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Synthesis and stereochemical stability of new atropisomeric 1-(substituted phenyl)pyrrole derivatives

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Dedicated to Professor Csaba Szántay on the occasion of his 80th birthday

Abstract

Addition of organometallic reagents to optically active methyl 1-(2-methoxycarbonyl-6-trifluoromethylphenyl)pyrrole-2-carboxylate provided the corresponding tetrasubstituted diols and/or pyrrolo[1,2-*a*]benzoxazepines as pure enantiomers or racemates depending on the organometallic reagents used. Rotational energy barriers around the interconnecting C–N bonds were estimated by molecular modeling calculations and NMR measurements with the aim of clarifying the stereochemical stability order of the new atropisomeric compounds. NMR methods for the determination of the enantiomeric purity of the new compounds are proposed.

Keywords: Atropisomers; 1-Arylpyrroles; Rotational energy; Stereochemical stability; Organometallics

1. Introduction

Optically pure atropisomers of axially chiral biaryls have been widely studied for their applications as chiral ligands or auxiliaries.[1,2] In the last decades numerous C_2 symmetrical compounds were synthesized and investigated, such as the BINOL[3] and biphenyl[4] derivatives, but significant results have been published on the successful applications of several C_1 symmetrical compounds, too.[5]

Recently, efficient synthesis and optical resolution of the very first representative of atropisomeric 1-arylpyrrole derivatives have been published by our laboratory.[6] The optically active 1-(2-carboxy-6-trifluoromethylphenyl)pyrrole-2-carboxylic acid (**1**) was successfully applied as chiral discriminating agent in the ee determination of different chiral amines by NMR spectroscopy.[7] These preliminary works showed that the atropisomers of **1** are stable at ambient temperature. Thus we focused our interest on the simultaneous transformation of the two carboxylic groups into ester and carbinol functions with the aim of producing new members of that atropisomeric 1-arylpyrrole family (potential chiral ligands or organocatalysts) and investigating their conformational stability.

2. Results and discussions

2.1. Preparation of compounds 2–6

Synthesis of the desired atropisomeric diols **3** and **4** was accomplished starting from *R*-(−)-**1** via its dimethyl ester (*R*-(−)-**2**, Scheme 1). The phenyl groups (in **3**) were introduced by addition of an excess of phenyllithium. Usual workup procedure provided the optically active 1-(2-diphenylhydroxymethyl-6-trifluoromethylphenyl)-2-diphenylhydroxymethylpyrrole (*R*-(−)-**3**) in good yield. However, the same procedure resulted in the formation of practically racemic 4,4,6,6-tetramethyl-10-trifluoromethyl-4*H*,6*H*-pyrrolo[1,2-*a*]

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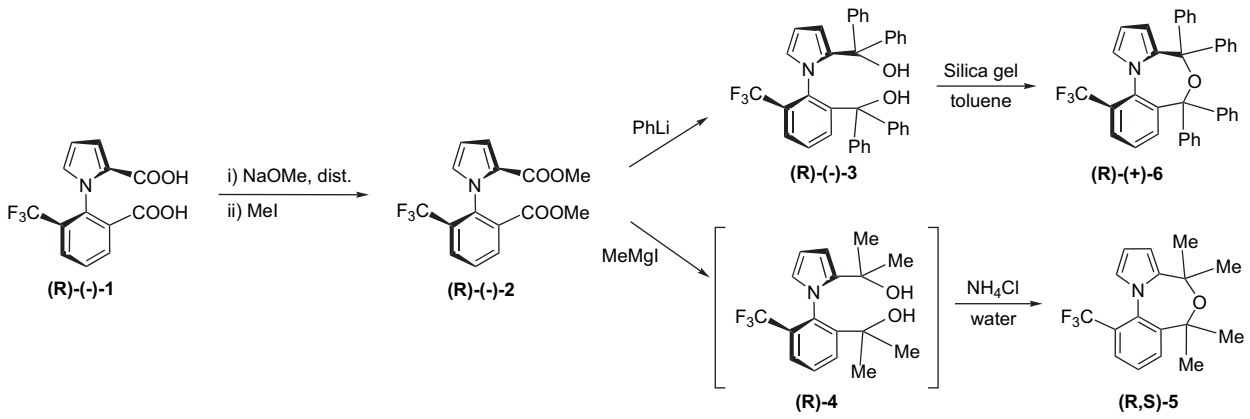


Scheme 1. Synthesis of compounds (*R*)-**3**, (*R*,*S*)-**5**, and (*R*)-**6**.

[4,1]benzoxazepine (**5**) as the main product and the diol **4** could not be separated in pure form when methylmagnesium iodide was used for the preparation of the tetramethyl derivative (**4**). Attempts to avoid spontaneous ring closing reaction and racemization during the aqueous workup procedure and chromatographic purifications have failed even neutral or basic conditions were applied.

