomers at the available spectrometer frequency (500 MHz for ^1H). Fig. 1 shows the 470 MHz ^{19}F NMR spectra of three samples with different optical composition in the presence of β-cyclodextrin in D_2O.

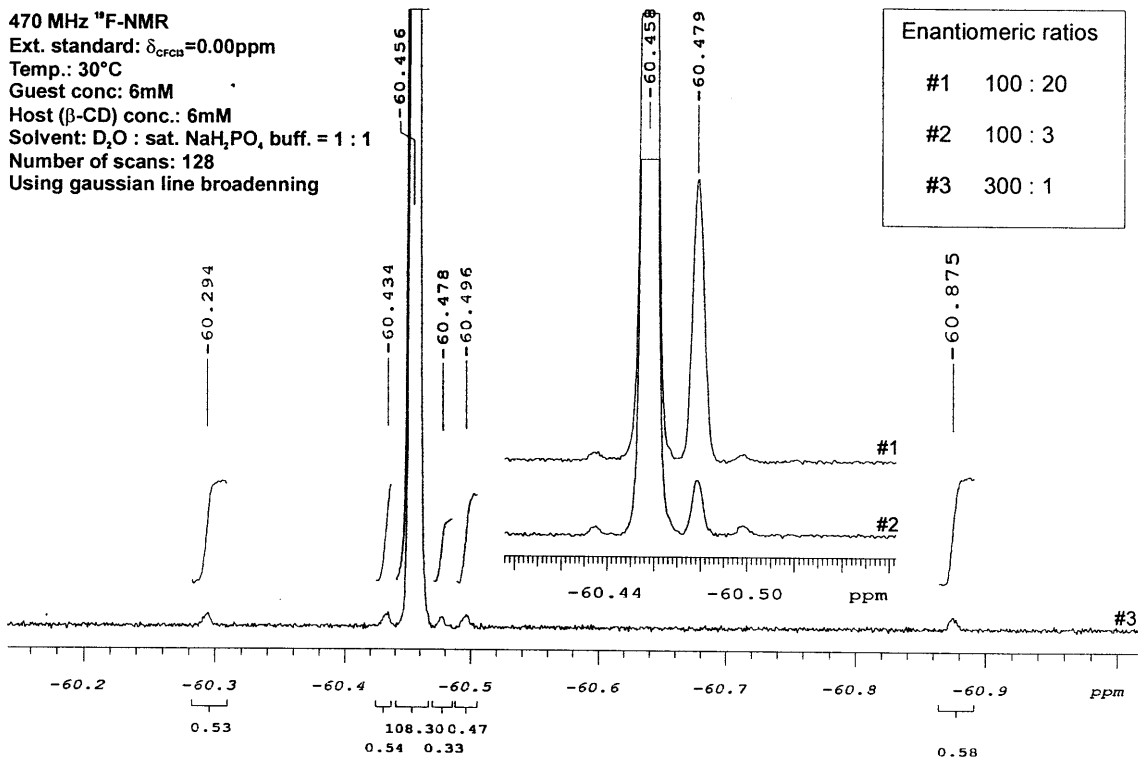
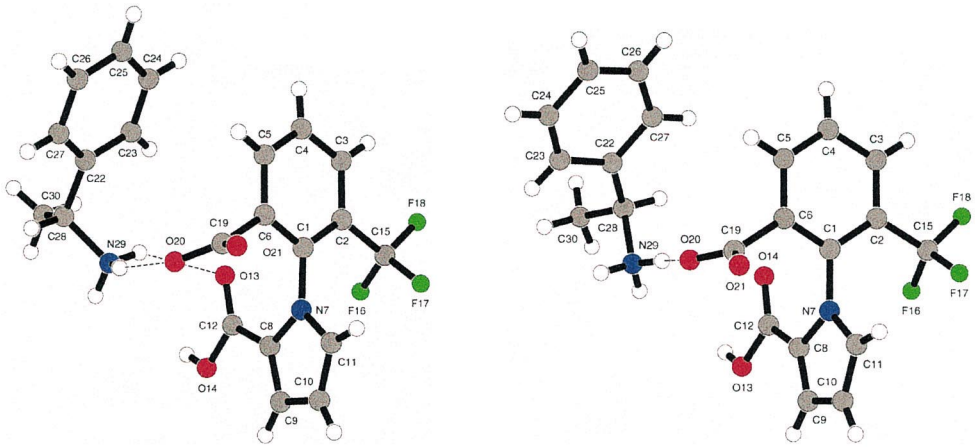


