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TETRAHEDRON: *ASYMMETRY*

# Atropisomerism in monopyrroles

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**Abstract**—As observed by NMR, iodopyrroles **1a** and **1b** (ethyl and methyl 3,5-dimethyl-4-[(1′-iodo-2′,2′-dimethyl)propyl]pyrrole-2-carboxylate) and a variety of related derivatives with iodine replaced by methoxy **2**, thiomethyl **3**, acetic acid esters **4**, propionic acid ester **5** or malonic esters **6** exhibit restricted rotation about the C(4)–C(1′) bond due to the bulky *tert*-butyl group and an *ortho* effect from the sterically crowded 3,5-dimethylpyrrole. Most of the compounds, which are members of the rare class of atropisomers due to restricted rotation about an $sp^3$–$sp^2$ C–C bond, undergo diastereomeric enrichment by preparative TLC and crystallization. From dynamic NMR studies of the enriched diastereomers one can determine kinetic and thermodynamic parameters associated with the atropisomerism, e.g., $\Delta G^{\ddagger}$ ~24 kcal/mol for **1** and **5** (313 K), ~22 kcal/mol for **3** (273 K), and ~25 kcal/mol for **6** (313 K) in $C_2D_2Cl_4$ solvent. 

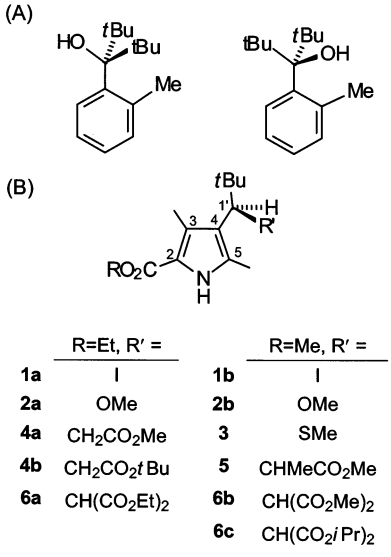
## 1. Introduction

Atropisomerism is usually associated with biaryl systems, where bond rotation about the $sp^2$–$sp^2$ C–C bond is sufficiently restricted so as to lead to separable conformers.[1,2] Typically, this means a free energy barrier of 26.2 kcal/mol at 300 K and a half-life of 1000 s. Restricted rotation about an $sp^2$–$sp^3$ C–C bond has been observed less often.[3] In systems involving fluorenes, with sufficiently large substituents judiciously placed to interfere with bond rotation, atropisomers have been isolated.[1,2,4] One of the simplest examples has only one aromatic ring: the di-*tert*-butyl compound of Fig. 1A, whose atropisomers have been isolated.[5] There are far fewer examples of atropisomerism of the biaryl type among pyrrole compounds,[6] a research area of current interest to us. In the following, we report what we believe to be the first examples (Fig. 1B) of $sp^2$C–$sp^3$C atropisomerism in a monopyrrole.

## 2. Results and discussion

### 2.1. Iodopyrroles 1a and 1b

Over 25 years ago, Khan and Plieninger[7] reported on the synthesis of **1a** from a β-free pyrrole **7a** by reaction with pivaldehyde in the presence of HI (Scheme 1). Although **1a** was characterized, only its melting point and combustion analysis data were published. NMR data were absent and not mentioned. We repeated the synthesis and isolation of pure **1a** and also prepared methyl ester **1b**, both of which are useful compounds in the synthesis of highly hindered bilirubins and biliverdins. Interestingly, the $^1$H NMR spectrum of **1a** was




| | R=Et, R′ = | | R=Me, R′ = |
|---|---|---|---|
| **1a** | I | **1b** | I |
| **2a** | OMe | **2b** | OMe |
| **4a** | $CH_2CO_2Me$ | **3** | SMe |
| **4b** | $CH_2CO_2tBu$ | **5** | $CHMeCO_2Me$ |
| **6a** | $CH(CO_2Et)_2$ | **6b** | $CH(CO_2Me)_2$ |
| | | **6c** | $CH(CO_2iPr)_2$ |

**Figure 1.** (A) Isolable atropisomers with one aromatic ring. (B) Atropisomeric monopyrroles with restricted rotation about the C(4)–C(1′) bond. The absolute configuration at C(1′) is arbitrary.

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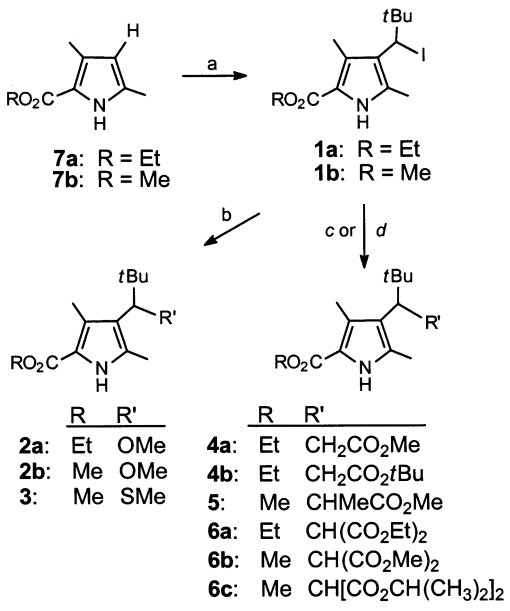



*Reagents and conditions.*

(a) $(CH_3)_3CCHO$, HI, $Ac_2O$, $H_3PO_2$
(b) $CH_3OH$ or $CH_3SH$

| (c) LDA / THF + | (d) NaH / THF + |
|---|---|
| **4a**: $CH_3CO_2Me$ | **6a**: $CH_2(CO_2Et)_2$ |
| **4b**: $CH_3CO_2tBu$ | **6b**: $CH_2(CO_2Me)_2$ |
| **5**: $CH_3CH_2CO_2Me$ | **6c**: $CH_2(CO_2iPr)_2$ |

**Scheme 1.**

consistent with diastereotopic hydrogens from the $CH_2$ group of the ethyl ester unit (Fig. 2A), and all of the proton (Fig. 2B) and $^{13}C$ NMR signals (Fig. 3) were doubled in both **1a** and **1b**. Since **1a** and **1b** possess but a single stereogenic center, a second element of chirality (namely an axis of chirality along the C(4)–C(1′) bond) must be present in order to account for the apparent diastereomers seen by NMR, which suggests that **1a** and **1b** are mixtures of diastereomeric atropisomers (Fig. 4). However, chromatography (TLC) failed to separate isomers of **1a** and **1b**, and induced decomposition. (These iodo compounds are stable as solids but rather unstable or reactive in solution.)

Integration of the $^1H$ NMR signals indicated an 88:12 ratio in **1a** and a 7:3 ratio in **1b**. Crystallization of **1b** changed the ratio from 7:3 to 93:7, as determined by $^1H$ NMR integration, but after standing in $CDCl_3$ solvent for 72 hours at room temperature, the ratio returned to 7:3, which we take to represent an equilibrated mixture. (The 88:12 ratio observed for **1a**, a ratio that we attribute to the lower reaction temperature used in its synthesis, drifted to 7:3 under the same experimental conditions.) Near diastereomerically pure **1a** (99:1) was

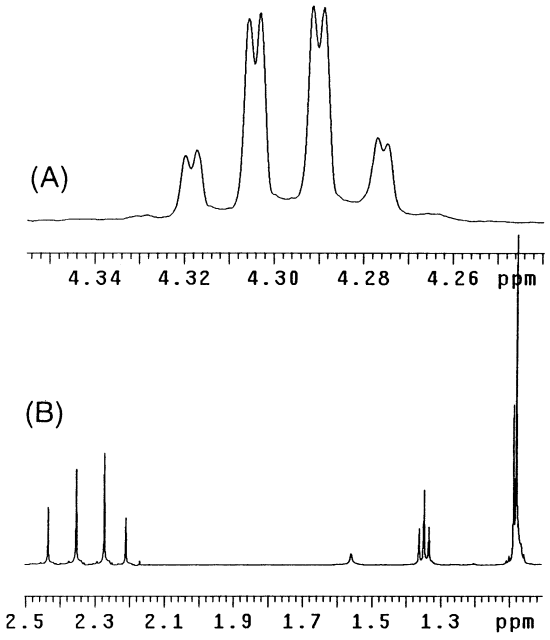



**Figure 2.** Partial $^1H$ NMR spectra of **1a** showing (A) diastereotopic $-OCH_2-$ hydrogens and (B) showing signal doubling. (Signal doubling is also observed in **1b**.)

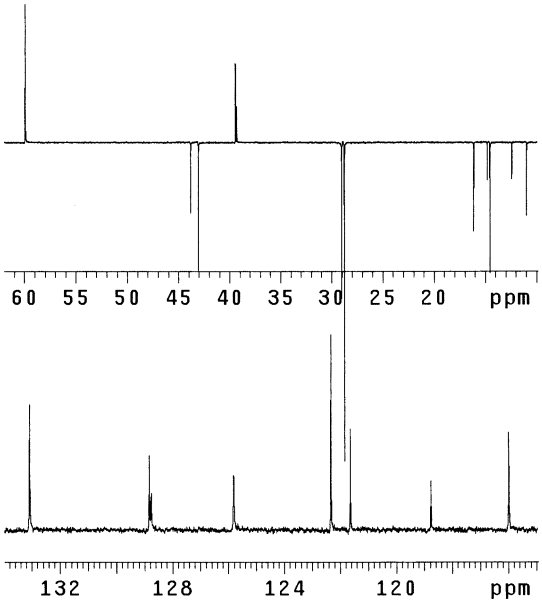



**Figure 3.** Partial $^{13}C$ NMR APT spectra of **1a** showing signal doubling in the high field aliphatic region (top) and in the pyrrole ring carbon region (bottom). The carbon signals are also doubled in **1b**.

obtained by crystallization from hexane–dichloromethane with slow evaporation of the dichloromethane at 0°C. Similarly, a highly enriched (93:7) sample of **1b** was obtained by crystallization from hexane–dichloromethane (by evaporation of the latter at 0°C). These diastereomerically enriched samples were used to study the rates of interconversion of the atropisomers.

