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Stereochemistry of Planarchiral Compounds, XIV [1]. Static and Dynamic Stereochemistry of 3,3′-Dimethoxy-2,2′-bi(1,6-methano[10]annulenyl)

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Summary. The title compound **6** was prepared from 3-methoxy-1,6-methano[10]annulene (**4**) *via* lithiation and oxidative coupling of the intermediate **5** with copper(II)chloride. Three stereoisomers (two rotamers of the racemate, **6a** and **6b**, and the *meso*-form **6c**) were obtained and their configurations assigned both by ^{1}H NMR spectroscopy and by X-ray crystal structure analysis of **6a**.

Starting the reaction sequence from optically active 2-bromo-1,6-methano[10]annulene, (−)-**3**, of known absolute chirality $(S)_p$ established the absolute stereochemistry of (+)-**6a** as $(R)_p(R)_a(R)_p$ and $(R)_p(S)_a(R)_p$ for the dextrorotatory rotamer **6b**. 3-Methoxy-1,6-methanol[10]annulene (**4**) as well as **6a** and **6b** were easily resolved by enantioselective chromatography of the racemic mixtures on cellulose triacetate (*CTA*) in ethanol. A rotational barrier of $\Delta G^{\#} = 132\,\mathrm{kJ \cdot mol^{-1}}$ between **6a** and **6b** was determined both by thermal equilibration and by CD-kinetics.

Finally, also the *meso*-form **6c** – because of its high rotational barrier (118 kJ) – could be resolved on *CTA* in its enantiomers ($[\alpha]_D = 200°$ in ethanol). From chiroptical comparison (CD) with **6a** and **6b**, resp., the chirality $(R)_p(S)_a(S)_p$ was deduced for (+)-**6c**.

Keywords. Torsional chirality; X-ray crystal structure; Enantioselective chromatography on cellulose triacetate; Circular dichroism; Absolute chirality.

Stereochemie planarchiraler Verbindungen, 14. Mitt. Statische und dynamische Stereochemie von 3,3′-Dimethoxy-2,2′-bi(1,6-methano[10]annulenyl)

Zusammenfassung. Die Titelverbindung **6** wurde aus 3-Methoxy-1,6-methano[10]annulen (**4**) durch Lithiierung und anschließende oxidative Kupplung des Zwischenproduktes **5** mit Kupfer(II)chlorid erhalten. Dabei entstanden **3** Stereoisomere (2 Rotamere des Racemates, **6a** und **6b**, und die *meso*-Form **6c**), deren Konfiguration sowohl durch ^{1}H-NMR-Spektroskopie als auch durch Röntgenstrukturanalyse von **6a** bestimmt wurden.

Ausgehend von optisch aktivem 2-Brom-1,6-methano[10]annulen, (−)-**3**, bekannter Absolutkonfiguration $(S)_p$, konnte durch diese Reaktionsfolge die absolute Chiralität von (+)-**6a** als $(R)_p(R)_a(R)_p$ [und $(R)_p(S)_a(R)_p$ für (+)-**6b**] ermittelt werden. Sowohl **4** als auch **6a** und **6b** waren durch enantioselektive Chromatographie an Cellulose triacetat (*CTA*) in Ethanol glatt in ihre Enantiomeren trennbar. Die Rotationsbarriere zwischen **6a** und **6b** wurde sowohl durch thermische Äquilibrierung als auch CD-Kinetik zu $\Delta G^{\#} = 132\,\mathrm{kJ \cdot mol^{-1}}$ bestimmt.

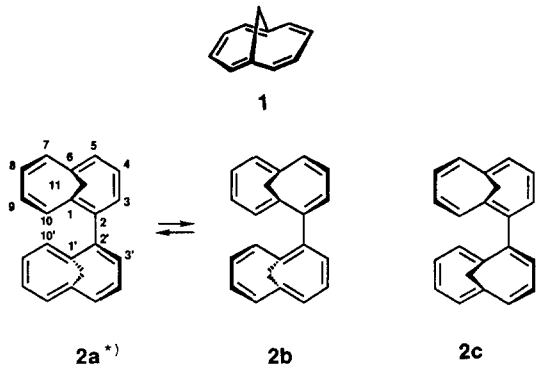
Schließlich ließ sich auch die "Mesoform" **6c** wegen ihrer hohen Rotationsbarriere von

118 kJ·mol^{-1} an *CTA* glatt in ihre Enantiomeren trennen ($[\alpha]_D = 200°$ in Ethanol). Aus einem chiroptischen Vergleich mit **6a** bzw. **6b** (CD) wurde für (+)-**6c** die Chiralität $(R)_p(S)_a(S)_p$ abgeleitet.

