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Efficient synthesis of optically active 1-(2-carboxymethyl-6-ethylphenyl)-*1H*-pyrrole-2-carboxylic acid: a novel atropisomeric 1-arylpyrrole derivative

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ABSTRACT

An efficient synthesis and resolution of (±)-1-(2-carboxymethyl-6-ethylphenyl)-*1H*-pyrrole-2-carboxylic acid has been developed for the preparation of novel optically active atropisomers. The ee values were measured by a ^{1}H NMR spectroscopic method using quinidine as the chiral complexing agent. Absolute configurations of the separated enantiomers were determined using single crystal X-ray diffraction measurements of both the disodium salt and the (*R*)-1-phenylethylamine salt of the enantiomerically pure dicarboxylic acid, separately. The analysis of the CD spectra with the aid of TD-DFT quantum chemical calculations confirmed the assignment of configurations.

1. Introduction

Recently, numerous new C_1-symmetric compounds have been published as outstanding chiral ligands in transition metal catalysts or as organocatalysts in enantioselective reactions. Besides proline[1] and other pyrolidine derivatives,[2–4] which contain asymmetric centre(s) in the molecules, compounds with axial chirality elements[5,6] have also been applied in such reactions providing optically active products in high ee, similar to the results achieved with the well-known C_2-symmetric ligands[7] (e.g., BINOL,[8] and TADDOL[9] and derivatives, Scheme 1). Several years ago, we described the synthesis of 1-(2-carboxy-6-trifluoromethyl-phenyl)pyrrole-2-carboxylic acid **1** (Scheme 1) enantiomers,[10] the very first representatives of the optically active, atropisomeric 1-arylpyrrole derivatives.

It was also demonstrated that **1** is an outstanding shift reagent for determination of the ee values of dialkylaminomethyl group containing chiral oxirane, oxetane and *cis*-but-2-ene-1,4-diol derivatives by ^{1}H NMR spectroscopy.[11] Recently, several new 1-(substituted phenyl)pyrrole derivatives have been synthesised in our laboratory with the aim of further investigation of their regioselective metallation reactions.[12,13] In spite of the fact that alkyl substituents of the benzene ring in C(2) and/or C(6) positions decrease reactivity of the molecule against metallation, we have choosen 1-(2-ethyl-6-methylphenyl)pyrrole **2** as a model compound because it can be easily prepared from commercially available 2-ethyl-6-methylaniline and functionalisation of one side of the pyrrole ring could already provide a racemic mixture of atropisomers via a short synthetic route. Molecular modelling calculations demonstrated that the rotational barriers around the C(1)–N bond in 1-(2,6-disubstituted phenyl)-*1H*-pyrrole-2-carboxylic acids are around 30–40 kcal/mol or higher (AM1 calculations); high enough to separate and keep the enantiomers of the target molecules for a long time without spontaneous racemisation at ambient temperature. Herein, the development of efficient synthesis and resolution of 1-(2-carboxymethyl-6-ethylphenyl)-*1H*-pyrrole-2-carboxylic acid **3** is reported.

2. Results and discussion

2.1. Synthesis of 1-(2-carboxymethyl-6-ethylphenyl)-1*H*-pyrrole-2-carboxylic acid 3

The starting material **2** was prepared from 2-ethyl-6-methylaniline and 2,5-dimethoxytetra-hydrofuran by Gross's method,[14] and then reacted with two molar equivalents of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine-activated butyllithium (BuLi–TMEDA) in diethyl ether (DEE) with the lithiated species being quenched with dry ice at −75 °C. The crude products contained mixtures of a dicarboxylic acid **3** and monocarboxylic acids **4** and **5** (Scheme 2). The yields and product ratios depended on the duration and the temperaure of the lithiation step (Table 1). The best results could be achieved with a 3 h lithiation reaction at 23 °C (Table 1, line 4).

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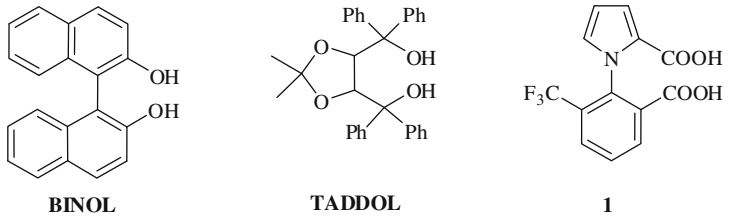
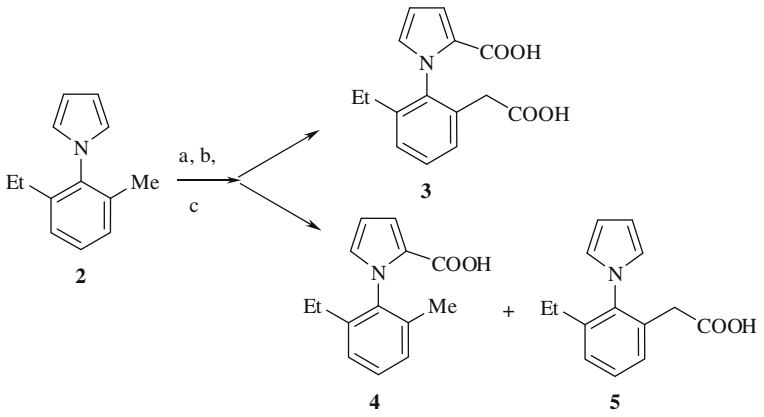