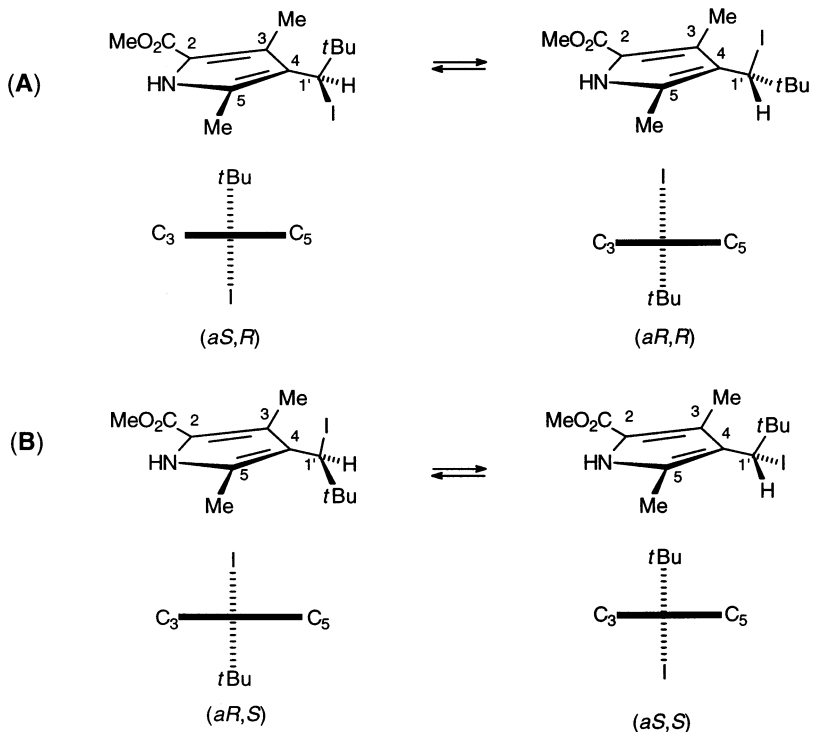



**Figure 4.** The diastereomers of methyl 3,5-dimethyl-4-[(2′2′-dimethyl-1′-iodo)propyl]-pyrrole-2-carboxylate **1b**, as viewed from C(4) to C(1′). There are two atropisomeric pairs: (**A**) and (**B**), and two enantiomeric pairs: (*aR*,*R*)+(*aS*,*S*) and (*aS*,*R*)+(*aR*,*S*).

### 2.2. Methyl ether 2 and methyl thioether 3

Treatment of **1b** with methanol gave methyl ether **2b**, via solvolysis of the labile iodide; whereas the corresponding ethyl ester **2a** had been reported previously.[7] Both **2a** and **2b** exhibited an ~7:3 ratio of two sets of signals in their $^1$H NMR spectra, and the $^{13}$C NMR signals were doubled. Again, apparent thermodynamic equilibrium of atropisomeric diastereomers was achieved at a 7:3 ratio at room temperature. Although the methyl ethers are much more stable than their iodo precursors and can be handled easily in solution or in the solid state, neither gave evidence for separation on TLC. Nor could diastereomeric enrichment be achieved by crystallization.

Bubbling methanethiol through a solution of **1b** in tetrahydrofuran was strongly exothermic and led to a quantitative conversion to thioether **3**. Its $^1$H and $^{13}$C NMR spectra indicated a 73:27 mixture of diastereomers, and preparative TLC afforded an 85:15 diastereomeric enrichment. Crystallization at 0°C from pre-cooled methylene chloride and hexane, while removing the methylene chloride in a stream of air at 0°C gave crystals further enriched to d.r. of 98:2, and these were used for dynamic NMR measurements.

### 2.3. Acetic acid esters 4

Alkylation of the anions of methyl or *t*-butyl acetate generated from reaction of LDA at −78°C to −55°C in THF in the presence of HMPA[8] with **1a** gave 88 and 82% yields of **4a** and **4b**, respectively. Both purified products afforded crystalline fractions whose NMR spectra indicated a 65:35 mixture of atropisomers. The same ratios were observed in the corresponding mother liquors. Chromatography (TLC or radial) failed to separate the atropisomers of **4a** and **4b**, thus precluding a kinetic study of their interconversion. This necessitated the introduction of an ester residue larger than acetic acid ester vicinal to the C(1′) stereogenic carbon center.

### 2.4. 2-Propionate ester 5

Alkylation as above of the anion of methyl propionate with iodide **1b** gave a 95% yield of **5** as a mixture of diastereomers. GC–MS indicated two components with identical MS fragmentation patterns. Separation by radial chromatography on silica gel afforded 54% of a less polar component **5-lp** and 40% of a more polar **5-mp**. The NMR spectra were consistent with configurational diastereomers, each consisting of two atropisomers. Unlike the other pyrroles of this study, **5** has a second stereogenic center (in the 2-propionic ester group). NMR nicely distinguished diastereomers **5-lp** and **5-mp**, with the groups near the stereogenic α-carbon of the aliphatic ester side chain showing the largest chemical shift differences. For example, in the $^1$H NMR spectrum, the α-$CH_3$ protons of **5-lp** appeared at 0.83 and 0.85 ppm, but in **5-mp** they appeared at 1.37 and 1.38 ppm; and the aliphatic ester methoxy protons of **5-lp** were seen at 3.81 and 3.82 ppm, while those of **5-mp** were at 3.288 and 3.294 ppm. Similarly, in the $^{13}$C NMR spectrum, the α-CH of **5-lp** appeared at 38.87 and 39.09 ppm, while that of **5-mp** appeared at 42.30 and 42.81 ppm; and the aliphatic ester carbonyl carbon of **5-lp** was seen at 178.92 and 179.26 ppm while in **5-mp** it resonated at 176.35 and 176.72 ppm.

Both **5-lp** and **5-mp** solidified slowly on standing, but **5-lp** was more prone to crystallization. Recrystallization at ambient temperature of the almost 1:1 mixture of **5-lp** atropisomers (828 mg) afforded 184 mg (22%) of a single atropisomer. It had mp 128–129°C. Recrystallization of the more polar diastereomer **5-mp** was much more difficult. From 621 mg of the mixture of atropisomers, a fraction (477 mg, 77%) was obtained, whose $^1$H NMR still showed two atropisomers present in an ~60:40 ratio. Several recrystallizations at room temperature or at 0°C from hexane, hexane–ethyl acetate or hexane–dichloromethane (evaporating the dichloromethane at 0°C) afforded only equilibrated mixtures of atropisomers (ratios 69:31). The same equilibrium ratios were found in the mother liquors of **5-mp**. The solid fraction of **5-mp** had mp 105–106°C. Thus, the higher melting point of one of the rotamers of **5-lp** suggests that during the crystal packing the lattice preferentially accommodates only one atropisomer. In the case of lower melting, more polar **5-mp**, once crystallization begins, there is no distinction between atropisomers, and both are included in the crystal in a ratio typical of equilibration. Despite numerous attempts, TLC separation of atropisomers within each of diastereomers **5-lp** and **5-mp** could not be achieved. The single atropisomer obtained for **5-lp** was used for dynamic NMR measurements in a study of the kinetics of atropisomerization.

### 2.5. Malonic esters 6

Reaction of **1a** with sodio diethyl malonate, prepared from diethyl malonate by reaction with sodium ethoxide in ethanol or sodium hydride in THF afforded a high yield of **6a**. In contrast, **1b** gave mainly **2b** (and 30% of **6b**) when reacted with sodio dimethyl malonate in refluxing methanol and a 93% yield when the alkylation was carried out in THF using the sodio malonate generated using NaH in THF. Solvolysis of **1b** seems to be comparatively more rapid in refluxing methanol than that of **1a** in refluxing ethanol. Consequently, NaH was used as the base in the syntheses of **6b** and **6c**. Product **6a** was found to be a 69:31 mixture of atropisomers, as indicated by $^1$H NMR. The atropisomers were separated by preparative TLC, applying a very low load of <10 mg on each 20×20 cm plate made with an 0.75 mm thick silica gel layer and developed twice with hexane–cyclohexane–ethyl acetate (4:4:2 by vol.) at room temperature. The zone of diastereomer overlap on the TLC plate was discarded and the less polar fraction was obtained 97% diastereomerically pure after crystallization at 0°C. In contrast, the more polar fraction did not crystallize. The latter, a thick oil reverted to a 7:3 mixture of atropisomers at room temperature. The less polar crystalline (mp 79–80°C) material was stable in the crystal but slowly reverted to a 7:3 mixture of atropisomers when dissolved in $C_2D_2Cl_4$ solvent at 25°C (Fig. 5). We used it for a comprehensive kinetic study of diastereomer interconversion.

Malonic ester **6b** was obtained as a 65:35 oily mixture of atropisomers which was separated by preparative TLC on silica gel at 5°C into a less polar, crystalline fraction (mp 119–120°C) and an oily, more polar fraction. Remarkably, the less polar, crystalline atropisomer crystallized spontaneously from the ~7:3 (oily) atropisomer mixture. The oil, after removal of the crystals, again produced crystals as the thermodynamically less favored atropisomer converted to the more crystalline atropisomer, which was removed by crystallization—a conversion akin to an asymmetric transformation of the second kind. The crystalline atropisomer of **6b** thus isolated was 96% diastereomerically pure by $^1$H NMR. The crystalline, less polar fraction (mp 119–120°C) was sufficiently diastereomerically pure for kinetic studies of its atropisomerization.