In the case of the tetraphenyl diol **3** the ring closing reaction had to be accelerated with addition of silica gel and warming of the toluene solution of **3** for several hours. Under these conditions optically active 4,4,6,6-tetraphenyl-10-trifluoromethyl-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepine (*R*-(+)-**6**) could be obtained in good yield. It should be mentioned that the synthesis of compounds **2**, **3**, and **6** was also accomplished starting from *S*-(+)-**1** enantiomer resulting in the corresponding optically active products in the *S* atropisomeric series.

2.2. Determination of the enantiomeric excess values

Solution NMR spectroscopic methods have been developed to assess the enantiomeric compositions of the starting material (**1**), the intermediates (**2** and **3**), and the products (**5** and **6**). The enantiomeric purities of **1** and **2** were determined by ^{19}F NMR spectroscopy in aqueous solution using 2-hydroxypropyl-β-cyclodextrin (2HP-β-CD) as chiral complexing agent. Fluorine based detection has been previously developed for the ee determination of **1** with β-cyclodextrin[6] (β-CD) to overcome selectivity and sensitivity problems due to the excess of the auxiliary agent. Improving the method with the application of the better soluble 2HP-β-CD allowed us to achieve good selectivity with **2**, which had lower solubility than **1**. Esterification of both *R*-(−)-**1** and *S*-(+)-**1** was verified for enantioselectivity in parallel. Figure 1a shows that the CF_3 signals of the (+) and (−) enantiomers of **2** are baseline separated at −61.97 and −62.01 ppm. Standard addition of (−)-**2** was introduced to verify validity of the method (Fig. 1b). One advantage of the proposed method is that optical impurities smaller than 1% can be quantitatively determined by exploiting the 0.55% integrals of the natural abundance of ^{13}C satellites. The corresponding signals of **1** were found to be at −60.46 and −60.48 ppm. On the basis of these measurements the ee values of the samples **1** and **2** were calculated and we concluded that the esterification of **1** occurred without any racemization.

Signals of compounds **3**, **5**, and **6** were not separable by cyclodextrines to the level suitable for ee determination. We therefore applied Yb(TFC)$_3$ lanthanide shift reagent in apolar aprotic solvent, another well established methodology[8–10] available for the ee measurements of these compounds. Gratifyingly, the exchange between the complexed and uncomplexed forms of the investigated compounds was found to be very fast on the chemical shift timescales (^{1}H and/or ^{19}F) owing to the weak interaction with Yb(TFC)$_3$. Because of this, no signal broadening has interfered the baseline separation of the enantiomeric resonance pairs. Figure 2 shows the ^{19}F NMR spectra used for the analysis of the enantiomeric purity of **3**. The singlets of the CF_3 groups representing the enantiomers of **3** were found at −57.78 and −57.84 ppm. The same methodology was extended to the NMR analysis of **5** as well. The methyl resonances of compound **5** showed enantiodiscrimination in the presence of Yb(TFC)$_3$ therefore the basic ^{1}H NMR

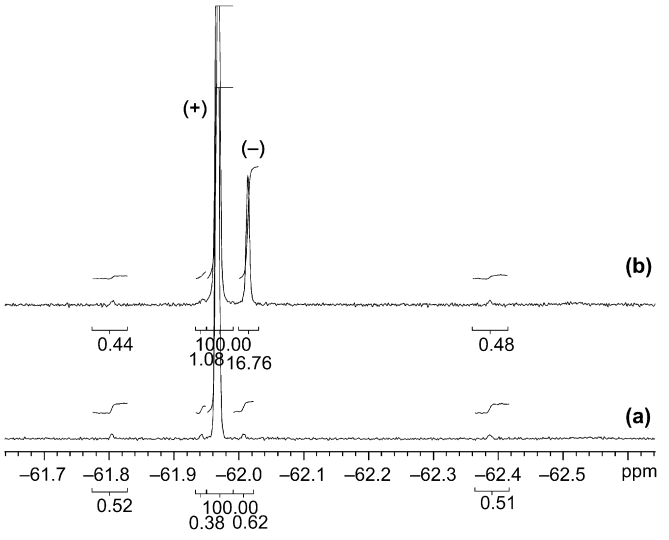


Figure 1. (a) ^{19}F NMR (470 MHz) spectrum of optically pure (+)-**2** (2 mM) in the presence of 8 mM 2HP-β-CD (D_2O, 25 °C). (b) Spectrum spiked with (−)-**2** to confirm enantioselectivity of the proposed NMR method. We note that fluorine coupled ^{13}C satellites are visible in both spectra.