Scheme 1. Structures of BINOL, TADDOL and dicarboxylic acid **1**.



Scheme 2. Consecutive dilithiation and carboxylation of **2** (reaction conditions: (a) 2(TMEDA-BuLi), (b) CO_2, (c) H^+/H_2O).

Table 1
Conditions and results of the consecutive dilithiation and carboxylation of **2**

Conditions	Products (ratio[a])	Yield[b] (%)
Et_2O, 0 °C, 2 h	**3** + **4** + **5** (62:3:35)	19
Et_2O, 0 °C, 4 h	**3** + **5** (77:23)	49
Et_2O, 22 °C, 2 h	**3** + **4** + **5** (93:1:6)	77
Et_2O, 23 °C, 3 h	**3** + **4** + **5** (92:1:7)	80

[a] Product distribution was determined from the ^1H NMR spectra of the crude product mixture.
[b] The yield of the isolated crude carboxylic acid mixture related to the starting material **2**.

Pure dicarboxylic acid **3** was isolated from the crude mixture by simple recrystallisation from chloroform, due to the much smaller solubility of **3** than that of the monocarboxylic acids **4** and **5**.

2.2. Resolution of dicarboxylic acid 3

Resolution of **3** could be accomplished via diastereoisomeric salt formation with half equivalent amount of (*R*)-1-phenylethylamine ((*R*)-**6**) in a mixture of ethyl acetate and ethanol (Scheme 3).

It should be mentioned that ethyl alcohol had a crucial role in the enantiomeric discrimination process because a racemic mixture of **3** was found in the crystallised diastereoisomeric salt when pure ethyl acetate was used as the solvent. The best results could be achieved when 1 g of *rac*-**3** was dissolved in 40 ml of ethyl acetate containing 0.1 ml of ethanol. Under these conditions, (−)-**3** crystallised in the diastereoisomeric salt with (*R*)-**6** and it could be separated from the reaction mixture in good yield and ee (Scheme 3). On the other hand, increased amount of ethyl alcohol radically decreased the yield and the enantiomeric excess of the crystalline diastereoisomeric salt.

In order to prepare enantiomerically pure **3**, two methods were developed. First, the non-racemic enantiomeric mixture (− > +)-**3** [or (+ > −)-**3**] could be recrystallised from ethanol providing an almost racemic composition of the enantiomers of **3** in the crystalline phase while a much purer enantiomer remained in the filtrate (Scheme 4). This method could be used for medium pure samples of **3**. Crystallisation of the racemate indicated that formation of the heterochiral associates is preferred against the homochiral ones in solution (the melting points: *rac*-**3**: 212–213 °C; (−)-**3**: 144–146 °C).

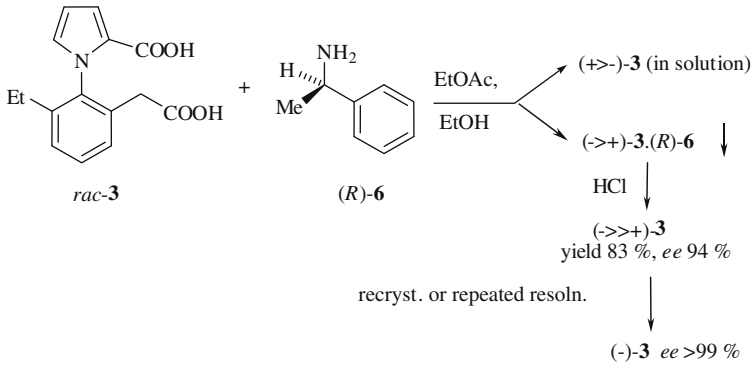
The second method for enantiomeric enrichment was the repeated resolution of non-racemic enantiomeric mixtures with optically active 1-phenylethylamine. More than 90% of the major enantiomer could be isolated from the diastereoisomeric salt in >99% ee when the molar amount of the (*R*)-**6** or (*S*)-**6** resolving agent used was equivalent to the molar amount of the major enantiomer content of the enantiomeric mixture. Thus, both pure enantiomers of **3** could be prepared using the corresponding enantiomer of **6**.