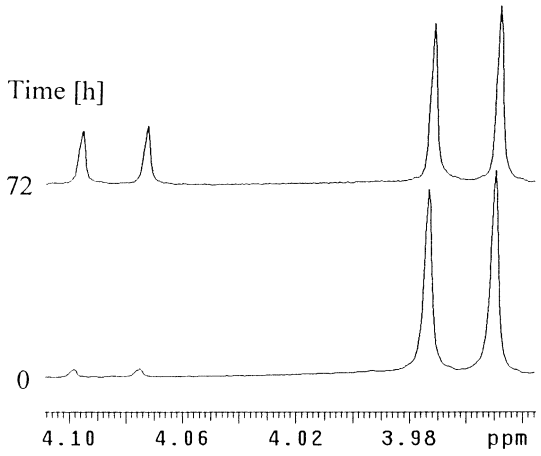



**Figure 5.** Partial $^1$H NMR spectrum of pure **6a** in $CDCl_3$ showing the diastereotopic malonic ester methine signals at time 0, and after standing for 72 h at 25°C. The emergence of the new signals corresponds to the formation of an atropisomer by rotation about the C(4)–C(1′) bond (see Figs. 1 and 4). The equilibrium reached after 72 h corresponds to a 7:3 ratio of atropisomers, the same as that observed in the synthesis of **6a**, before chromatographic separation. Similar clear changes may be observed for all the NMR signals, but those for the malonic ester methine, the C(1′)–H, the N–H and the C(5)–$CH_3$ protons are nicely separated.

Similarly, the diisopropyl malonate ester **6c** was obtained in 90% yield as a thick oily mixture of atropisomers (66:34). Separation of the diastereomers was achieved by preparative TLC on silica gel and recrystallization at 0°C from ethyl acetate–hexane to afford a crystalline less polar isomer (mp 98–99°C) of sufficient purity (98%) for a kinetic study of atropisomerization.

### 2.6. Atropisomerism

The process of interconversion of atropisomeric diastereomers of **1**–**6** (as shown for **1b** in Fig. 4) may be expressed as a reversible isomerization equilibrium:

$$A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} A'$$

The equilibrium constant $K$ may thus be expressed as:

$$\frac{[A']_{eq}}{[A]_{eq}}=\frac{[A]_0-[A]_{eq}}{[A]_{eq}}=\frac{k_1}{k_2}=K \quad (1)$$

where $[A]_{eq}$ and $[A']_{eq}$ are the equilibrium concentrations of the diastereomers and $[A]_0$ is the initial concentration of one diastereomer present at the start of an isomerization ($t=0$). Here, the isomerization occurs by rotation about the pyrrole C(4)–C(1′) carbon–carbon bond, corresponding to a configurationally labile axis of chirality.

From the rate law for a reversible isomerization:

$$\frac{d[A]}{dt}=-k_1[A]+k_2[A'] \quad (2)$$

one may derive the integrated rate expression:

$$\ln\frac{[A]_0-[A]_{eq}}{[A]-[A]_{eq}}=(k_1+k_2)t \quad (3)$$

which is the equation used for treating the NMR intensity data below.

Combining Eqs. (1) and (2) gives:

$$\frac{d[A]}{dt}=-k_1[A]+\frac{k_1}{K}[A']=-k_1[A](1-[A'])/[A]K \quad (4)$$

from which it is clear that while the reaction has an initial rate of $k_1[A]$, it slows as A′ accumulates. Consequently, only the NMR integral intensities from the initial stages were used. As [A] approaches $[A]_{eq}$, the constructed linear plots become unreliable. When $[A']/[A]=K$, the reaction is at equilibrium, and the observed rate falls to zero. Since the diastereomeric groups are anisochronous, and their integral ratios do not change when the sample is at equilibrium, no changes in the NMR spectra (e.g. coalescence) should be observed over time at moderately elevated temperatures.

For practical purposes [A] and [A′] are determined by integration of relevant well-separated $^1$H NMR signals and followed over time at fixed intervals and at controlled temperature. Typically, several pairs of signals were followed, and the mean values of rate constants were used for subsequent energy calculations. The concentrations at equilibrium $[A]_{eq}$ and $[A']_{eq}$ were determined at time 'infinity', i.e. when no further spectral changes were found. Plots of $-\ln([A]-[A]_{eq})$ versus time (in s) were found to be linear, with slopes equal to $(k_1+k_2)$. Since the ratio $k_1{:}k_2$ can be calculated from the equilibrium concentrations (integrals), the individual values of $k_1$ and $k_2$ could be obtained. And from such values of $k$, the free energy of activation ($\Delta G^{\ddagger}$) could be determined from the Eyring equation $\Delta G^{\ddagger}=RT[23.76-\ln(k/T)]$.[9] From kinetics, the difference between the free energies of activation ($\Delta G^{\ddagger}$) for the forward and backward isomerizations is equal to the Gibbs free energy for the equilibrium, $\Delta G°$, which may also be determined from the ratio $k_1/k_2$. From thermodynamic considerations, $\Delta G°$ may be found directly from the equilibrium concentrations, determined by NMR and from $\Delta H°$ and $\Delta S°$ obtained by plotting $R\ln K_{eq}$ versus $1/T$ at four different temperatures (for the atropisomerism of **6a**). The validity of the $k_1$ and $k_2$ data was affirmed by the observation that the independent kinetic and thermodynamic methods led to identical $\Delta G°$ values.

Using the approach outlined above, we were able to calculate a comprehensive set of kinetic and thermodynamic data for the atropisomerism of **1**–**6**. For example, with a 93:7 atropisomerically enriched sample of **6b**, the progressive increase of the minor atropisomer over time is displayed in Fig. 6. From these and similar data from the pyrrole NH, C(3)–$CH_3$, and C(5)–$CH_3$, C(1′)–H and malonate α-methine signals, the integrated ($^1$H NMR) ratios were conveniently followed and measured in $CDCl_2CDCl_2$ solvent at 293, 313, 333 and 353 K. The NMR integration data for **1b** at 313 K and equilibrium constants are shown in Table 1, from which we compute the values of $-\ln([A]-[A]_{eq})$ found in Table 2.

Using the data from Table 2 for the C(1′)–H $^1$H NMR signal of **1b**, a plot of $-\ln([A]-[A]_{eq})$ versus time (Fig. 7) shows excellent linearity over the range of measurements. Similarly good data fits were found for plots of $-\ln([A]-[A]_{eq})$ versus time for the N–H, C(3)–$CH_3$ and C(5)–$CH_3$ signals. From the slopes of best fit lines for all four signals measured (Tables 1 and 2), one may determine $(k_1+k_2)$ for the atropisomerism, and from the corresponding equilibrium constants ($K$), the mean rate constants: $k_1=7.21\times10^{-5}$ s$^{-1}$ and $k_2=1.51\times10^{-4}$ s$^{-1}$ were determined. It is also possible to compute the free energies of activation for the forward and back reactions, $\Delta G_1^{\ddagger}$ and $\Delta G_2^{\ddagger}$ from $k_1$ and $k_2$ using the Eyring equation:[9] the mean $\Delta G_1^{\ddagger}=24.28$ kcal/mol and the mean $\Delta G_2^{\ddagger}=23.82$ kcal/mol at 313 K.

Similar kinetic studies were carried out for **3**, **5** and **6** (Table 3). We could not achieve sufficient diastereomeric separation beyond the 7:3 mixture of **2** needed to carry out such studies with **2**. It is clear from the data for **3** that when the C(1′) group is as small as methoxy, $\Delta G^{\ddagger}$ is too small to promote facile separation of atropisomers at ambient temperature to 0°C. While the methylthio group affords barely sufficient steric hindrance to atropisomerism about the C(4)–C(1′) bond, it is clear that iodo substituent provides a substantially larger barrier to free rotation, presumably because the C–I bond is longer (~2.2 Å) than the C–S bond (~1.8 Å), and the C–O bond is even shorter (~1.4 Å).[10] A methylene group adjacent to C(1′), as in **4**, is apparently too small to slow the rotational isomerization sufficiently. The bulkier 2-propionic ester group of **5** is, perhaps surprisingly, slightly less effective than iodo in raising the barrier. From the large ($^3J=11.3$ Hz) vicinal spin–spin NMR coupling constant between C(1′) and C(α)–H of both atropisomers of **5**, we assume an *anti-periplanar* orientation of the two hydrogens and very likely a gearing effect in the restricted rotation about the C(1′)–C(α) bond. The malonic esters are significantly more effective in raising the activation energy, but there is little advantage in increasing the size of the malonic ester ($CO_2R$) R-group; cf. **6a**, **6b** and **6c**.