Introduction

Axialchiral biaryls have gained great interest because of their application as ligands in enantioselective catalysis. In this context and also because of their interesting structure we have studied in some detail the static and dynamic stereochemistry of 2,2′-bi(1,6-methano[10]annulenyls) (**2**) [1–3]. Whereas 1,6-methano[10]annulene (**1**) if substituted either in position **2** or **3** becomes planarchiral [4–6], biannulenyls, structurally related to 1,1′-binaphthyls, combine elements of both planar and axial (torsional) chirality within one molecule (see **2**). The two possible combinations of planar chiralities $(R)_p$ and $(S)_p$ result in a racemic and a *meso*-form $(R)_p(R)_p/(S)_p(S)_p$ and $(R)_p(S)_p$, resp. The additionally present element of axial chirality gives rise to the interesting dynamic stereochemistry of these "biaryls" [1–3]. For the racemic form two diastereomers, namely $(R)_p(R)_a(R)_p$ and $(R)_p(S)_a(R)_p$ and their enantiomers $[S)_p(S)_a(S)_p$ and $(S)_p(R)_a(S)_p)]$ (see **2a** and **2b**) result. For the *meso*(*syn*)-form (**2c**) only two enantiomers are feasible: $(R)_p(R)_a(S)_p$ and $(R)_p(S)_a(S)_p$, the possible separation of which depends on the rotational barrier around the 2-2′-bond [3]. For the unsubstituted 2,2′-bi(1,6-methano[10]annulenyl) (**2**) the rotational barrier around the C2-C2′-bond is only 63 kJ·mol^{-1} [7] which leads to very fast racemization at room temperature.

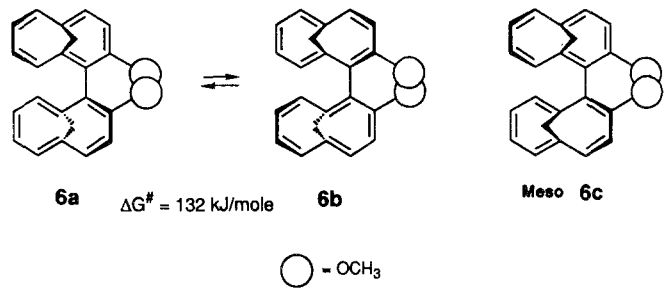
An increase of this barrier should be possible by substitution of the biannulenyl in appropriate positions.



*) Of 2 and 6 only one enantiomer is shown

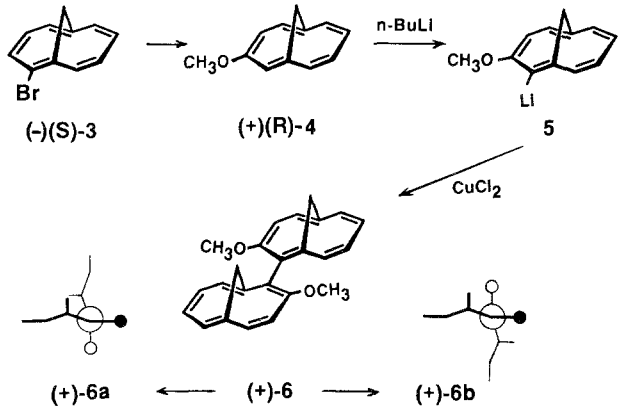
So far we have studied 10,10′-disubstituted 2,2′-bi(1,6-methano[10] annulenyls), namely the dibromo compound [1–3]. In this case the rotational barrier around the central biaryl bond (2,2′) (89 kJ·mol^{-1} for the racemate and 58 kJ·mol^{-1} for the *meso* isomer) [2] depends mainly on the interaction between H-3 and the substituent on C-10′ (and H-3′ with C-10, resp.).

In order to obtain stable rotamers of the *meso*-form **2c** this barrier had to be enhanced above appr. 90 kJ·mol^{-1}. According to molecular model considerations, 3,3′-disubstituted 2,2′-bi(1,6-methano[10]annulenyls) seemed to be promising candidates to attain this goal. Their synthesis and stereochemistry is reported in this communication.



Results and Discussion

An appropriate starting material for the synthesis of the desired isomeric 3,3′-dimethoxy annulenyls **6** is 3-methoxy-1,6-methano[10]annulene (**4**), accessible in a three step reaction sequence from the parent 1,6-methano[10]annulene (**1**, R = H) *via* the 2-bromo derivative **3** [7]. For the preparation of the title compound **6**, **4** was metallated with *n*-butyl-lithium making use both of the increased α-CH-acidity and of the donor property of the ether oxygen. Oxidative coupling of the intermediate **5** with anhydrous copper(II)chloride at −78 °C afforded a mixture of the torsional isomers (of the racemate) (**6a**, **6b**) and the *meso*(*syn*)-form **6c**. On chromatography of the mixture of diastereomeric biannulenyls **6** on silicagel or alumina in a variety of solvents (hexane, ether, *THF*, dioxane, methanol, dichloromethane, triethylamine etc.), one rotamer of the racemate (**6a**, mp. 126–129 °C) was always eluted first followed by an unresolved mixture of **6c** with the second rotamer of the racemate **6** (**6b**). This situation changed if aromatic solvents (especially toluene) were applied: while here, too, the same racemic form (**6a**) – as with the aliphatic solvents – was eluted first, the *meso*-form (second fraction) and the second rotamer **6b** of the racemate (third fraction) could be quantitatively separated – even on a gram scale (with mp. s 79–80 and 105–107 °C, resp.) in relative amounts of 13, 16 and 5%, resp.