Enantiomeric compositions (ee values) of the optically active samples were determined by ^1H NMR spectroscopy. Quinidine was applied as a chiral shift reagent and the resonances of the β-protons of the pyrrole ring were used for ee determination. On the basis of these measurements, the specific rotation power of the enantiomerically pure (+)-**3**: $[\alpha]_D$ = +85.5 (*c* 1, ethanol), ee 100%).

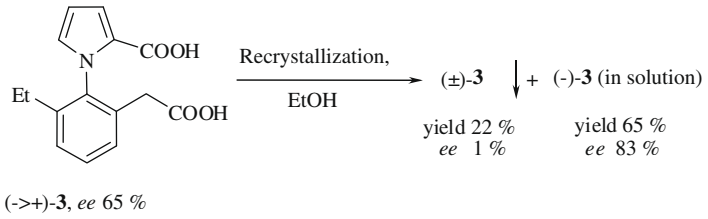
2.3. Single crystal X-ray diffraction measurements

Our attempts to get single crystals from the enantiomerically pure **3** samples have failed. Single crystal X-ray diffraction measurements could be carried out using the disodium salt of (−)-**3** which crystallised from an aqueous solution as a tetrahydrate. The asymmetric unit arrangement of (−)-**3**·Na_2·$(H_2O)_4$ is shown in Figure 1, some parameters of the unit cell of the crystal and the diffraction measurement are listed in Table 2. The crystal structure reveals an infinite catemer-polymeric structure, which creates *pseudo* centrosymmetric ladder-type arrangements in the vicinity of the Na^+ cations and their ligand sphere.

A single crystal structure determination was also performed for the (*R*)-(−)-**3**·(*R*)-**6** salt, resulting in the structure depicted in Figure 2.



Scheme 3. Resolution of dicarboxylic acid **3**.



Scheme 4. Enantiomeric enrichment of (− > +)-**3** by recrystallisation.

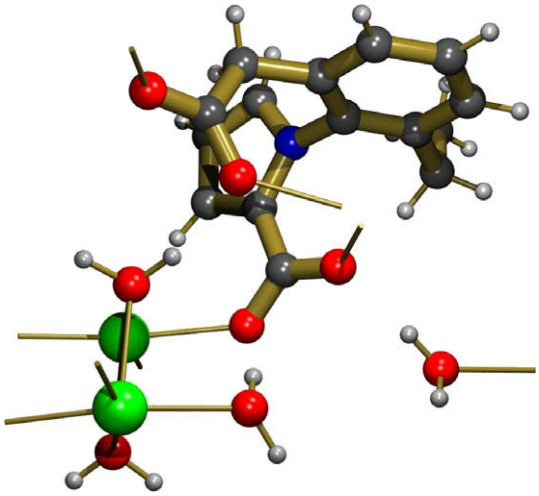


Figure 1. Structure of the asymmetric unit from the (*R*)-(−)-**3**·Na_2·$(H_2O)_4$ catemer crystal.

Table 2
Selected crystal data for (*R*)-(−)-**3**·Na_2·$(H_2O)_4$ salt and (*R*)-(−)-**3**·(*R*)-**6** salt

Property	Compound	
	(*R*)(−)-**3**·Na_2·$(H_2O)_4$	(*R*)-(−)-**3**·(*R*)-**6**
Formula weight	389.31	394.46
Crystal system	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$ (No. 19)	$P2_1$ (No. 4)
a (Å)	7.828(1)	10.7946(3)
b (Å)	8.273(1)	6.6627(2)
c (Å)	27.154(4)	14.3178(4)
α (°)	90	90
β (°)	90	103.898(3)
γ (°)	90	90
V (Å^3)	1758.5(4)	999.61(5)
T (K)	153	140
Crystal size (mm)	0.09 × 0.15 × 0.18	0.05 × 0.05 × 0.20
Z	4	2
D(calcd) (g/cm^3)	1.470	1.311
Radiation μ(Å)	0.7107	1.5418
Tot./Uniq. Data, $R_{(int)}$	56213, 1826, 0.101	8837, 2191, 0.060
N_{ref}, N_{par}	1826, 254	2191, 280
R_1, wR^2, S	0.0372, 0.0809, 1.08	0.0400, 0.0916, 0.95
Flack *x*	n.a.	0.0(3)

Some parameters of the unit cell of the (*R*)-(−)-**3**·(*R*)-**6** salt crystal and the diffraction measurement are also listed in Table 2.