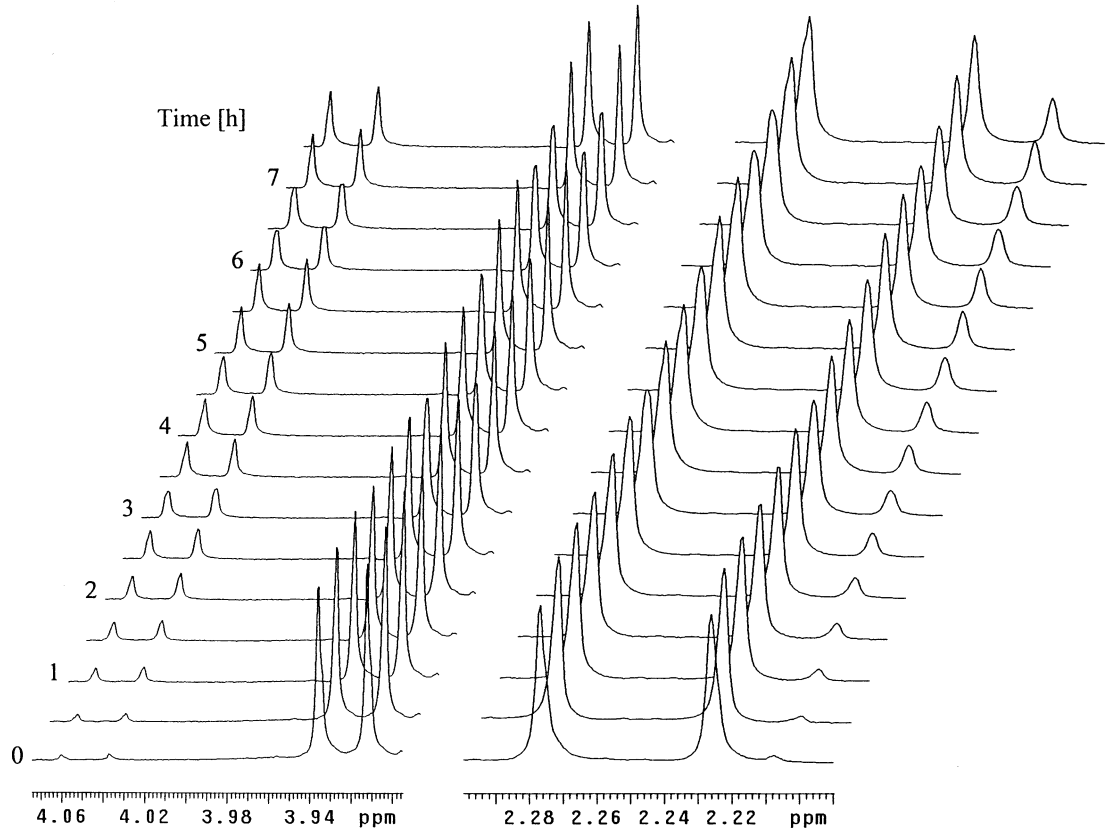



**Figure 6.** Partial $^1$H NMR spectra of **6b** showing the changes of (left) the malonate methine hydrogen at 4.06, 3.94 ppm; and (right) the pyrrole ring methyls at C(3), 2.28 ppm, and at C(5), 2.23, 2.21 ppm, over time (h) in $C_2D_2Cl_4$ at 313 K.

**Table 1.** $^1$H NMR integration ratios for the N–H, C(1′)–H, C(3)–$CH_3$ and C(5)–$CH_3$ diastereotopic hydrogens of **1b**, determined over an 8 h equilibration at 313 K in $CDCl_2CDCl_2$ solvent

| Measurement | Time (s) | NMR signal intensity measured | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N–H | | C(1′)–H | | C(3)–$CH_3$ | | C(5)–$CH_3$ | |
| | | $\delta^a = 8.59$ | 8.50 | 5.22 | 5.16 | 2.38 | 2.30 | 2.22 | 2.15 |
| 1 | 660 | 88.7 | 11.3 | 89.7 | 10.3 | 9.8 | 90.2 | 90.2 | 9.8 |
| 2 | 2460 | 82.4 | 17.6 | 82.6 | 17.4 | 17.0 | 83.0 | 82.7 | 17.3 |
| 3 | 4260 | 78.1 | 21.9 | 77.5 | 22.5 | 22.0 | 78.0 | 77.6 | 22.4 |
| 4 | 6060 | 75.3 | 24.7 | 74.1 | 25.9 | 25.4 | 74.6 | 74.1 | 25.9 |
| 5 | 7860 | 73.4 | 26.6 | 72.0 | 28.0 | 27.8 | 72.2 | 71.8 | 28.2 |
| 6 | 9660 | 71.9 | 28.1 | 70.4 | 29.6 | 29.4 | 70.6 | 70.2 | 29.8 |
| 7 | 11460 | 71.0 | 29.0 | 69.3 | 30.7 | 30.5 | 69.5 | 69.1 | 30.9 |
| 8 | 13260 | 70.5 | 29.5 | 68.7 | 31.3 | 31.2 | 68.8 | 68.4 | 31.6 |
| 9 | 15060 | 70.0 | 30.0 | 68.2 | 31.8 | 31.7 | 68.3 | 67.9 | 32.1 |
| 10 | 16860 | 69.7 | 30.3 | 67.9 | 32.1 | 32.0 | 68.0 | 67.7 | 32.3 |
| 11 | 18660 | 69.7 | 30.3 | 67.7 | 32.3 | 32.3 | 67.7 | 67.4 | 32.6 |
| 12 | 20460 | 69.6 | 30.4 | 67.5 | 32.5 | 32.5 | 67.5 | 67.2 | 32.8 |
| 13 | 22260 | 69.5 | 30.5 | 67.4 | 32.6 | 32.5 | 67.5 | 67.2 | 32.8 |
| 14 | 24060 | 69.3 | 30.7 | 67.3 | 32.7 | 32.6 | 67.4 | 67.1 | 32.9 |
| 15 | 25860 | 69.2 | 30.8 | 67.3 | 32.7 | 32.7 | 67.3 | 67.1 | 32.9 |
| 16 | 27660 | 69.1 | 30.9 | 67.3 | 32.7 | 32.7 | 67.3 | 67.1 | 32.9 |
| 17 | 29460 | 69.2 | 30.8 | 67.3 | 32.7 | 32.7 | 67.3 | 67.0 | 33.0 |
| $[A]_{eq}$[b,c] | | 69.2 | | 67.3 | | | 67.3 | 67.1 | |

[a] $\delta$, ppm.
[b] Where $[A]_{eq}$ = [dominant isomer] at equilibrium.
[c] Average value of $K_{eq} = 0.477$ at 313 K.

**Table 2.** Values of $[A]-[A]_{eq}$ ($=\Delta$) and $\ln([A]-[A]_{eq})$ ($=\ln$) for the dominant diastereomer of **1b** during the course of its equilibration in $CDCl_2CDCl_2$ at 313 K.

| Measurement | $^1$H NMR signals | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | N–H | | C(1′)–H | | C(3)–$CH_3$ | | C(5)–$CH_3$ | |
| | Δ | ln | Δ | ln | Δ | ln | Δ | ln |
| 1 | 19.5 | 2.9704 | 22.4 | 3.1091 | 22.9 | 3.1311 | 23.1 | 3.1398 |
| 2 | 13.2 | 2.5802 | 15.3 | 2.7279 | 15.7 | 2.7537 | 15.6 | 2.7473 |
| 3 | 8.9 | 2.1861 | 10.2 | 2.3224 | 10.7 | 2.3702 | 10.5 | 2.3514 |
| 4 | 6.1 | 1.8083 | 6.8 | 1.9169 | 7.3 | 1.9879 | 7.0 | 1.9459 |
| 5 | 4.2 | 1.4351 | 4.7 | 1.5476 | 4.9 | 1.5892 | 4.7 | 1.5476 |
| 6 | 2.7 | 0.9933 | 3.1 | 1.1314 | 3.3 | 1.1939 | 3.1 | 1.1314 |
| 7 | 1.8 | 0.5878 | 2.0 | 0.6931 | 2.2 | 0.7885 | 2.0 | 0.6931 |
| 8 | 1.3 | 0.2624 | 1.4 | 0.3365 | 1.5 | 0.4055 | 1.3 | 0.2624 |
| 9 | 0.8 | −0.2231 | 0.9 | −0.1054 | 1.0 | 0.0000 | 0.8 | −0.2231 |
| 10 | 0.5 | −0.6931 | 0.6 | −0.5108 | 0.7 | −0.3567 | 0.6 | −0.5108 |

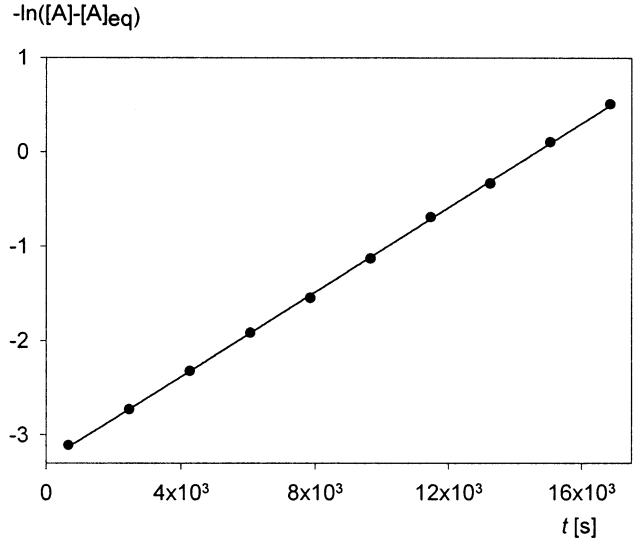



**Figure 7.** Plot of $-\ln([A]-[A]_{eq})$ versus time for iodide **1b** in $C_2D_2Cl_4$ at 313 K from the $^1$H NMR data for the C(1′)–H signal of Table 2.

A more complete study of the atropisomerism of **6a** was conducted: dynamic NMR study at four different temperatures (293, 313, 333 and 353 K) in order to compute $\Delta H^{\ddagger}$ and $E_a$. As above, at each temperature, $k_1$ and $k_2$ were determined experimentally and from these data $\Delta G_1^{\ddagger}$ and $\Delta G_2^{\ddagger}$ were calculated (Table 4). Using $\ln(k/T)=23.76-\Delta H^{\ddagger}/RT+\Delta S^{\ddagger}/R$, Eyring plots of $\ln(k/T)$ versus $1/T$ gave parallel straight lines for $k_1$ and $k_2$, and from the slope, one finds $\Delta H^{\ddagger}=20.95$ and 20.23 kcal/mol for the forward and back isomerizations, respectively (Fig. 8). From the intercepts, one finds $\Delta S^{\ddagger}=-13.59$ and $-14.53$ cal/deg/mol for the forward and reverse reactions, respectively. Similarly, using $\ln k=-E_a/RT+\ln A$, Arrhenius plots of $\ln k$ versus $1/T$ gave $E_a=21.58$ and 20.86 kcal/mol for the forward and reverse reactions. The $A$ factors, computed from the intercepts, are $1.95\times10^{10}$ and $1.21\times10^{10}$ for the forward and back reactions, respectively (Fig. 8). Finally, a plot of $R\ln K_{eq}$ versus $1/T$ gave $\Delta H^{\circ}=0.86$ kcal/mol and $\Delta S^{\circ}=1.40$ cal/deg/mol (Fig. 9). The $\Delta G^{\circ}$ values from $\Delta G^{\circ}=\Delta H^{\circ}-T\Delta S^{\circ}$ match up well with those determined from $\ln(k_1/k_2)$: 0.45 versus 0.45 (293 K), 0.42 versus 0.42 (313 K), 0.39 versus 0.38 (333 K) and 0.37 versus 0.37 (353 K), respectively.