Figure 1. Determination of the e.e. values of **1** by ^{19}F NMR spectroscopy

Resonance line of the major optical component of sample #3 prepared for single-crystal X-ray crystallography is found at −60.457±0.001 ppm, whereas that of its optical impurity is at −60.478±0.001 ppm. In cases of #1 and #2 enantiomeric ratios were measured by the integration of the corresponding resonances of the optical isomers, but for amounts of optical impurities smaller than 1% it is more accurate to relate the integral of the optical impurity to the ^{19}F–^{13}C satellites instead of relative to the resonance of the major optical component. (Note the asymmetric appearance of the satellites due to ^{12}C versus ^{13}C isotope effect observed on ^{19}F.) On the basis of these measurements the e.e. values of the samples were calculated. The specific rotation power of the pure enantiomer of **1** is $[\alpha]_D^{25}=44.3$ (*c* 2, ethanol).

2.4. Single-crystal X-ray diffraction studies

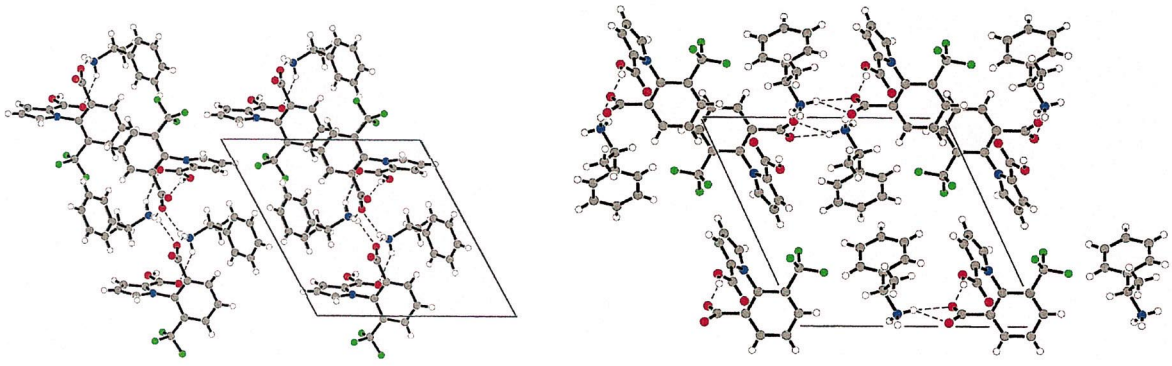
The enantiomers of the acid **1** crystallize as fine powders therefore we prepared single crystals from (+)-**1**·(*R*)-**5** and (+)-**1**·(*S*)-**5** diastereoisomeric salts for X-ray studies. The molecular structures of the two salts in the crystals are shown in Fig. 2. On the basis of these structures we can report that the absolute configuration of (+)-**1** is (*S*).



(+)-**1**.(*R*)-**5** (+)-**1**.(*S*)-**5**

Figure 2. The molecular structures of (+)-**1**·(*R*)-**5** and (+)-**1**·(*S*)-**5** salts in the crystals

Although the crystal structures of the two salts are similar to each other (both diastereoisomeric salts crystallized in monoclinic form), the hydrogen bonding structures are different. The H-bridges are shown in Fig. 3 with dotted lines and listed in Table 3.