Seemingly normal displacement ellipsoids for both crystal structures may exclude racemic twinning or rough errors such as space group ambiguities. On the basis of these measurements, we could not conclude with certainty on the absolute configuration of (−)-**3** unequivocally. Uncertainty of the diffraction measurements stems from a combination of the size and of inferior quality of the available single crystals, also hampered possibly by a pseudo-centric arrangement of Na^+- and O^--ions in the (−)-**3**·Na_2·$(H_2O)_4$ salt.

2.4. Determination of the absolute configuration by CD spectroscopy

The CD spectra of (+)-**3** and (−)-**3** are shown in Figure 3a. The CD spectroscopic empirical rules employed frequently for the determination of the absolute configuration of carbonyl compounds or benzene derivatives cannot be applied here since the electronic systems of the various chromophores are strongly interacting. The spectra of the two isomers of **3** can be assigned by comparison with the spectra of the stereochemically known isomers of **1**, a molecule differing from **3** only in possessing a CF_3 group instead of an ethyl group in the C(6) position of the benzene ring. As reported in an earlier paper, the absolute configurations of the enantiomers of **1** could be determined reliably by XRD measurements, which concluded that (+)-**1** corresponds to the (*R*)- and (−)-**1** to the (*S*)-isomer.[10] The CD spectra obtained from (+)-(*R*)-**1** and (−)-(*S*)-**1** are shown in Figure 3b. As can be seen, the spectrum of (+)-**3** shows a close similarity to the spectrum of (−)-**1**, whereas the spectrum of (−)-**3** looks similar to the spectrum of (+)-**1**, which supports the assignment of (+)-**3** as the (*S*)- and (−)-**3** as the (*R*)-isomer.

More detailed information on the relationship between the stereostructure and CD spectrum of **3** was obtained with help of the-

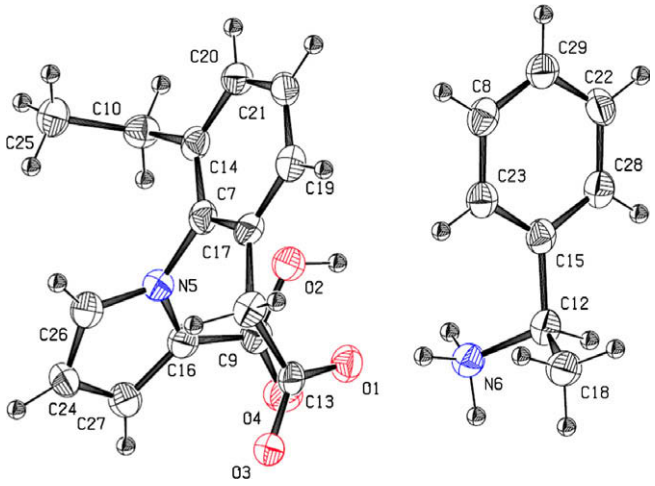


Figure 2. The asymmetric unit structure of the (*R*)-(−)-**3**·(*R*)-**6** salt in 50% probability atomic displacements representation.

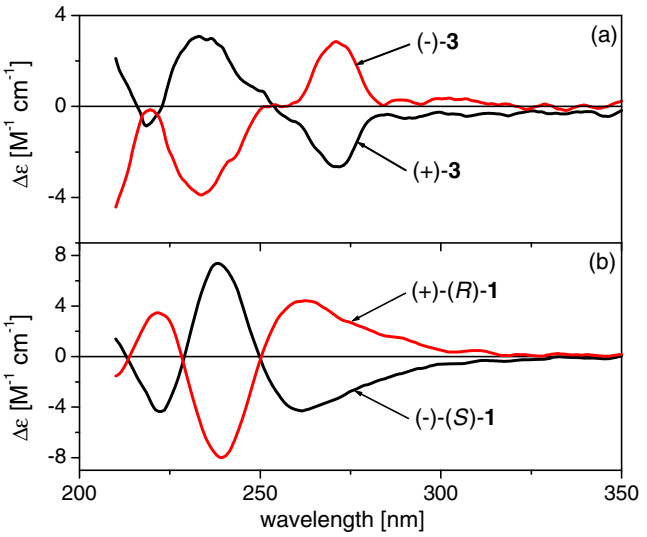


Figure 3. Experimental CD spectra of the enantiomers of 1-arylpyrrole derivatives **3** and **1** in ethanol solution.

oretical chemical calculations carried out for the (*S*)-isomer. First, a conformational analysis based on molecular mechanics calculations was performed. The geometries of the 15 most stable conformers were fully optimised then by density functional theory (DFT) method. It was found that conformers (*S*)-**3a** and (*S*)-**3b** (see Fig. 4a) have the lowest energies, their concentrations are 48% and 35%, respectively, at 25 °C. The energies, the oscillatory strengths and the rotatory strengths of the electronic transitions of these two conformers were computed in time-dependent DFT (TD-DFT) calculations.[15] The calculated CD spectrum of (*S*)-**3** was obtained as the weighted sum of the computed spectra of (*S*)-**3a** and (*S*)-**3b**, presuming Gaussian band shapes of widths $\sigma = 0.3$ eV.[16] The resulting spectrum is displayed in Figure 4b. As can be seen, the calculated spectrum of (*S*)-**3** is in satisfactory agreement with the observed spectrum of (+)-**3**, providing further evidence for the assignment of the absolute configuration.