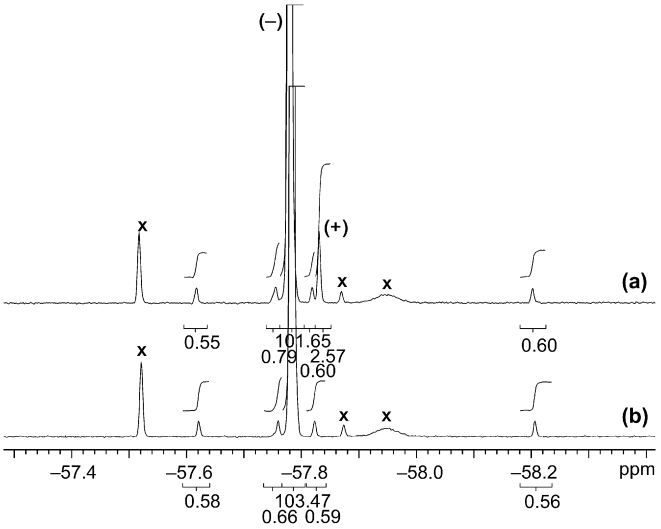


Figure 2. (a) ^{19}F NMR (470 MHz) spectrum of optically pure (−)-**3** (3 mM) in the presence of 30 mM Yb(TFC)$_3$ chiral shift reagent (C_6D_6, 22 °C). (b) Spectrum spiked with (+)-**3** to confirm enantioselectivity of the proposed NMR method. We note that fluorine coupled ^{13}C satellites and minor filtration impurities (denoted by x) are visible in both spectra.

spectrum was appropriate for the analysis (see Fig. 3). Interestingly, **5** was found to be racemic while **3** has retained its enantiomeric purity in the reactions shown in Scheme 1. We

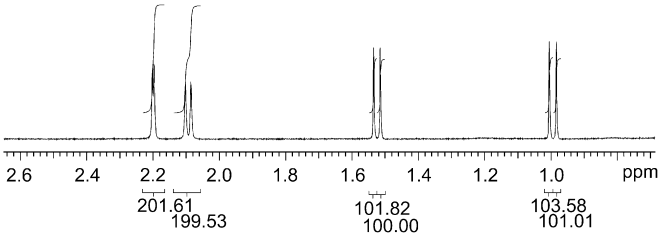


Figure 3. Aliphatic region of the ^{1}H NMR (500 MHz) spectrum of racemic (±)-**5** (40 mM) in the presence of 60 mM Yb(TFC)$_3$ chiral shift reagent (C_6D_6, 22 °C). Doubling of the four methyl singlets indicates enantiodiscrimination.

think that this is overwhelmingly due to the higher steric occupancy of the phenyl substituents (in comparison to the methyls), which does not allow racemization via free rotation around the C–N bond during the pyrrolobenzoxazepine forming reaction.

Due to its bulky, sterically congested structure, pyrrolobenzoxazepine **6** formed diastereoisomeric complexes neither with Yb(TFC)$_3$ nor with cyclodextrins. Nevertheless, the high specific rotation value of **6** ($[\alpha]_D^{25}$ +166.3 (*c* 0.6, MeOH)) showed that the benzoxazepine ring formation occurred without racemization. This fact was confirmed by HPLC measurements using a chiral stationary phase column.

2.3. Determination of the rotational barriers

In order to rationalize the observed substituent dependent stereochemical instability in the **4**→**5** versus **3**→**6** reactions, activation energies of rotation around the C–N bonds have been determined for each model compounds investigated. In case of **1** we also employed an experimental way to obtain thermodynamic data (see below). First, the activation energy values were estimated using AM1 semiempirical quantum chemical method. The geometries of the transition states of **1**–**6** model compounds are visualized in Figure 4, whereas the calculated and experimentally determined activation energy values are collected in Table 1.

The smallest barrier of rotation was found for **5**, which undergoes racemization at room temperature. Those compounds (**1**–**4**), which were found to remain enantiopure during the course of the NMR measurements have there $\Delta G^{\#}$ values above +32 kcal/mol, as seen for **1**. By viewing the growing order of the activation energies **2**<**4**<**3**, one can generally state that the diphenylhydroxymethyl group causes much higher steric resistance than the dimethylhydroxymethyl group. The rotational barrier decreases dramatically after the benzoxazepine ring closing reactions. Comparison of the activation