A first structural assignment of these isomers was possible by ^{1}H NMR spectroscopy (Fig. 1): the torsional isomers **6a** and **6b** have C_2 symmetry; hence, the protons of corresponding positions in the "annulene halves" are equivalent and only 9 signals appear in the spectrum. In the *meso*(*syn*)-form **6c**, however, twice the number of resonances can be observed because of the lower symmetry.

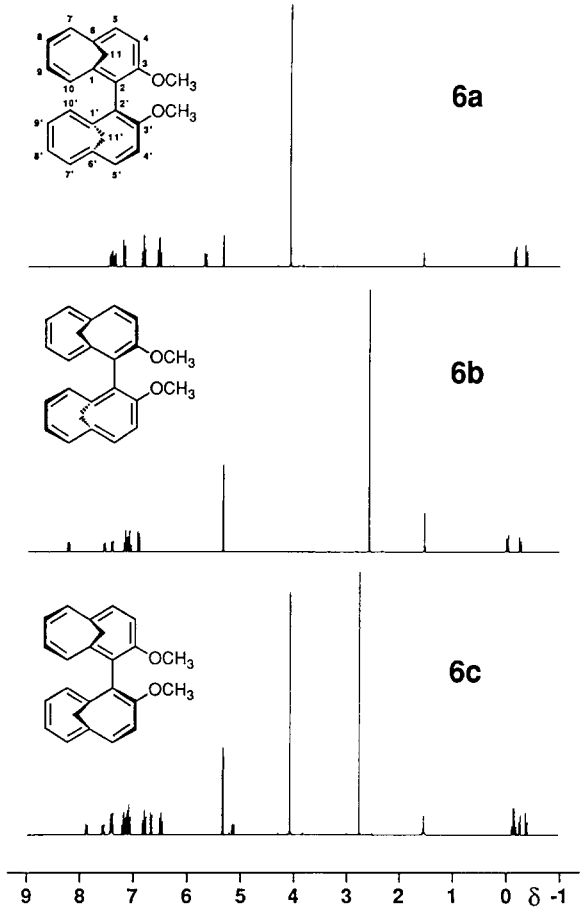


Fig. 1. ^{1}H NMR spectra of the stereoisomeric dimethoxy biannulenyls **6a**–**6c** (300 MHz, CD_2Cl_2)

The perimeter protons H-4 and H-5 of **6a** appear as an AB-system ($\delta = 7.42$ and 7.18 ppm; $J = 9.19$ Hz). Proton H-10 is influenced by the magnetic anisotropy of the adjacent annulene ring and thus experiences a significant highfield shift to $\delta = 5.66$ ppm. Both the singlet of the methoxy groups ($\delta = 4.07$ ppm) and the AB-system of the bridge protons H-11a and H-11b ($\delta = -0.17$ and -0.37 ppm) appear in a region typical for substituted 1,6-methano[10]annulenes.

Final structural proof was gained from X-ray structural analysis. Suitable crystals of **6a** could be obtained from pentane. A stereoscopic view of this structure is depicted in Fig. 2.

From this structure the following conclusions can be drawn:

1. The crystals belong to the chiral space group $P2_12_12_1$; therefore, each crystal consists of one enantiomer only. This was proved by recording the chiroptical properties ($[\alpha]_D$, CD) of a solution of a single crystal on the one hand and by enantioselective chromatography of the same solution on cellulose triacetate (*CTA*, [5, 6, 9]) on the other hand which revealed an enantiomeric purity of >98%.

2. The relative configurations of the planar – and axialchiral moieties of the biannulenyl **6a** are $(R)_p(R)_a(R)_p$ and $(S)_p(S)_a(S)_p$, resp.

3. The CH_2-bridges are *anti* to each other and the annulene units are twisted around the C-2/C-2′-bond. The torsion angle (C-1/C-2/C-2′/C-3′) amounts to 63.8°.