3. Conclusion

On the basis of our experimental results, we have concluded that the organometallic approach can be applied efficiently to the synthesis of atropisomeric 1-(disubstituted phenyl)pyrrole derivatives. The conformationally stable dicarboxylic acid **3** could be prepared in good yield and in 93% selectivity.

Resolution of **3** could be accomplished with a half equivalent method using (*R*)-1-phenylethylamine (*R*)-**6** as the resolving agent. Efficiency (S = yield × ee)[17] of the enantiomer separation strongly depended on the ethanol content of the solvent. Without any ethanol almost racemic mixture crystallised in the diastereoisomeric salt. The yield radically decreased if the ethyl acetate contained more than 1% ethanol, and an optimum resolution could be achieved when the ethanol content of the solvent was at about 0.3% ($S = 0.78$). The non-racemic enantiomeric mixture of compound **3** behaved as a true racemate: an almost racemic mixture crystallised from ethanol during rectrystallization while the enantiomerically enriched mixture remained in the filtrate.

A sensitive ^{1}H NMR method was also developed using quinidine as the chiral complexing agent for the determination of the ee values of optically active dicarboxylic acid **3**. The chiral alkaloid seemed to be much better additive than the usual transition metal containing shift reagents because of the narow shape of the NMR peaks. In spite of the single crystal growing difficulties, a combination of the XRD measurements of (−)-**3**·Na_2·$(H_2O)_4$ and (−)-**3**·(*R*)-**6** salts with comparative CD spectroscopic investigations and molecular mechanics calculations on optically active dicarboxylic acids **1** and **3** provided strong evidence for the absolute configuration of (*R*)-(−)-**3** and (*S*)-(+)-**3**. The prepared new atropisomeric compounds can serve as precursors of chiral ligands or building blocks.

4. Experimental

4.1. General

All commercial starting materials were purchased from FULKA AG and Merk-Schuchardt and were used without further purification. Diethyl ether and tetrahydrofuran were obtained anhydrous by distillation from sodium wire after the characteristic blue colour of in situ generated sodium diphenylketyl had been found to persist. TMEDA was also distilled from sodium wire before use. Concentration of the butyllithium solution was determined by double titration method.[18] All experiments were carried out in Schlenk-flasks under a dry nitrogen atmosphere.

^{1}H NMR and ^{13}C NMR spectra were recorded in deuterochloroform solution or hexadeutero dimethylsulfoxide solution at 300 MHz proton resonance frequency (BRUKER DRX 300). The signals of COOH groups are absent because their place and form are strongly concentration dependent. Chemical shifts are given in ppm related to the internal standard tetramethylsilane ($\delta = 0$ ppm). IR spectra were recorded on an appliance type PERKIN ELMER 1600 with a Fourier Transformer. Data are given in cm^{-1}. The UV and CD spectra were obtained in ethanol. The UV spectra were taken on an Agilent 8453 diode array spectrometer, the CD spectra were recorded on a Jasco J-810 spectropolarimeter.

4.2. X-ray data collections and structure determinations

The (−)-**3**·Na_2·$(H_2O)_4$ salt X-ray diffraction experiments were carried out on a Rigaku R-AXIS Rapid IP diffractometer using an X-Stream 2000 unit operating at $T = 153$ K. Data were collected using standard ω-scan procedures, with monochrome (graphite) Mo Kα radiation: $C_{15}H_{21}NNa_2O_8$ Fwt.: 389.31, colourless chunk, size: 0.09 × 0.15 × 0.18 mm, orthorhombic, space group $P2_12_12_1$ (No. 19), $a = 7.828(1)$ Å, $b = 8.273(1)$ Å, $c = 27.154(4)$ Å, $V = 1758.5(4)$ Å^3, $T = 153(2)$ K, $Z = 4$, $D_C = 1.470$ Mg/m^3, numerical absorption correction ($T_{max}/T_{min} = 0.971/0.985$). 56,213 reflections, 1826 unique [$R_{int} = 0.10$]; and $1616 > 2\sigma(I)$, initial structure model by direct methods, hydrogen atoms either calculated from as-