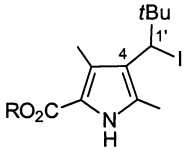
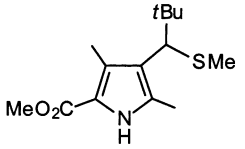
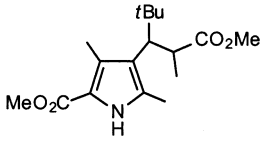
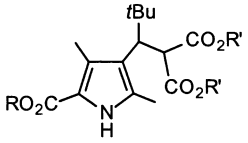
## 3. Concluding comments

A new class of atropisomeric pyrroles with restricted rotation about an $sp^2$–$sp^3$ carbon–carbon bond has been prepared and analyzed. Kinetic studies indicate that the ease of rotational isomerism[11] about the C(4)–C(1′) bond of **1**–**6** correlates with the size of the R′ group and bond lengths at C(1′) of Scheme 1: $CH(CO_2R)_2>CHMeCO_2Me\sim I>SCH_3>CH_2CO_2R>OCH_3$. Atropisomers **1**–**6** slowly reach a $\sim$7:3 equilibrium at room temperature. For the isolation of atropisomers that are stable at room temperature, the size of the R′ group must be enlarged, such as when the malonic ester tertiary hydrogen of **6a** or **6b** is replaced by methyl. That raises the activation barrier to atropisomerism to $\sim$32 kcal/mol at 382 K in $C_2D_2Cl_4$.[12]

## 4. Experimental

All NMR spectra were obtained on a Varian Unity Plus spectrometer operating at the $^1$H frequency of 500 MHz in $CDCl_3$ solvent (unless otherwise noted). Chemical shifts are reported in $\delta$ (ppm) referenced to the residual $CHCl_3$ $^1$H signal at 7.26 ppm, and $CDCl_3$ $^{13}$C signal at 77.00 ppm. The $^1$H NMR spectra in $C_2D_2Cl_4$ were referenced to the residual $^1$H signal at $\delta=5.94$ ppm. For the dynamic NMR measurements, the probe temperature was controlled by a standard unit of the Unity Plus system. A $J$-modulated spin-echo experiment (Attached Proton Test) was used to assign $^{13}$C NMR spectra. The underlined NMR signals belong to the dominant diastereomer throughout. Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected. Gas chromatography–mass spectrometry analyses were carried out on a Hewlett–Packard 5890A

**Table 3.** Kinetic and thermodynamic parameters calculated for the atropisomerism of pyrroles at 313 K

| | | $k_1$ x $10^5$ | $k_2$ x $10^5$ | $\Delta G_1^{\ddagger}$ | $\Delta G_2^{\ddagger}$ | $\Delta G°$ |
|---|---|---|---|---|---|---|
|  | **1a**: R = Et | 9.388 | 17.777 | 24.13 | 23.73 | 0.40 |
| | **1b**: R = Me | 7.213 | 15.135 | 24.28 | 23.82 | 0.46 |
|  | **3**: [b] | 1.576 | 3.780 | 21.93 | 21.46 | 0.47 |
|  | **5**: | 10.162 | 10.750 | 24.08 | 24.05 | 0.03 |
|  | **6a**: R = R′ = Et | 1.741 | 3.448 | 25.17 | 24.74 | 0.43 |
| | **6b**: R = R′ = Me | 2.263 | 4.160 | 25.01 | 24.63 | 0.38 |
| | **6c**: R = Me, R′ = *i*Pr | 1.599 | 3.181 | 25.22 | 24.79 | 0.43 |

[a] $\Delta G_1^{\ddagger}$ (free energy of activation for the forward reaction), $\Delta G_2^{\ddagger}$ (free energy of activation for the reverse reaction) and $\Delta G°$ (equilibrium free energy) in kcal/mole; $k$ in $s^{-1}$. [b] T = 273 K.

**Table 4.** Kinetic and thermodynamic parameters for **6a** from variable temperature dynamic NMR experiments

| | Temperature (K) | | | |
|---|---|---|---|---|
| Experimental[a] | 293 | 313 | 333 | 353 |
| $k_1$ | $1.505 \times 10^{-6}$ | $1.741 \times 10^{-5}$ | $1.361 \times 10^{-4}$ | $8.232 \times 10^{-4}$ |
| $k_2$ | $3.261 \times 10^{-6}$ | $3.448 \times 10^{-5}$ | $2.433 \times 10^{-4}$ | $1.465 \times 10^{-3}$ |
| $K_{eq}$ | 0.4615 | 0.5056 | 0.5596 | 0.5619 |
| $\Delta G_1^{\ddagger}$ | 24.95 | 25.17 | 25.46 | 25.77 |
| $\Delta G_2^{\ddagger}$ | 24.50 | 24.75 | 25.07 | 25.36 |
| $\Delta\Delta G^{\ddagger}$ | 0.45 | 0.42 | 0.39 | 0.41 |
| $\Delta G^{\circ}$[b] | 0.45 | 0.42 | 0.38 | 0.40 |

[a] $k$ in $s^{-1}$; $\Delta G_1^{\ddagger}$ (free energy of activation for the forward reaction), $\Delta G_2^{\ddagger}$ (free energy of activation for the reverse reaction) and $\Delta G°$ (equilibrium free energy) in kcal/mol.
[b] Calculated from $\ln K_{eq} = -\Delta G°/RT$.

capillary gas chromatograph (30 m DB-1 column) equipped with Hewlett–Packard 5970 mass selective detector. Radial chromatography was carried out on Merck silica gel $PF_{254}$ with gypsum preparative layer grade, using a Chromatotron (Harrison Research, Inc., Palo Alto, CA). The same type of silica gel was used for preparative TLC on 20×20 cm glass plates with layer thickness of 0.75 mm. Combustion analyses were carried out by Desert Analytics, Tucson, AZ. Commercial reagents and HPLC grade solvents were dried and purified following standard procedures.[13] Ethyl 3,5-dimethyl-1*H*-pyrrole-2-carboxylate was synthesized according to a literature procedure.[14]

### 4.1. Methyl 3,5-dimethyl-1*H*-pyrrole-2-carboxylate, 7b

To an acetate buffer [NaOH (36 g, 0.9 mol) and glacial acetic acid (375 mL)] was added a solution of dimethyl malonate (160 mL, 1.40 mol) in acetic acid (80 mL), and the mixture was cooled in an ice bath. A solution of $NaNO_2$ (203 g, 2.94 mol) in $H_2O$ (320 mL) was added over 3 h with gentle stirring, then the mixture was allowed to warm overnight to ambient temperature. Sodium chloride (250 g) was added, and after stirring for 45 min, the mixture was extracted with diethyl ether (4×250 mL). After evaporation of the ether solvent, the resulting crude dimethyl oximinomalonate solution[15] was used immediately in the following step.

To a mechanically-stirred mixture of pentane-2,4-dione (103 mL, 1.00 mol), zinc (196.2 g, 3.00 g), acetic acid (950 mL) and anh. sodium acetate (205 g, 2.50 mol), preheated to 80°C, was added a solution of the above oxime in acetic acid (30 mL). The rate of addition was such as to maintain the internal temperature at 80–85°C (3 h). Then the mixture was heated under reflux for 3 h

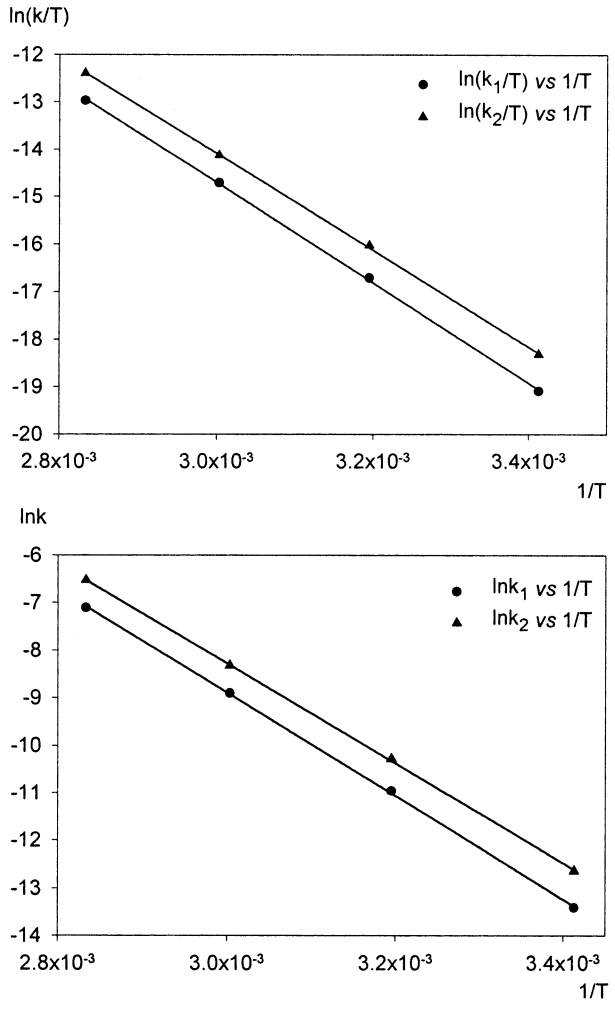



**Figure 8.** Best fit straight lines for the forward (●) and back (▲) atropisomerization of **6a**: (upper) Eyring plot at four different temperatures, $R=0.9998$. The slope $=-\Delta H^{\ddagger}/R$ and the intercept $=23.76+\Delta S^{\ddagger}/R$. (lower) Arrhenius plot at four different temperatures, $R=0.9998$ and $R=0.9999$ for $k_1$ and $k_2$, respectively. The slope $=-E_a/R$ and the intercept $=\ln A$.