(+)-**1**.(*R*)-**5** (+)-**1**.(*S*)-**5**

Figure 3. Packing of (+)-**1**·(*R*)-**5** and (+)-**1**·(*S*)-**5** salts in the crystals

Table 3
Data of the hydrogen bonds in the (+)-**1**·(*R*)-**5** and (+)-**1**·(*S*)-**5** crystals

D–H	A	*d*(H···A) (Å)	*d*(D···A) (Å)	<DHA (°)	Symm. operation for the A atom
			(+)-**1**·(*R*)-**5**		
O14–H13	O21	1.794	2.555	153.55	[*x*, *y*+1, *z*]
N29–H29A	O20	2.050	2.801	141.39	[−*x*+1, *y*+1/2, −*z*+1]
N29–H29A	O21	2.641	3.228	124.39	[*x*, *y*+1, *z*]
N29–H29B	O20	1.949	2.771	152.81	
N29–H29C	O13	2.156	2.919	143.32	
			(+)-**1**·(*S*)-**5**		
O13–H13	O21	1.840	2.614	156.68	[*x*, *y*+1, *z*]
N29–H29A	O21	2.306	3.169	163.60	[*x*, *y*+1, *z*]
N29–H29B	O21	2.207	3.086	169.05	[−*x*, *y*+1/2, −*z*+1]
N29–H29B	O20	2.336	2.925	123.68	[−*x*, *y*+1/2, −*z*+1]
N29–H29C	O20	1.951	2.745	147.82	
N29–H29C	O14	2.614	3.129	117.74	

D: donor atom, A: acceptor atom.

It is worthwhile mentioning that the sizes of the two unit cells are very similar and contain two-two salt units (Fig. 3 and Table 4). Furthermore, the densities of the two crystals are almost equal. These similarities may explain the moderate efficiency of the resolution.

Table 4
Physical data for (+)-**1**·(*R*)-**5** and (+)-**1**·(*S*)-**5** crystals

	(+)-**1**·(*R*)-**5**	(+)-**1**·(*S*)-**5**
Formula	$C_{21}H_{19}F_3N_2O_4$	$C_{21}H_{19}F_3N_2O_4$
Molecular weight	420.38	420.38
Space group	*P*21	*P*21
Crystal form	Monoclinic	Monoclinic
a (Å)	12.3977(12)	12.169(8)
b (Å)	7.4905(14)	7.221(8)
c (Å)	12.5196(14)	12.809(8)
α (°)	90.00	90.00
β (°)	118.95(6)	115.10(2)
γ (°)	90.00	90.00
V (Å^3)	1017.4(2)	1019.2(14)
Z	2	2
d (g cm^{-3})	1.372	1.370

3. Conclusions

A novel, efficient method has been developed for the synthesis of (±)-1-[2-carboxy-6-(trifluoromethyl)phenyl]-pyrrole-2-carboxylic acid **1** by systematic investigation of the dimetallation process of 1-[2-(trifluoromethyl)phenyl]pyrrole **2**. The enantiomers of **1** are stable at ordinary temperature and they have been successfully separated via diastereoisomeric salt formation.

The absolute configurations of the optically active isomers have been determined from the single-crystal structures of the two diastereoisomeric salts. Comparison of the two structures allow us to conclude that the different hydrogen bonding systems are responsible for the chiral discrimination, even the cell dimensions, the density and the crystal forms are very similar to each other.

A novel, sensitive ^{19}F NMR spectroscopic method has also been elaborated for the determination of the e.e. values of optically active **1**. Host–guest complex formation of **1** with β-cyclodextrin resulted in sharp, base line separation of the ^{19}F NMR signals. The efficiency of the resolution is $S \approx 0.28$ and both enantiomers were prepared in enantiomerically pure form (e.e.>98%). Thus, these atropisomers can be used as new resolving agents or intermediates of novel optically active ligands.