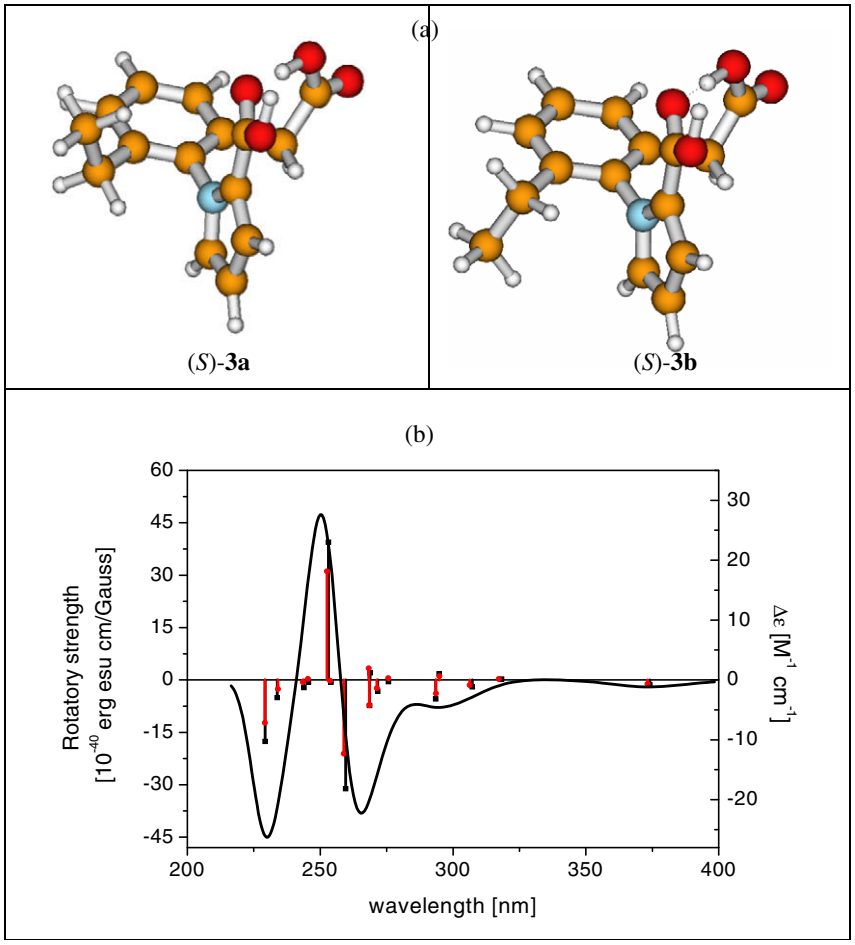


Figure 4. (a) The most stable conformers of (*S*)-**3**. (b) The theoretically calculated CD spectrum of (*S*)-**3**. The rotatory strengths of conformers (*S*)-**3a** and (*S*)-**3b**, weighted by their molar ratios, are denoted by black and red bars, respectively.

sumed geometries or located from difference density maps and kept riding, model refined by least-squares, final $R_1 = 0.0372$ and $wR_2 = 0.0809$ for all (1826) intensity data, number of parameters = 254, goodness-of-fit = 1.08, an absolute structure parameter was not used/determined as Friedel pairs were merged in the refinement procedure due to low anomalous dispersion with Mo radiation.

The (−)-**3**·(*R*)-**6** salt X-ray diffraction experiments were carried out on an Oxford Diffraction Gemini CCD diffractometer at low temperatures using an Oxford—Cryostream unit operating at $T = 140$ K. Data were collected using standard ω-scan procedures, with monochrome (graphite) Cu Kα radiation: $C_{15}H_{14}NO_4 \cdot C_8H_{12}N$, Fwt.: 394.46, colourless chunk, size: 0.05 × 0.05 × 0.20 mm, monoclinic, space group $P2_1$ (No. 4), $a = 10.7946(3)$ Å, $b = 6.6627(2)$ Å, $c = 14.3178(4)$ Å, $\beta = 103.898(3)°$, $V = 999.61(5)$ Å^3, $T = 140(2)$ K, $Z = 2$, $D_C = 1.311$ Mg/m^3, numerical absorption correction ($T_{max}/T_{min} = 0.995/0.981$). 8837 reflections, 2191 unique [$R_{int} = 0.06$]; and 1677 > 2$\sigma(I)$, initial structure model by direct methods, hydrogen atoms either calculated from assumed geometries or located from difference density maps and kept riding, model refined by least-squares, final $R_1 = 0.0400$ and $wR_2 = 0.0916$ for all (2191) intensity data, number of parameters = 280, goodness-of-fit = 0.95. The absolute structure parameter Flack $x = 0.0(3)$ resulted in a too high standard uncertainty from the refinement procedure rendering the absolute structure unreliable. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 690325 (for (−)-**3**·Na_2·$(H_2O)_4$) and CCDC 690326 (for the (−)-**3**·(*R*)-**6** salt). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223336033 or e-mail: deposit@ccdc.cam.ac.uk].