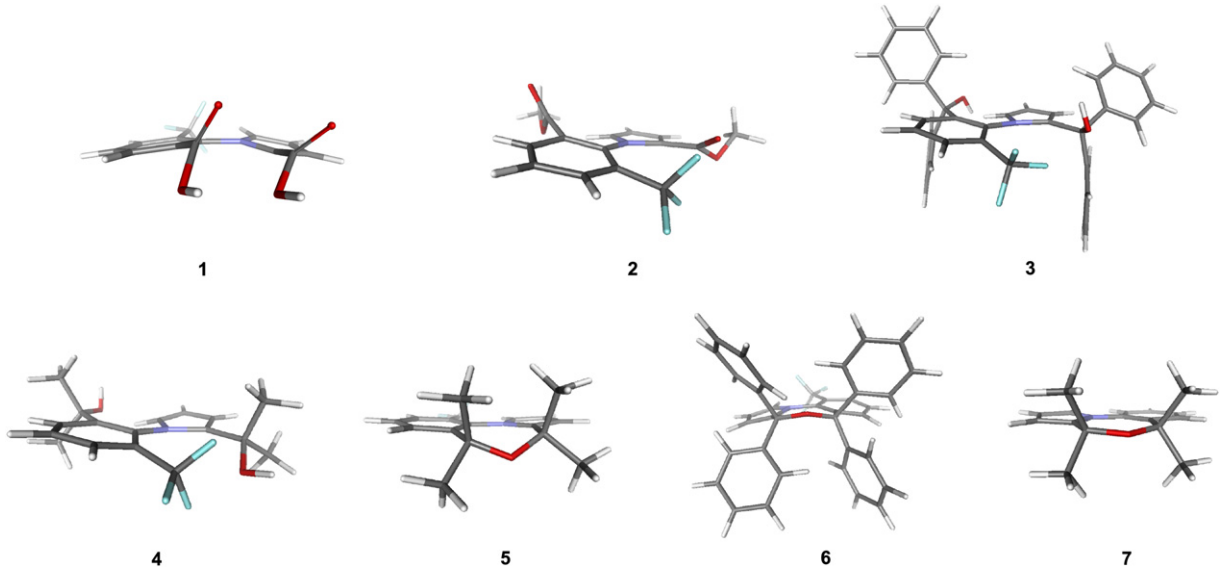


Figure 4. Transition state geometries of compounds **1**–**7** calculated by AM1 method (red: oxygen, blue: nitrogen, green: fluoro atom).

Table 1
Calculated and experimentally determined activation energies for isomerization of compounds **1**–**7**

Compound	$\Delta G^{\#}_{\text{calculated}}$ (kcal/mol)	$\Delta G^{\#}_{\text{measured}}$ (kcal/mol)
1	32.9	31.6
2	45.1	—
3	114.3	—
4	87.0	—
5	22.2	—
6	49.0	—
7	17.9	13.9

energies of isomerization of compounds **5** and **6** shows that introduction of the four phenyl rings leads to higher conformational rigidity in case of **6** than for compound **5** where methyls are present (Table 1).

In addition to the AM1 calculations, sample stability allowed us to determine the $\Delta G^{\#}$ of **1** experimentally. To achieve this, pure *R*-(−)-**1** atropisomer was dissolved into DMSO and put into a drying cabinet heated to 150±1 °C. With this way the racemization process described by Eq. 1

$$(-) \underset{k_{-1}}{\overset{k_{+1}}{\rightleftarrows}} (+) \tag{1}$$

was accelerated by raising the rate constants k_{+1} and k_{-1} of the process with the temperature. As illustrated in Figure 5, the enantiomeric composition was determined from time to time by sampling the solution and quenching the racemization by rapid cooling to room temperature. Because at room temperature no racemization is possible, the DMSO solution of *R*-(−)- **1** already containing growing amounts of *S*-(+)-**1** was transferred to the aqueous 2HP-β-CD solution appropriate for the enantiomeric analysis.

By having the various (−)/(+) ratios as a function of time (*t*) one can

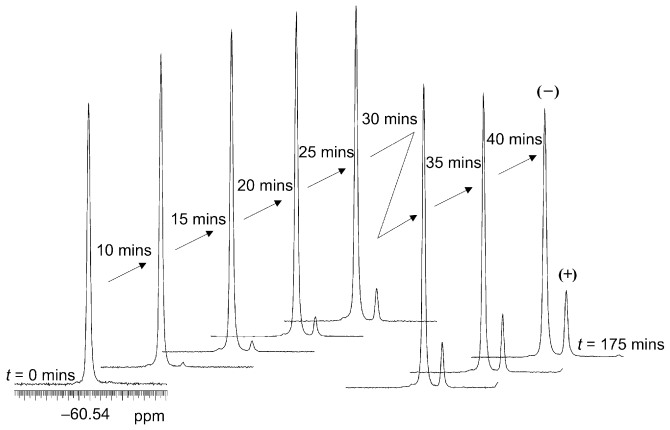


Figure 5. Analyses of the enantiomeric purities of samples **1** by ^{19}F NMR (470 MHz) performed in a study to determine the $\Delta G^{\ddagger}$ of the C–N rotation barrier. Spectra are recorded in buffered D_2O at 25 °C in the presence of 2HP-β-CD (0.1 M NaH_2PO_4) after various *t* incubation periods (the differences are shown) held at 423 K in DMSO.