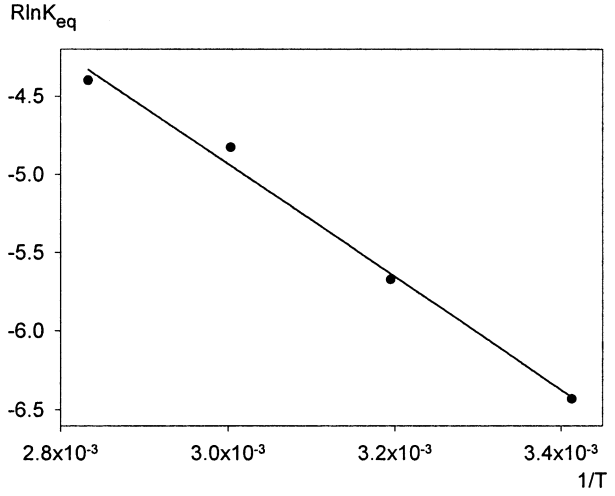



**Figure 9.** Best-fit straight line ($R=0.992$) for the temperature dependence of $R \ln K_{eq}$ versus $1/T$ for **6a**. The slope $=-\Delta H^{\circ}/R$ and the intercept $=\Delta S^{\circ}$/R.

and poured while hot into 12 L of ice-water. After 1 h at 0°C, the product was collected by filtration, washed with $H_2O$ (3×1 L) and dried under vacuum. Recrystallization from $CH_3OH$–$H_2O$ afforded pyrrole **7b** (100.8 g, 66%); mp 98–99°C; $^1$H NMR: $\delta$ 2.24 (3H, s), 2.30 (3H, s), 3.82 (3H, s), 5.79 (1H, d, $^4J=2.7$ Hz), 8.75 (1H, brs) ppm; $^{13}$C NMR: $\delta$ 12.77, 12.79, 50.81, 111.18, 117.37, 128.97, 133.10, 162.50 ppm; MS: $m/z$ (%) 153 [$M^{+\bullet}$](100), 138 (13), 122 (82), 121 (85), 93 (51). Anal. calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.72; H, 7.49; N, 9.04%.

### 4.2. General procedure for the syntheses of iodides 1a and 1b

Acetic anhydride (60 mL) was added slowly to 57% hydriodic acid (60 mL) with occasional cooling to maintain an internal temperature of ~40–42°C. Then 50% hypophosphorus acid ($H_3PO_2$, 6 mL) was added, followed by β-free pyrrole, **7a** or **7b** (30 mmol). After the pyrrole had completely dissolved and the temperature had been lowered to 30–32°C, pivalaldehyde (4.3 mL, 40 mmol) was added over 10 min with vigorous stirring while maintaining the temperature. After stirring for an additional 25 min, the mixture was slowly (10 min) diluted with ice-cold water (450 mL). The product was collected by suction filtration, washed with cold water (5×50 mL) and dried overnight under vacuum ($P_2O_5$) to afford near quantitative yields of iodides **1a** and **1b**.

**4.2.1. Ethyl 3,5-dimethyl-4-(2′,2′-dimethyl-1′-iodopropyl)-1*H*-pyrrole-2-carboxylate, 1a**. Compound **1a** was isolated in 94% yield; mp 161–163°C (atropisomeric ratio 88:12) (lit.[7] mp 168–169°C); $^1$H NMR: $\delta$ 1.08, 1.09 (9H, 2×s), 1.347, 1.348 (3H, 2×t, $J=7.1$ Hz), 2.21, 2.27 (3H, 2×s), 2.36, 2.43 (3H, 2×s), 4.29, 4.30 (2H, $AB\mathrm{X}_3$, $^3J=7.1$ Hz), 5.21, 5.26 (1H, 2×s), 8.74, 8.81 (1H, 2×br.s) ppm; $^{13}$C NMR: $\delta$ 11.00, 12.31, 14.51, 14.85, 16.04, 28.72, 28.98, 39.24, 39.39, 43.14, 43.88, 59.91, 59.94, 115.95, 118.74, 121.56, 122.24, 125.71, 128.67, 129.15, 133.38, 161.71, 161.90 ppm.

Careful crystallization of 500 mg of the mixture from above from 6 mL of dichloromethane at 0°C and 6 mL of hexane (by partial evaporation of $CH_2Cl_2$ at 0°C using a stream of air) led to isolation of highly diastereomerically enriched (d.r. = 99:1) diastereomer **1a** (214 mg) mp 157–159°C and $^1$H NMR corresponding to the underlined signals above.

**4.2.2. Methyl 3,5-dimethyl-4-(2′,2′-dimethyl-1′-iodopropyl)-1*H*-pyrrole-2-carboxylate, 1b**. Compound **1b** was isolated in 86% yield; mp 134–135°C (atropisomeric ratio 7:3); $^1$H NMR: $\delta$ 1.075, 1.083 (9H, 2×s), 2.21, 2.27 (3H, 2×s), 2.35, 2.43 (3H, 2×s), 3.825, 3.830 (3H, 2×s), 5.20, 5.26 (1H, 2×s), 8.74, 8.81 (1H, 2×br.s) ppm; $^{13}$C NMR: $\delta$ 10.97, 12.39, 14.76, 16.10, 28.73, 28.99, 39.25, 39.40, 42.95, 43.67, 51.05, 51.07, 115.76, 118.55, 121.65, 122.33, 125.94, 128.91, 129.12, 133.35, 161.92, 162.08 ppm. Careful crystallization from 0°C pre-cooled dichloromethane and hexane (by evaporation of the $CH_2Cl_2$ at 0°C) led to isolation of a sample highly enriched in one atropisomer (93:7), mp 137–138°C. Anal. calcd for

$C_{13}H_{20}INO_2$: C, 44.71; H, 5.77; N, 4.01. Found: C, 44.96; H, 6.00; N, 4.05%.

### 4.3. Methyl 3,5-dimethyl-4-(2′,2′-dimethyl-1′-methoxypropyl)-1*H*-pyrrole-2-carboxylate, 2b

A solution of iodide **1b** (1.05 g, 3 mmol) in methanol (50 mL) was heated under reflux for 1 h. After cooling, the mixture was diluted with $CHCl_3$ (100 mL), washed with $H_2O$ (3×50 mL), dried ($MgSO_4$), filtered and the solvent was evaporated under vacuum. The residue was purified by radial chromatography on silica gel ($CH_2Cl_2$:$CH_3OH$ = 100:0.5 v/v) and recrystallization from EtOAc/hexane to afford **2b** (0.39 g, 50%); mp 120–121°C (atropisomeric ratio 67:33); $^1$H NMR: $\delta$ 0.91 (9H, s), 2.18, 2.24 (3H, 2×s), 2.30, 2.38 (3H, 2×s), 3.14 (3H, s), 3.83 (3H, s), 3.89 (1H, s), 8.68, 8.69 (in concd soln 9.40, 9.48) (1H, 2×br.s) ppm; $^{13}$C NMR: $\delta$ 11.50, 12.31, 12.44, 13.53, 26.49, 26.74, 37.94, 50.81, 50.83, 56.61, 56.69, 85.59, 86.73, 116.61, 117.43, 118.33, 118.82, 128.02, 129.06, 131.53, 132.41, 162.32, 162.63 ppm. MS: *m*/*z* (%) 253 [M$^{+\bullet}$] (4), 222 (3), 221 (5), 196 (90), 164 (100). Anal. calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.65; H, 9.17; N, 5.61%.

### 4.4. Methyl 3,5-dimethyl-4-(2′,2′-dimethyl-1′-methylthiopropyl)-1*H*-pyrrole-2-carboxylate, 3

Methanethiol (CAUTION, highly toxic, stench) was bubbled through a solution of 1.05 g (3 mmol) iodide **1b** in anhydrous THF (15 mL) for 10 min. The effluent condenser end was attached to a 15 cm long trap filled with saturated aqueous $Pd(OAc)_2$ followed by a bleach trap, and the gas flow was discontinued when copious yellow precipitate was formed in the first trap. The reaction is highly exothermic leading to THF reflux, which was maintained for 30 min. more by external heating. After cooling, the mixture was diluted with chloroform (100 mL), washed with water (3×100 mL) and dried over anhydrous $MgSO_4$. After filtration and evaporation, the residue was purified by radial chromatography (gradient hexane:ethyl acetate = 85:15–75:25) and recrystallization (EtOAc–hexane) to afford 0.78 g (97%) of **3**; mp 131–133°C (atropisomeric ratio 73:27); $^1$H NMR: $\delta$ 1.02, 1.03 (9H, 2×s), 1.80, 1.82 (3H, 2×s), 2.19, 2.25 (3H, 2×s), 2.46, 2.52 (3H, 2×s), 3.66, 3.73 (1H, 2×s), 3.826, 3.829 (3H, 2×s), 8.70, 8.71 (1H, 2×br.s) ppm; $^{13}$C NMR: $\delta$ 11.23, 12.46, 13.31, 14.63, 15.45, 15.76, 28.66, 28.86, 37.99, 38.04, 50.88, 50.90, 54.81, 56.33, 116.13, 117.64, 118.89, 119.54, 128.16, 129.26, 131.61, 131.93, 162.10, 162.28 ppm. MS: *m*/*z* (%) 222 (18), 221 (21), 212 (91), 190 (21), 180 (100), 146 (18). Anal. calcd for $C_{14}H_{23}NO_2S$: C, 62.41; H, 8.61; N, 5.20. Found: C, 62.50; H, 8.90; N, 5.47%.