Compound **2** was prepared from 2-ethyl-6-methylaniline and *cis,trans*-2,5-dimethoxy-tetrahydrofuran in glacial acetic acid according to the literature procedure.[14]

4.3. 1-(2-Ethyl-6-methylphenyl)pyrrole 2[13,14]

82%; Bp 130–132 °C/22 mmHg; IR (film) ν_{max}: 725, 759, 785 (ArC-H), 1495 (ArC-C), 2968 (AlkC-H); ^{1}H NMR ($CDCl_3$) δ_H: 7.23 (1H, d, *J* 7.5, Ph), 7.15 (1H, d, *J* 9.0, Ph), 7.13 (1H, t, *J* 9.0, Ph), 6.57–6.67 (2H, t like m, *J* 2.0 H_α), 6.27–6.37 (2H, t like m, *J* 2.0, H_β), 2.32 (2H, q, *J* 7.6, Et), 2.01 (3H, s, Me), 1.09 (3H, t, *J* 7.6, Et); ^{13}C NMR ($CDCl_3$) δ_C: 142.4, 139.5, 136.6, 128.4, 128.1, 126.6, 122.1, 108.6, 24.3, 17.5, 15.9.

4.4. Consecutive dimetallation and carboxylation of 2

Compound **2** (5.4 mmol, 1.00 g) was added at the desired temperature, (Table 1) to a solution of the activating agent TMEDA (10.8 mmol, 1.26 g) and a hexane solution of butyllithium (1.3 mol/l, 11.88 mmol, 9.2 ml) in dry diethyl ether (15 ml). After stirring for 1, 2, or 4 h at the desired temperature the reaction mixture was quenched with dry ice. At 20 °C, distilled water (20 ml) and diethyl ether (15 ml) were added, the phases were separated and the aqueous solution was washed with diethyl ether (3 × 15 ml). The aqueous solution was acidified with 15% citric acid solution. The aqueous phase was extracted with ethyl acetate

(3 × 20 ml). The collected organic solutions were dried over sodium sulfate and concentrated in vacuo. Product distributions were determined from the ^{1}H NMR spectra of the crude acidic products. In order to obtain the pure dicarboxylic acid **3**, the crude product was recrystallised from chloroform. The yield given below in parentheses refers to the efficiency of the recrystallisation.

4.4.1. 1-(6-Carboxymethyl-2-ethylphenyl)pyrrole-2-carboxylic acid 3[13]

Colourless crystals (50% from chloroform) mp: 212–213 °C; IR (KBr) ν_{max}: 3448 (OH), 1667, 1716 (CO); ^{1}H NMR (DMSO- d_6) δ_H: 0.97 (3H, t, *J* 7.6, Et), 2.10 (2H, q, *J* 7.6, Et), 2.98 (1H, d, *J* 16.2 CH_2), 3.28 (1H, d, *J* 16.2, CH_2), 6.28–6.34 (1H, t like m, *J* 2.7, H_β), 6.77–6.82 (1H, t like m, *J* 1.7, H), 6.95–7.01 (1H q like m, *J* 1.5, H) 7.18–7.40 (3H, m, Ph); ^{13}C NMR (DMSO-d_6) δ_C: 172.1, 160.8, 141.1, 138.7, 132.9, 129.8, 128.2, 128.1, 127.2, 124.2, 117.5, 109.2, 36.4, 23.5, 14.9. UV–vis (EtOH, λ [nm], ε [M^{-1} cm^{-1}]): 262, 25300; 215 (sh), 28700.

Pure sample of the monocarboxylic acid **5** could be obtained by monometallation of **2** in the presence of *N*,*N*,*N*′,*N*″,*N*″-pentamethylethylenetriamine as it is described in the literature.[13]

4.4.2. 1-(6-Carboxymethyl-2-ethylphenyl)pyrrole 5[13]

Colourless crystals (55% from hexane) mp: 132–133 °C; IR (KBr) ν_{max}: 3462 (OH), 1704 (CO); ^{1}H NMR (DMSO- d_6) δ_H: 7.12–7.48 (3H, m, Ph), 6.58–6.72 (2H, t like m, *J* 1.8, H_α), 6.18–28 (2H, t like m, *J* 1.8, H_β), 3.18 (2H, s, CH_2), 2.21 (2H, q, *J* 7.6, Et), 1.00 (3H, t, *J* 7.6, Et); ^{13}C NMR (DMSO-d_6) δ_C: 172.5, 141.7, 139.0, 133.3, 128.6, 128.4, 127.7, 122.4, 108.7, 36.2, 23.7, 15.7.