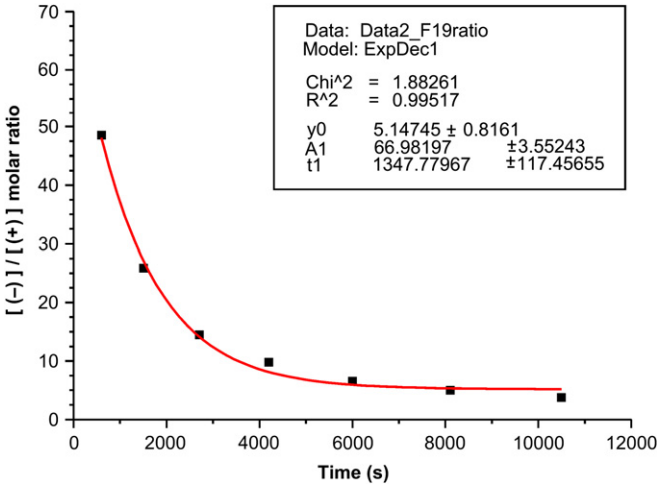


Figure 6. The enantiomeric (−)/(+) ratios for **1** plotted against the incubation time spent at 423 K. Values are from the integrals of the ^{19}F NMR experiments shown in Figure 5 and $k_{+1}=1/(2\times t1)$ according to the fitted equation.

$$\frac{[(-)]}{[(+)]} = 1 + e^{-2k_{+1}t} \tag{2}$$

construct the plot seen in Figure 6 and determine the rate constant of the process by exponential fitting according to Eq. 2. When k_{+1} is substituted in Eq. 3 $\Delta G^{\ddagger}$ can be determined for the elevated temperature (423 K),

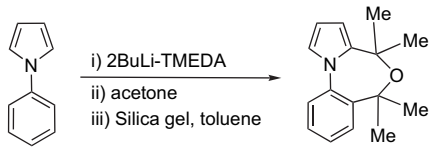
$$k_{+1} = (k_B T/h) e^{-\Delta G^{+}/RT} \tag{3}$$

where k_B is the Boltzmann-constant, *h* is the Planck-constant, *R* is the universal gas constant and *T* is the temperature.[11,12] The first-order kinetic process can be further characterized by the $\tau_{1/2}$ half-life of the racemization using Eq. 4.

$$\tau_{1/2} = \ln 2/(2k_{+1}) \tag{4}$$

Performing these calculations we have found for **1** that the $\Delta G^{\ddagger}$=+32.9 kcal/mol corresponds to a $\tau_{1/2}$=2.3 h at 423 K whereas the same value at 298 K is $\tau_{1/2}$=516 years. This confirms that *R*-(−)-**1** retains its optical activity at room temperature once separated from its enantiomer. The theoretically determined and the experimental $\Delta G^{\ddagger}$ values for **1** are in good agreement. By comparing the large differences between the calculated barriers of C–N rotation in Table 1 we also conclude that the low level of computational accuracy (AM1) seems to be reliable to confirm and predict whether the investigated compounds follow the experimentally underscored trends.

Molecular modeling calculations were extended to compound **7**. Comparison of the calculated activation energy of **7** with $\Delta G^{\#}$ of **5** gave information on the contribution of the CF_3 group to the hindrance of rotation (it increases the stability of a given atropisomer of **5** in about 4.3 kcal/mol). Compound **7** was synthesized earlier via dilithiation of 1-phenylpyrrole, addition of 2 molar equiv of acetone, and ring closure by silica gel (Scheme 2).[13]



7

Scheme 2. Synthesis of compound **7**.

Then the rotational barrier around the C–N bond was experimentally determined from the coalescence temperature (T_c=284 K) looking at the resonances of the diastereoisomeric methyl groups in the ^{1}H NMR spectra measured at different temperatures.[14] Comparison of the calculated and experimentally determined activation energy values (Table 1) shows that the calculation gave an overestimation of the rotational barrier. Smaller difference but the same tendency could be observed in the case of compound **1** where the calculated $\Delta G^{\#}$ value was also higher than the experimentally determined one (Table 1). Taking these facts in mind one can understand racemization of **5** during its formation at ambient temperature.

Spontaneous ring closing reaction of the tetramethyldiol derivative (**4**) occurred in protic media by protonation of the hydroxyl groups followed by water elimination. Easy formation of the cationic intermediates may be due to the electron donating effects of the methyl groups. Fast intramolecular reaction between the benzylic type cation and the hydroxyl oxygen atom results in the pyrrolobenzoxazepine **5**. The conformational isomers may interchange before or after the ring closure because of the small rotational barrier of **5** as it was discussed above.

Contrary to the tetramethyl derivative **4**, the rotational barrier of **6** is high enough (49 kcal/mol) to avoid racemization. Experimental results demonstrated that the tetraphenyl diol **3** is chemically stable in protic media at ambient temperature; pyrrolobenzoxazepine ring could be closed when it was warmed to 60 °C for several hours in the presence of an acidic catalyst. In other words differences in electronic properties of the methyl and phenyl substituents in benzylic positions cause significant differences in the chemical and atropisomeric stabilities of the diols **4**, **3**, and the pyrrolobenzoxazepines **5** and **6** as well.