Preparative TLC of **3** (180 mg) on 18 20×20 cm plates (hexane:EtOAc = 85:15) led to isolation of a diastereomerically enriched sample (110 mg, d.r. = 85:15). Crystallization of this fraction from pre-cooled methylene chloride and hexane by removing the former in a stream of air at 0°C gave 65 mg of further enriched to 98:2 (in pre-cooled to −10°C $CDCl_3$) atropisomer of **3**, mp 129–130°C and $^1$H NMR corresponding to the underlined signals above.

### 4.5. General procedure for the syntheses of 4a, 4b and 5

A solution of methyl or *t*-butyl acetate (30 mmol), or methyl propionate in anhydrous THF (18 mL) was added slowly via syringe to a $N_2$-protected solution of LDA (freshly prepared from dry isopropylamine (4.1 mL, 31.2 mmol) in THF (35 mL) and *n*-BuLi in hexane (2.5 M,12 mL, 30 mmol) at −78°C. After stirring for 1 h at the same temperature, a solution of the iodide (3.63 g, 10 mmol of **1a** or 3.49 g, 10 mmol of **1b**) and anhydrous HMPA[8] (3.48 mL, 20 mmol) in THF (25 mL) was added over 15 min. The mixture was stirred for 1 h at −78°C, then the temperature was raised to −55°C over 30 min. The reaction was quenched with sat. aq. $NH_4Cl$ (20 mL). The mixture was diluted with 0.2% aq. HCl (150 mL) and the product was extracted with $CHCl_3$ (4×50 mL). The combined organic extracts were washed with $H_2O$ (4×50 mL), dried over anhydrous $MgSO_4$ and after filtration through a short pad of silica gel, the solvent was evaporated under vacuum. The residue was purified by radial chromatography on silica gel eluting with hexane: EtOAc = 100:10–100:20. The resulting pure fractions were recrystallized from hexane–EtOAc to afford pure pyrroles.

#### 4.5.1. Ethyl 3,5-dimethyl-4-[2′,2′-dimethyl-1′-(methoxycarbonylmethyl)propyl]-1*H*-pyrrole-2-carboxylate, 4a.

Obtained in 88% yield from **1a**; mp 95–98°C (atropisomer ratio 65:35). $^1$H NMR: $\delta$ 0.91, 0.92 (9H, 2×s), 1.33, 1.34 (3H, 2×t, $J$ = 7.1 Hz), 2.21, 2.28 (3H, 2×s), 2.32, 2.39 (3H, 2×s), 2.69, 2.72 (1.4 H, *AB*X, $^3J$ = 10.3 Hz, $^2J$ = 14.8 Hz; $^3J$ = 6.5 Hz, $^2J$ = 14.8 Hz), 2.75, 2.82 (0.6 H, *AB*X, $^3J$ = 5.6 Hz, $^2J$ = 15.4 Hz; $^3J$ = 10.0 Hz, $^2J$ = 15.4 Hz), 3.02, 3.08 (1H, 2×AB*X*, $^3J$ = 5.6, 10.0 Hz; $^3J$ = 6.5, 10.3 Hz), 3.49, 3.52 (3H, 2×s), 4.26, 4.27 (2H, 2×*AB*X$_3$, $^3J$ = 7.1 Hz), 8.62, 8.71 (1H, 2×br.s) ppm. $^{13}$C NMR: $\delta$ 11.21, 12.37, 13.47, 14.45, 14.46, 14.84, 28.15, 28.37, 34.41, 34.57, 35.97, 36.00, 42.27, 43.63, 51.27, 51.29, 59.47, 59.52, 116.44, 117.23, 120.85, 121.13, 126.81, 129.30, 129.77, 132.13, 161.79, 161.88, 173.66, 173.95 ppm. MS: *m*/*z* (%) 309 [M$^{+\bullet}$](22), 252 (100), 206 (55), 164 (41), 147 (9). Anal. calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.53. Found: C, 66.15; H,8.82; N, 4.69%.

#### 4.5.2. Ethyl 3,5-Dimethyl-4-[2′,2′-dimethyl-1′-(*t*-butoxycarbonylmethyl)propyl]-1*H*-pyrrole-2-carboxylate, 4b.

Obtained in 82% yield; mp 103–106°C (atropisomer ratio 65:35). $^1$H NMR: $\delta$ 0.91, 0.92 (9H, 2×s), 1.19, 1.22 (9H, 2×s), 1.336, 1.339 (3H, 2×t, $J$ = 7.1 Hz), 2.20, 2.27 (3H, 2×s), 2.33, 2.40 (3H, 2×s), 2.58, 2.65 (1.4 H, *AB*X, $^3J$ = 11.6 Hz, $^2J$ = 14.0 Hz; $^3J$ = 5.8 Hz, $^2J$ = 14.0 Hz), 2.63, 2.70 (0.6 H, *AB*X, $^3J$ = 6.0 Hz, $^2J$ = 14.2 Hz; $^3J$ = 10.5 Hz, $^2J$ = 14.2 Hz), 2.94, 3.00 (1H, 2×AB*X*, $^3J$ = 6.0, 10.5 Hz; $^3J$ = 5.8, 11.6 Hz), 4.27, 4.28 (2H, 2×*AB*X$_3$, $^3J$ = 7.1 Hz), 8.52, 8.61 (1H, 2×br.s) ppm. $^1$H NMR ((CD$_3$)$_2$SO): $\delta$ 0.84, 0.85 (9H, 2×s), 1.11, 1.12 (9H, 2×s), 1.25 (3H, br.t, $J$ = 7.0 Hz), 2.09, 2.16 (3H, 2×s), 2.23, 2.29 (3H, 2×s), 2.53, 2.59 (1.4 H, *AB*X, $^3J$ = 10.9 Hz, $^2J$ = 14.2 Hz; $^3J$ = 5.8 Hz, $^2J$ = 14.2 Hz), 2.57, 2.61 (0.6 H, *AB*X, $^3J$ = 5.8 Hz, $^2J$ = 14.0 Hz; $^3J$ = 10.4 Hz, $^2J$ = 14.0 Hz), 2.87, 2.92 (1H, 2×AB*X*,

$^3J=5.8$, 10.4 Hz; $^3J=5.8$, 10.9 Hz), 4.14, 4.17 (2H, 2×$AB$X$_3$, $^3J=7.0$ Hz), 10.97, 11.04 (2H, 2×br.s) ppm. $^{13}$C NMR: $\delta$ 11.41, 12.54, 13.57, 14.49, 14.52, 15.00, 27.65, 27.66, 28.18, 28.42, 35.94, 36.03, 36.04, 36.14, 42.70, 44.35, 59.49, 59.53, 79.62, 79.71, 116.28, 117.15, 121.09, 121.40, 127.55, 129.63, 130.01, 131.90, 161.78, 161.79, 172.60, 172.94 ppm. $^{13}$C NMR ((CD$_3$)$_2$SO): $\delta$ 11.22, 11.81, 13.31, 14.20, 14.48, 14.51, 27.25, 27.28, 28.00, 28.21, 35.46, 35.49, 35.62, 35.64, 42.38, 43.87, 58.58, 58.65, 78.81, 78.86, 115.44, 116.30, 119.72, 120.16, 126.25, 128.14, 130.59, 132.36, 160.70, 160.71, 171.80, 171.94 ppm. MS: $m/z$ (%) 351 [M$^{+\bullet}$] (26), 294 (100), 238 (76), 194 (55), 148 (11), 57 (72). Anal. calcd for $C_{20}H_{33}NO_4$: C, 68.34; H, 9.46; N, 3.99. Found: C, 68.36; H, 9.70; N, 4.16%.

**4.5.3. Methyl 3,5-dimethyl-4-[2′,2′-dimethyl-1′-(1″-methoxycarbonylethyl)propyl]-1*H*-pyrrole-2-carboxylate, 5**. Isolated in 95% yield as a mixture of two diastereomers. They were separated by radial chromatography on silica gel (hexane:ethyl acetate gradient from 90:10 to 80:20 v/v) to afford less polar diastereomer **5-lp** as a thick oil (1.65 g, 54%; atropisomer ratio 59:41). $^1$H NMR: $\delta$ 0.83, 0.85 (3H, 2×d, $J=7.0$ Hz), 0.86 (9H, s), 2.24 (3H, s), 2.29, 2.30 (3H, 2×s), 2.95, 3.05 (1H, 2×dq, $J=11.3$, 7.0 Hz), 3.00, 3.07 (1H, 2×d, $J=11.3$ Hz), 3.692, 3.694 (3H, 2×s), 3.81, 3.82 (3H, 2×s), 8.71, 8.77 (1H, 2×br.s) ppm. $^{13}$C NMR: $\delta$ 11.45, 12.70, 14.06, 15.18, 19.13, 19.22, 28.73, 28.89, 36.79, 36.84, 38.87, 39.09, 47.82, 49.19, 50.82, 50.87, 51.64, 51.67, 116.65, 117.10, 120.95, 121.53, 127.08, 129.06, 130.03, 132.18, 161.92, 162.04, 178.92, 179.26 ppm. MS: $m/z$ (%) 309 [M$^{+\bullet}$] (8), 252 (100), 220 (27), 196 (34), 164 (34). Anal. calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.53. Found: C, 66.20; H, 8.95; N, 4.65%.