4. Experimental

4.1. General

All commercial starting materials were purchased from FLUKA AG and Merck–Schuchardt and were used without further purification. *n*-Butyllithium was supplied by Chemetall GmbH Lithium Division, Frankfurt.

Diethyl ether and tetrahydrofuran were rendered anhydrous by distillation from sodium wire after the characteristic blue color of in situ generated sodium diphenylketyl had been found to persist. TMEDA was also distilled from sodium wire before use. The concentration of the butyllithium solution was determined by double titration method.[12] All experiments were carried out in Schlenk-flasks under a dry nitrogen atmosphere.

^1H NMR spectra were recorded in hexadeuteriodimethylsufoxide or deuteriochloroform solution at 250 MHz (Bruker AC 250). Chemical shifts refer to tetramethylsilane ($\delta = 0$ ppm), coupling constants are given in Hz. The signal of the COOH group is absent because its place and form are strongly concentration dependent. The enantiomer ratios of (+)- and (−)-**1** samples were determined from the ^{19}F spectra recorded at 30±1°C on a Varian $Inova_{500}$ spectrometer (operating at 500 MHz for ^1H) using a $^1H\{^{13}C, ^{15}N\}$ PFG triple-resonance 5 mm probe tunable for ^{19}F. Samples were prepared in 6±0.1 mM concentrations with a 1:1 host-to-guest ratio, mixing D_2O and saturated (25°C) NaH_2PO_4 buffer in a 1:1 ratio. ^{19}F chemical shifts are given relative to the external standard $CFCl_3$ in $CDCl_3$. The enantiomeric ratio was assessed by integration of the pertinent NMR resonances after Gaussian-weighted Fourier-transformation of the FID without prior baseline correction. The T_1 relaxation time of CF_3 groups was measured by the inversion recovery sequence and was found to be $T_1 = 1.28 \pm 0.09$ s in the presence of 6-β-cyclodextrin (6 mM). The relaxation delay was set to 8 s to satisfy the $5 \times T_1$ condition for the accuracy of the integrals. Analytical grade β-cyclodextrin was purchased from Cyclolab, Hungary.

Single-crystal X-ray diffraction measurements were accomplished by a Rigaku AFC6S diffractometer. All data on the single crystals are deposited at the Cambridge Crystallographic Data Centre; deposition numbers: CCDC 149573 for (+)-**1**·(*R*)-**5** and CCDC 149574 for (+)-**1**·(*S*)-**5**.

1-[2-(Trifluoromethyl)phenyl]pyrrole **2** was prepared from 2-(trifluoromethyl)aniline and *cis*,*trans*-2,5-dimethoxytetrahydrofuran in glacial acetic acid according to the literature procedures.[5,13]

4.2. Metallation (general procedure)

TMEDA (10.0 mmol, 1.16 g) or KO*t*Bu (10.0 mmol, 1.12 g) or TMP (11.0 mmol, 1.55 g) (or double these amounts) were dissolved in dry tetrahydrofuran or diethyl ether (25.0 ml) and cooled to the given temperature (see Table 1). A 15% hexane solution of butyllithium (11.0 mmol, 7.3 ml or 22.0 mmol, 14.6 ml) was added dropwise to the solution then 1-[2-(trifluoromethyl)phenyl]pyrrole **2** (10.0 mmol, 2.11 g) was dropped into it. After 60 minutes stirring at the given temperature the mixture was poured into a dry ice–diethyl ether slurry. At 20°C 25 ml of distilled water was added, the phases were separated and the aqueous solution was washed with diethyl ether (3×15 ml). The mixture of the carboxylic acids **1**, **3** and **4** was isolated from the aqueous solution by acidification with 15% citric acid solution. The crude product either oiled out or precipitated from the solution as crystals. The crystals were filtered, the oils were separated by extraction with dichloromethane (25 ml) and the collected dichloromethane solutions were dried over sodium sulfate and concentrated in vacuo. The crude products were used for determination of the product distribution by ^{1}H NMR spectroscopy. The crude products were then treated with hexane to remove the valeric acid side product and with chloroform to wash out the monocarboxylic acids **3** and **4** from the insoluble dicarboxylic acid **1**. In order to prepare pure **1**, it was recrystallized from ethyl acetate. Pure samples of the monocarboxylic acids **3** and **4** were prepared from the chloroform solution by concentration in vacuo followed by repeated crystallizations from ethyl acetate for **3** and hexane for **4**.