3. Conclusions

Chemical transformation of the atropisomeric dicarboxylic acid **1** into its methyl ester (**2**), tetrasubstituted diols (**3** and **4**), and pyrrolobenzoxazepine derivatives (**5** and **6**) demonstrated that new optically active members of the atropisomeric 1-arylpyrrole family can be synthesized from the easily available optically active dicarboxylic acid if the introduced substituents are bulky enough and does not induce spontaneous ring closure reaction.

Experimental NMR methods have been optimized to follow the enantiomeric composition of the reaction products. In parallel, AM1 calculations were performed for rapid estimation of the activation energies ($\Delta G^{\#}$). The combination of calculations and measurements let us to conclude that the opened structures (**1**–**4**) need much higher activation energies for rotation around the interconnecting C–N bond than in the cases of the pyrrolobenzoxazepines (**5**, **6**, and **7**). As expected, the trifluoromethyl substituent in C6 position increases the activation energy by about 4.3 kcal/mol related to the C6 unsubstituted pyrrolobenzoxazepine **7**. The four methyl groups in **5** cause much smaller steric hindrance than the four phenyl groups in **6** and the electron donating effects of the methyl groups lend extra stability and easy formation of the benzylic cation type intermediates in the **4**→**5** reaction. These two effects may have crucial importance in the spontaneous ring closing and racemization of **5** at ambient temperature.

On the other hand, compounds **3** and **6** are stereochemically stable enough to become potential new chiral ligands in enantioselective reactions.

4. Experimental

4.1. Generalities

All commercial starting materials were purchased from FULKA AG and Merk-Schuchardt and were used without further purification. *n*-Butyllithium was supplied by Chemetall GmbH Lithium Division, Frankfurt. Diethyl ether and tetrahydrofuran were obtained anhydrous by distillation from sodium wire after the characteristic blue color of in situ generated sodium diphenylketyl had been found to persist. TMEDA and PMDTA were also distilled from sodium wire before use. Concentration of the butyllithium solution was determined by double titration method.[13] All experiments were carried out in Schlenk-flasks under a dry nitrogen atmosphere.

Routine ^{1}H NMR spectra were recorded in $CDCl_3$ solution or in DMSO-d_6 on a BRUKER WP 250 spectrometer (250 MHz for ^{1}H). Proton chemical shifts are reported in parts per million relative to the internal standard tetramethylsilane (δ_{TMS}=0 ppm). The enantiomeric ratios of optically active samples of **1** and **2** were determined from the ^{19}F spectra recorded at 25 °C on a Varian Inova$_{500}$ spectrometer (operating at 500 MHz for ^{1}H). ^{19}F chemical shifts are given relative to the internal standard $CFCl_3$ in $CDCl_3$. Analytical grade 2HP-β-CD was purchased from Cyclolab, Hungary. Enantiomeric ratios of **3** and **5** were also measured at 25 °C on a Varian Inova$_{500}$ spectrometer using ytterbium-trifluoromethyl-camphorate Yb(TFC)$_3$ purchased from Wilmad, USA. Computations were performed at the AM1 semiempirical level implemented in the MOPAC package of InsightII® commercial software on a Silicon Graphics® Octane® (R10000) machine. Exponential fitting was performed in MicrocalOrigin® 6.0. IR spectra were recorded on an appliance type PERKIN ELMER 1600 with a Fourier Transformer. Data are given in cm^{-1}. HPLC measurements were carried out on Chiracel AD column (256 nm UV detector, 0.8 mL/min, eluent hexane/ethanol=87:13). Specific rotation of the optically active samples was determined on a PERKIN ELMER 245 MC polarimeter using sodium lamp (289 nm). All mass spectra were recorded on a Finnigan MAT 95SQ hybrid-tandem

mass spectrometer. The electron ionization (EI) spectra were obtained at 70 eV using a heated direct inlet system. A Cs ion gun was used for FAB experiments and the energy of the bombarding Cs^+ beam was 30 keV. The matrix was glycerol. The exact mass determination was performed at the resolving power of 5000 and using PFK (perfluorokerosene) and glycerol adduct ions as references for EI and FAB measurements, respectively.