Chromatographic separation of atropisomers of **5-lp** was not observed. Crystallization at room temperature from hexane gave 22% recovery of solid single atropisomer corresponding to **5-lp**, mp 128–129°C which was used for kinetic measurements.

The more polar fractions afforded diastereomeric **5-mp** (1.24 g, 40%) as a thick oil (atropisomer ratio ~60:40). Atropisomer separation of **5-mp** was not found either by chromatography or by recrystallization, which yielded solid fraction with mp 105–106°C (atropisomer ratio 69:31). $^1$H NMR: $\delta$ 0.97, 0.99 (9H, 2×s), 1.37, 1.38 (3H, 2×d, $J=6.8$ Hz), 2.17, 2.25 (3H, 2×s), 2.33, 2.40 (3H, 2×s), 2.71, 2.79 (1H, 2×d, $J=11.3$ Hz), 3.14, 3.26 (1H, 2×dq, $J=11.3$, 6.8 Hz), 3.288, 3.294 (3H, 2×s), 3.79, 3.80 (3H, 2×s), 8.43, 8.55 (1H, 2×br.s) ppm. $^{13}$C NMR: $\delta$ 10.98, 12.33, 14.00, 15.38, 19.67, 19.73, 30.40, 30.79, 35.20, 35.45, 42.30, 42.81, 47.99, 49.65, 50.72. 50.76, 50.96, 116.16, 116.79, 123.04, 123.50, 126.91, 129.12, 129.45, 131.53, 161.97, 162.03, 176.35, 176.72 ppm. MS: $m/z$ (%) 309 [M$^{+\bullet}$] (6), 252 (100), 220 (30), 196 (36), 164 (36). Anal. calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.53. Found: C, 66.09; H, 8.72; N, 4.50%.

**4.6. Ethyl 3,5-dimethyl-4-[2′,2′-dimethyl-1′-(diethoxycarbonylmethyl)propyl]-1*H*-pyrrole 2-carboxylate, 6a**

To abs. ethanol (40 mL) under an $N_2$ blanket sodium (690 mg, 30 mmol) was added slowly. After all of the Na had reacted, a solution of diethyl malonate (5.12 mL, 32 mmol) in ethanol (3 mL) was added and the mixture was stirred for 15 min. Then iodide **1a** (2.18 g, 6 mmol) and ethanol (8 mL) were added and the mixture was heated under reflux for 30 min. After cooling, the product was partitioned between $Et_2O$/$H_2O$ (2×100 mL/150 mL). The organic layer was washed with 1% HCl (2×50 mL), $H_2O$ (4×50 mL), dried ($MgSO_4$), filtered, and the solvent was removed under vacuum. Radial chromatography purification (hexane:ethyl acetate = 8:2, v/v) afforded pyrrole **6a** as a thick oil (2.18 g, 92%; atropisomer ratio 69:31). $^1$H NMR: $\delta$ 0.88, 0.89 (3H, 2×t, $J=7.1$ Hz), 0.90, 0.91 (9H, 2×s), 1.289, 1.293 (3H, 2×t, $J=7.1$ Hz), 1.33, 1.34 (3H, 2×t, $J=7.1$ Hz), 2.26, 2.29 (3H, 2×s), 2.33, 2.34 (3H, 2×s), 3.49, 3.58 (1H, 2×d, $J=11.6$ Hz), 3.78, 3.83 (2H, 2×$A$BX$_3$), 3.96, 4.08 (1H, 2×d, $J=11.6$ Hz), 4.19, 4.21 (2H, 2×A$B$X$_3$), 4.25, 4.26 (2H, $AB$X$_3$), 8.43, 8.83 (1H, 2×br.s) ppm. $^{13}$C NMR: $\delta$ 11.28, 12.64, 13.40, 13.88, 14.50, 14.52, 14.76, 15.69, 28.64, 28.92, 36.68, 36.74, 44.80, 46.53, 54.18, 54.67, 59.59, 59.68, 60.97, 61.07, 61.57, 61.58, 116.77, 117.25, 120.31, 121.00, 127.04, 129.68, 129.87, 132.46, 161.70, 161.75, 168.00, 168.08, 169.62, 169.87 ppm. MS: $m/z$ (%) 395 [M$^{+\bullet}$] (14), 338 (100), 265 (4), 220 (56), 174 (41), 146(9). Anal. calcd for $C_{21}H_{33}NO_6$: C, 63.77; H, 8.41; N, 3.54. Found: C, 63.83; H, 8.43; N, 3.59%.

A single atropisomer with 97% purity was obtained after preparative TLC on silica gel (cyclohexane: ethyl acetate = 8:2 v/v) and recrystallization at 0°C from ethyl acetate–hexane (mp 79–80°C), and was used for dynamic NMR measurements.

**4.7. General procedure for synthesis of 6b and 6c**

To an $N_2$-protected suspension of sodium hydride (900 mg, 30 mmol, 80% oil) in anhydrous THF (40 mL) at 10°C was added a solution of malonate ester (32 mmol) in THF (3 mL) over 10 min. After stirring for a further 10 min, the corresponding iodide **1a** or **1b** (6 mmol) and THF (5 mL) were added and the mixture was heated under reflux for 30 min. After cooling, the mixture was poured into cold 1% aq. HCl (100 mL) and diethyl ether (200 mL). The aqueous layer was extracted with $Et_2O$ (2×50 mL) and the combined ethereal extracts were washed with $H_2O$ until neutral (3×100 mL). After drying over anhydrous $MgSO_4$, filtration and evaporation, the crude product was purified by radial chromatography on silica gel eluting with hexane: ethyl acetate = 10:1 to 8:2 to afford diastereomeric mixtures of pyrroles **6**.

**4.7.1. Methyl 3,5-dimethyl-4-[1′-(dimethoxycarbonyl)-methyl-2′,2′-dimethylpropyl]-1*H*-pyrrole-2-carboxylate, 6b**. Obtained in 93% yield as a thick oil (atropisomer

ratio 65:35). $^1$H NMR: $\delta$ 0.89, 0.90 (9H, 2×s), 2.26, 2.29 (3H, 2×s), 2.32, 2.33 (3H, 2×s), 3.31, 3.34 (3H, 2×s), 3.48, 3.58 (1H, 2×d, $J$=11.8 Hz), 3.75 (3H, s), 3.79, 3.81 (3H, 2×s), 4.00, 4.13 (1H, 2×d, $J$=11.8 Hz), 8.61, 8.78 (1H, 2×br.s) ppm. $^{13}$C NMR: $\delta$ 11.11, 12.42, 14.52, 15.47, 28.54, 28.80, 36.52, 36.57, 45.29, 46.88, 50.76, 50.83, 52.04, 52.07, 52.60, 52.62, 53.66, 54.13, 116.58, 117.05, 119.91, 120.57, 126.82, 129.63, 130.05, 132.91, 161.98, 162.15, 168.34, 168.49, 169.95, 170.19 ppm. MS: $m/z$ (%) 353 [M$^{+\bullet}$] (10), 322 (4), 296 (100), 264 (20), 220 (27), 196 (38), 164 (26). Anal. calcd for $C_{18}H_{27}NO_6$: C, 61.17; H, 7.70; N, 3.96. Found: C, 61.36; H, 7.86; N, 3.98%.

A single atropisomer of 96% d.e. (mp 119–120°C) was obtained after preparative TLC on silica gel at 5°C (hexane: ethyl acetate = 7:3) and recrystallization at 0°C from ethyl acetate–hexane.

**4.7.2. Methyl 3,5-dimethyl-4-[1′-(diisopropoxycarbonyl)-methyl-2′,2′-dimethylpropyl]-1*H*-pyrrole-2-carboxylate, 6c**. Obtained in 90% yield as a thick oil (atropisomer ratio 66:34). $^1$H NMR: $\delta$ 0.75, 0.83 (3H, 2×d, $J$=6.3 Hz), 0.89, 0.91 (9H, 2×s), 0.98, 1.00 (3H, 2×d, $J$=6.3 Hz), 1.23, 1.24 (3H, 2×d, $J$=6.3 Hz), 1.27, 1.28 (3H, 2×d, $J$=6.3 Hz), 2.26, 2.28 (3H, 2×s), 2.33, 2.34 (3H, 2×s), 3.48, 3.58 (1H, 2×d, $J$=11.5 Hz), 3.79, 3.81 (3H, 2×s), 3.88, 4.00 (1H, 2×d, $J$=11.5 Hz), 4.63, 4.67 (1H, 2×septet, $J$=6.3 Hz), 5.03, 5.04 (1H, 2×septet, $J$=6.3 Hz), 8.43, 8.61 (1H, 2×br.s) ppm. $^{13}$C NMR: $\delta$ 11.32, 12.68, 14.79, 15.74, 20.56, 20.87, 21.07, 21.26, 21.39, 21.41, 21.49, 28.65, 28.93, 36.73, 36.80, 44.03, 45.76, 50.78, 50.85, 54.75, 55.25, 68.21, 68.41, 68.91, 68.93, 116.50, 117.01, 120.68, 121.35, 127.35, 129.95, 130.18, 132.62, 161.94, 162.07, 167.50, 167.51, 169.07, 169.33 ppm. MS: $m/z$ (%) 409 [M$^{+\bullet}$] (11), 352 (92), 310 (2), 266 (43), 224 (78), 222 (43), 206 (100), 174 (58), 57 (24). Anal. calcd for $C_{22}H_{35}NO_6$: C, 64.52; H, 8.62; N, 3.42. Found: C, 64.69; H, 8.90; N, 3.56%.

A single atropisomer of 98% d.e. (mp 99–100°C) was obtained after preparative TLC on silica gel (hexane:ethyl acetate = 8:2 v/v) and recrystallization at 0°C from ethyl acetate–hexane.

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