The minor component **5** of the monocarboxylic acids crystallised together with **4** from the filtrate of the recrystallised dicarboxylic acid **3**, therefore its spectral data were partially determined from that mixture.

4.4.3. 1-(2-ethyl-6-meylphenyl)pyrrole-2-carboxylic acid 4[13]

In a mixture with **5**, ^{1}H NMR (DMSO-d_6) δ_H: 7.10–7.40 (3H, m), 6.97 (1H, dd, *J* 2.2, 3.4, H_β), 6.92 (1H, t like m, *J* 2.0, $H_{\alpha'}$), 6.32 (1H, t like m, *J* 3.1, $H_{\beta'}$), 2.13 (2H, q, *J* 7.5, Et), 1.83 (3H, s Me), 0.93 (3H, t, *J* 7.5, Me).

4.5. Resolution of 3

Racemic dicarboxylic acid (±)-**3** (21.5 mmol, 5.89 g) was dissolved in a hot mixture of ethyl acetate (235, 6 ml) and ethanol (0.6 ml) and (*R*)-**6** (10.79 mmol, 1.31 g) was added into it. The reaction mixture was seeded with the (−)-**3**. (*R*)-**6** diastereoisomeric salt and it was allowed to crystallise during cooling to 20 °C. The diastereoisomeric salt was filtered off, washed with ethyl acetate (2 × 20 ml) and dried to yield white solid product (4.28 g, mp 184–186 °C, decomp.). This salt was dissolved in a mixture of ethyl acetate (65 ml) and aqueous hydrochloric acid solution (5%, 30 ml). The phases were separeted and the organic phase was washed with 5% aqueous hydrochloric acid solution (2 × 20 ml) and brine (1 × 20 ml). Then, the organic solution was dried over sodium sulfate and concentrated in vacuo to yield (−)-**3** (2.45 g, 83% of the (−)-enantiomer content of the racemate **3**), $[\alpha]_D$ = −80.0 (*c* 1, ethanol), ee 94%. The filtrate of the diastereoisomeric salt formation was concentrated in vacuo and the (+ > −)-**3** fraction (3.27 g, 111% of the (+)-enantiomer content of the racemate **3**), $[\alpha]_D$ = +58.3 (*c* 1, ethanol), ee 68%) was isolated from the residue in an analogous way to the workup of the diastereomeric salt. Repeated resolution of the non-racemic enantiomeric mixtures was carried out analogously but the amount of the applied resolving agent was equivalent with the corresponding enantiomer content of the starting optically active **3**. The (− > +)-**3** acid was resolved with (*R*)-**6** and (+ > −)-**3** was treated with (*S*)-**6** as resolving agent. The products (after diastereoisomeric salt decomposition) were (*R*)-(−)-**3**, mp 144–146 °C, $[\alpha]_D$ = −85.5 (*c* 1, ethanol) ee > 99%, CD (ethanol, λ [nm], $\Delta\varepsilon$ [M^{-1} cm^{-1}]): 271, +2.85; 233, −3.86 and (*S*)-(+)-**3** mp 144–146 °C, $[\alpha]_D$ = +85.5 (*c* 1, ethanol), ee > 99%, CD (ethanol, λ [nm], $\Delta\varepsilon$ [M^{-1} cm^{-1}]), respectively, 271, −2.64; 233, +3.09. Other spectroscopic data of the optically active products were identical with those of the racemic compound.

4.6. Enantiomeric enrichment of (− > +)-3 via recrystallisation

A sample of (+ > −)-**3** (2.28 g, $[\alpha]_D$ = +56.4 (*c* 1, ethanol), ee 66%) was recrystallised from ethanol (6.8 ml). The solid racemic was filtered off (0.49 g, $[\alpha]_D$ = +0.9 (*c* 1, ethanol), ee 1%) then the filtrate was concentrated in vacuo to yield (+)-**3** (1.45 g, $[\alpha]_D$ = +70.9 (*c* 1, ethanol), ee 83%).

5. Calculations

The conformational analysis was carried out applying MMFF94 force field[19] and Monte-Carlo algorithm. The quantum chemical calculations were performed using the 5.9 version of TURBOMOLE program package.[20] The DFT and TD-DFT calculations were carried out applying Becke-Perdew 86 (BP-86) functional[21,22] in combination with triple zeta valence polarised (TZVP) basis set[23] (in DFT calculations) or with triple zeta valence double polarised (TZVPP) basis set (in TD-DFT calculations), and using resolution of identity (RI) approximation.[24]

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