4.1.1. Methyl (*R*)-(−)-1-[2-methoxycarbonyl-6-(trifluoromethyl)phenyl]pyrrole-2-carboxylate (**2**)

A solution of (*R*)-1-[2-carboxy-6-(trifluoromethyl)phenyl]-pyrrole-2-carboxylic acid (**1**, 5.7 mmol, 1.71 g, ee 99.8%) in methanol (5 mL) was added to a methanol solution of sodium methylate (13 mmol, 0.70 g in 10 mL solvent) then the methanol was evaporated in vacuo. The residue was dissolved in dry dimethylformamide and methyl iodide (13 mmol, 1.9 g) was added into it. The reaction mixture was stirred for 1.5 h then it was poured into ice cold water (20 mL) and extracted with diethyl ether (3×10 mL). The organic solutions were collected, washed with water (10 mL), dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (Kiesel gel, eluent hexane/ethyl acetate=2:1). The pure diester **2** is a white solid, 1.57 g (84%, ee 99.8%), $[\alpha]_D^{25}$ +54.3 (*c* 0.646, MeOH), mp 68−70 °C. ^{1}H NMR ($CDCl_3$): δ=8.17 (1H (5), d, *J*=8.0 Hz), 7.96 (1H (3), d, *J*=8.0 Hz), 7.65 (1H (4), t, *J*=8.0 Hz), 7.09 (1H (β′), dd, *J*=3.8, 1.5 Hz), 6.85 (1H (α), t, *J*=0.9 Hz), 6.35 (1H (β), dd, *J*=3.8, 2.7 Hz), 3.66 (3H (CH_3), s), 3.65 (3H (CH_3), s). IR (KBr, cm^{-1}): 3013, 2896 (ν_{C-H}), 1706, 1675 ($\nu_{C=O}$). MS (EI) *m*/*z*=327 (100, M), 296 (7), 268 (13), 252 (44), 238 (22), 59 (8). HRMS (EI) *m*/*z* calcd for $C_{15}H_{12}F_3NO_4$ (327.0718). Found: 327.0718.

4.1.2. 4,4,6,6-Tetramethyl-10-trifluoromethyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepine (**5**)

Methylmagnezium iodide (20 mmol, 8.31 g) was prepared in dry diethyl ether (30 mL) by addition of methyl iodide (20 mmol, 2.84 g) to the magnesium turnings in diethyl ether. Then the solution of the dimethyl ester (*R*)-(−)-**2** (4.3 mmol, 1.41 g, ee 99.8%) in diethyl ether (10 mL) was added and the reaction mixture was refluxed for 4 h. Saturated aqueous ammonium chloride solution was added (30 mL), the phases were separated, and the organic solution was washed with brine (20 mL) before drying over sodium sulfate. Thin layer chromatography shown that the ethereal solution contains the diol **4** and the pyrrolobenzoxazepine **5** in about 1:3 ratio. Therefore silica gel (4 g) was added to the solution and it was stirred overnight at 25 °C. The solvent was evaporated in vacuo and the product was isolated from the residue by column chromatography (silica gel, eluent hexane/ethyl acetate=3:1) to yield practically racemic **5** (51%, ee 0.5%) as a light yellow oil (51%, ee 0.5%), $[\alpha]_D^{25}$ −2.1 (*c* 0.60, MeOH). ^{1}H NMR ($CDCl_3$): δ=7.77 (1H (5), d, *J*=7.94 Hz), 7.71 (1H (3), d, *J*=7.88 Hz), 7.42 (1H (4), t, *J*=7.88 Hz), 6.91 (1H (α), sym.m), 6.26 (2H (β′+β), m), 1.64 (3H (CH_3), s), 1.62 (3H (CH_3), s), 1.03 (3H (CH_3), s), 0.65 (3H (CH_3), s). IR (film, cm^{-1}): 2980 (ν_{C-H}). MS (EI) *m*/*z*=309 (17, M), 294 (100), 252 (58), 236 (14), 43 (18). HRMS (EI) calcd for $C_{17}H_{18}F_3NO$ 309.1340. Found: 309.13405.

4.1.3. (*R*)-(−)-1-[6-Diphenylhydroxymethyl-2-(trifluoromethyl)phenyl]-2-(diphenylhydroxymethyl)pyrrole (**3**)

A solution of bromobenzene (35.5 mmol, 5.57 g) in dry tetrahydrofuran (55 mL) was cooled down to −75 °C and a hexane solution of butyllithium (35.5 mmol, 24 mL, 1.5 mol/L solution) was added into the stirred solution. Then, in 15 min stirring, (*R*)-(−)-**2** (6.1 mmol, 2.0 g, ee 99.8%) was added and the reaction mixture was stirred for 30 min at −75 °C. At room temperature, water (50 mL) and diethyl ether (30 mL) were added into it. The phases were separated, the aqueous phase was washed with diethyl ether (2×25 mL), the collected organic solutions were washed with brine (25 mL), dried over sodium sulfate, and concentrated in vacuo. The residue was stirred with hexane (40 mL), and the solid was filtered off and washed with cold hexane to yield diol **3** as white crystalline material (2.24 g, 64% ee 99.9%), $[\alpha]_D^{25}$ −50.6 (*c* 0.60, MeOH), mp 175−177 °C. ^{1}H NMR (DMSO-d_6): δ=7.42−7.15 (18H (3+4+5+Ph), m), 6.95 (2H (Ph), m), 5.89 (1H (α), m), 5.85 (1H (β′), t, *J*=2.98 Hz), 5.56 (1H (β), sym.m), 5.49 (1H (OH), s), 3.11 (1H (OH), s). IR (KBr): 3515, 3431 (ν_{O-H}) cm^{-1}. MS (EI) *m*/*z*=575 (28, M), 557 (56), 481 (21), 464 (44), 393 (18), 298 (23), 183 (14). HRMS (EI) *m*/*z* calcd for $C_{37}H_{28}F_3NO_2$ (575.2072). Found: 575.2074.