1-[6-Carboxy-2-(trifluoromethyl)phenyl]pyrrolo-2-carboxylic acid ***1***:[5] mp: 216–217°C (from ethyl acetate). ^{1}H NMR (DMSO-d_6): δ 8.09 (1H, d, *J* 7.7), 8.01 (1H, d, *J* 7.7), 7.75 (1H, t, *J* 7.7), 7.01 (1H, sym m), 6.88 (1H, dd, *J* 3.8, 1.8), 6.23 (1H, dd *J* 3.8, 2.9).

1-[3-Carboxy-2-(trifluoromethyl)phenyl]pyrrole ***3***:[5] mp: 144–146°C (from ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 7.73 (1H, dd, *J* 8.0, 1.6), 7.66 (1H, t, *J* 7.7), 7.53 (1H, dd, *J* 7.5, 1.6), 6.88 (2H, t, *J* 2.0), 6.35 (2H, t, *J* 2.0); (DMSO-d_6): δ 7.82 (1H, t, *J* 7.7), 7.72 (1H, d, *J* 7.6), 7.59 (1H, d, *J* 7.6), 6.96 (2H, t, *J* 2.0), 6.24 (2H, t, *J* 2.0).

1-[6-Carboxy-2-(trifluoromethyl)phenyl]pyrrole ***4***: mp: 145–147°C (from hexane). ^{1}H NMR (DMSO-d_6): δ 8.1 (2H, m), 7.75 (1H, t, *J* 7.8), 6.77 (2H, sym. m), 6.15 (2H, t, *J* 1.9). Anal. calcd for: $C_{12}H_8F_3NO_2$ (255.19) C, 56.48; H, 3.14; N, 5.49; found: C, 56.51; H, 3.10; N, 5.53%.

4.3. Resolution

The dicarboxylic acid (±)-**1**, 26.8 mmol, 8.0 g) was dissolved in hot ethanol (80 ml) and an ethanol solution (15 ml) of (*R*)-α-methylbenzylamine (*R*)-**5** (13.4 mmol, 1.64 g) was poured into it. The crystallized diastereoisomeric salt was filtered off at 20°C, and recrystallized from ethanol (190 ml). The recrystallized salt was solved in ethyl acetate (60 ml) and acidified with 5% aqueous hydrochloric acid solution. The phases were separated, the organic solution was dried with sodium sulfate and concentrated in vacuo. The solid residue is (*S*)-**1** (4.3 mmol, 1.28 g), $[\alpha]_D$ +44.0 ($c=2$, ethanol), e.e. 99.3%. The filtrates of the diastereoisomeric salt formation and the recrystallization were collected and concentrated in vacuo. The (*R*>*S*)-**1** fraction (20.4 mmol, 6.1 g, e.e. 22%) was isolated from the residue in an analogous way to the workup of the diastereoisomeric salt. This acid was solved in ethanol (60 ml) and reacted with (*S*)-α-methylbenzylamine (*S*)-**5** (12.4 mmol, 1.50 g) and the precipitated diastereoisomeric salt was treated in a similar way to the first salt. The liberated acid was the (*R*)-**1** isomer (4.0 mmol, 1.20 g), $[\alpha]_D$ −43.6 ($c=2$, ethanol), e.e. 98.4%. Workup of the filtrates from the second salt formation and

recrystallization contained an approximately racemic dicarboxylic acid, which was regenerated by acidification as described above (±)-**1** (13.1 mmol, 3.9 g).

Acknowledgements

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