4.1.4. (*R*)-(+)-4,4,6,6-Tetraphenyl-10-(trifluoromethyl)-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepine (**6**)

Compound (*R*)-(−)-**3** (2.0 mmol, 1.15 g) was dissolved in toluene (50 mL) and silica gel (5 g) was added into it. Then the mixture was stirred at 60 °C for 4 h. The silica gel was filtered off and the solvent was evaporated to yield pure **6** as white solid (1.0 g, 90%, ee 99.9%) $[\alpha]_D^{25}$ +166.3 (*c* 0.60, MeOH), mp 199−200 °C. ^{1}H NMR ($CDCl_3$): δ=7.76 (2H (Ph), d, *J*=7.68 Hz), 7.58 (2H (Ph), d, *J*=7.73 Hz), 7.48−7.14 (10H (Ph), m), 6.98−6.88 (7H (Ph), m), 6.75 (1H (Ph), d, *J*=7.78 Hz), 6.61 (2H (α+5), m), 5.59 (1H (β′) t, *J*=3.35 Hz), 5.43 (1H (β), dd, *J*=1.17, 3.35 Hz). IR (KBr, cm^{-1}): 3089, 3058, 3032 (ν_{C-H}). MS (EI) *m*/*z*=557 (58, M), 480 (18), 464 (44), 393 (18), 298 (23), 183 (14), 105 (100), 77 (16). HRMS (EI) *m*/*z* calcd for $C_{37}H_{26}F_3NO$ (557.1966). Found: 557.1953.

4.1.5. 4,4,6,6-Tetramethyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepine (**7**)[8]

1-Phenylpyrrole (25 mmol, 3.6 g) was dissolved in dry diethyl ether (45 mL) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (55 mmol, 6.4 g, 8.3 mL) was added into it. The reaction mixture was cooled down to 0 °C and butyllithium (55 mmol) in hexane (40 mL) was added dropwise to the stirred solution. After 30 min acetone (52 mmol, 3.1 g, 4.1 mL) was added and then the reaction mixture was stirred until it warmed up to room temperature. Water (100 L) was added and the organic phase was separated, washed with brine (25 mL), dried over sodium sulfate, and concentrated in vacuo.

The residue was dissolved in toluene (40 mL), silica gel (6.0 g) was added, and the mixture was stirred at 40 °C for 2 h. The solvent was evaporated and residue was purified by column chromatography (silica gel, eluent: hexane/ethylacetate=3:1) to yield **7** as a solid material (3.5 g, 58%), mp 48–49 °C.

^{1}H NMR ($CDCl_3$): δ=7.49 (1H (Ph), d, J=7.6 Hz), 7.26–7.45 (3H (Ph), m), 6.92 (1H (α'), dd, J=2.8, 1.8 Hz), 6.25 (1H (β), t, J=3.2 Hz), 6.18 (1H (β'), dd, J=3.5, 1.8 Hz), 1.61 (6H (Me), s), 1.07 (3H (Me), s), 0.86 (3H (Me), s).

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References and notes

1. Clayden, J. *Angew. Chem., Int. Ed.* **1997**, *9*, 949.
2. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, NY, 1994.
3. Yang, F.; Xi, P.; Yang, L.; Lan, J.; Xie, R.; You, J. *J. Org. Chem.* **2007**, *72*, 5457.
4. Montoya-Pelaez, P. J.; Uh, Y.-S.; Lata, C.; Thompson, M. P.; Lemieux, R. P.; Crudden, C. M. *J. Org. Chem.* **2006**, *71*, 5921.
5. Kondo, K.; Kazuta, K.; Fujita, H.; Sakamoto, Y.; Yasuoki, M. *Tetrahedron* **2002**, *58*, 5209.
6. Fogassy, K.; Harmat, V.; Böcskei, Z.; Tárkányi, G.; Tőke, L.; Faigl, F. *Tetrahedron: Asymmetry* **2000**, *11*, 4771.
7. Faigl, F.; Thurner, A.; Kovári, J.; Tárkányi, G.; Tőke, L.; Mordini, A. *Tetrahedron: Asymmetry* **2002**, *13*, 59.
8. Hinckley, C. C. *J. Am. Chem. Soc.* **1969**, *91*, 5160.
9. Whitesides, G. M.; Lewis, D. W. *J. Am. Chem. Soc.* **1970**, *92*, 6979.
10. Wenzel, T. J. *NMR Shift Reagents*; CRC: New York, NY, 1987.
11. Stilbs, P. *Tetrahedron* **1973**, *29*, 2269.
12. Charlton, J. L.; Oleschuk, C. J.; Chee, G. L. *J. Org. Chem.* **1996**, *61*, 3452.
13. Faigl, F.; Schlosser, M. *Tetrahedron* **1993**, *49*, 10271.
14. Faigl, F.; Schlosser, M. Unpublished results, 1994.