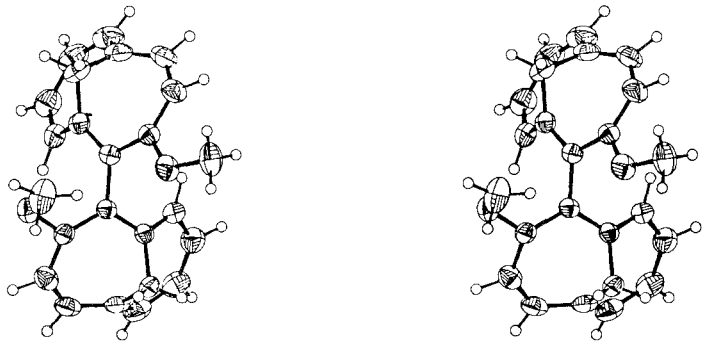


Fig. 2. X-ray crystal structure of **6a** (ORTEP drawing)

The 1,6-methano[10]annulene perimeters are tipped by appr. 16° with regard to the central 2-2′-bond. Thereby the protons H-10 and H-10′, resp., fall "below" the adjacent annulene ring and therefore reside within the range of the diamagnetic shielding of the aromatic system which is in full agreement with the NMR spectra (cf. Fig. 1, *vide supra*). The bond lengths of the perimeter skeleton (1.363–1.428 Å) as well as the bond angles of the bridges (C-1/C-11/C-6 and C-1′/C-11′/C-6′:98.9 and 99.0°, resp., are very similar to those of the parent structure **1**.

The starting compound 2-bromo-1,6-methano[10]annulene (**3**) is chiral and hence can be separated into pure enantiomers [of known absolute chirality $(-)(S)_p$] by chromatography on *CTA* [6]. Therefore, the synthetic sequence **3**–**6** can be used for the stereochemical correlation to deduce the absolute planar chiralities of all compounds (**4**–**6**) involved.

From $(-)(S)_p$-**3** thereby the dextrorotatory methoxy derivative $(R)_p$-**4** was obtained. Whereas the change of the descriptors $(S)_p \rightarrow (R)_p$ is due to the priority of C3 to H2 (according to the sequence rule), the change of the optical rotation $(-) \rightarrow (+)$ is a remarkable experimental result. From $(+)(R)_p$-**4** on coupling – *via* **5** as described for the inactive compound – only the enantiomers of the racemic forms (**6a**, **6b**) [$(R)_p(R)_a(R)_p$ and $(R)_p(S)_a(R)_p$] can be formed, but no *meso*-form **6c**. That is what we found: the isolated rotamers **6a** and **6b** are both dextrorotatory and have both the same planar chirality $(R)_p$, but differ in their axial chiralities.

In order to confirm this assumption, an optically active sample of **6a** – $(R)_p(R)_a(R)_p$ – (*vide supra*) was refluxed in toluene for 2 h, thus allowing equilibration with the other rotamer $(R)_p(S)_a(R)_p$ (**6b**). After cooling, this isomer was isolated and identified both by TLC and its UV-spectrum; for its CD-spectrum see Fig. 3. From the

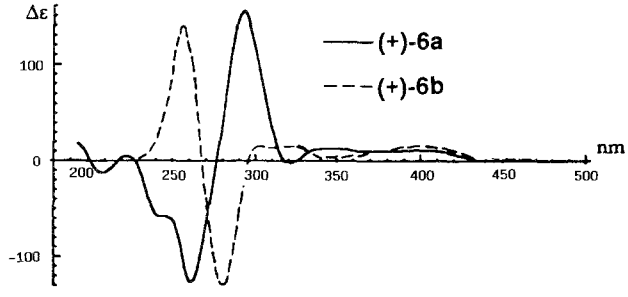


Fig. 3. CD-spectra of the two optically active rotamers (+)-**6a** and (+)-**6b** in ethanol

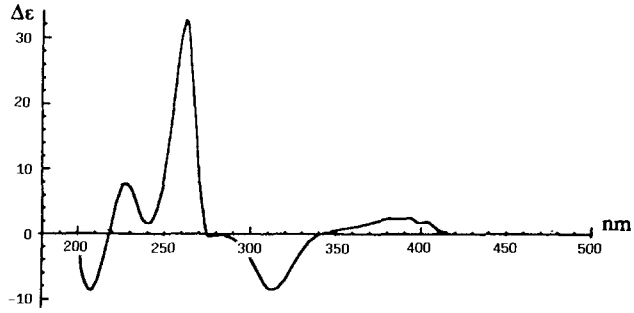


Fig. 4. CD-spectrum of (+)(*R*)-3-methoxy-1,6-methano[10]annulene (**4**) in ethanol

corresponding data a torsional barrier $\Delta G^{\#}$ of 132 kJ·mol^{-1} was calculated; the same value was deduced from CD-kinetics (cf. also Fig. 3). The (expected) increase of this barrier as compared to that of the rotamers of the 10,10′-dibromo derivative (88 kJ·mol^{-1}, cf. [2]) is remarkable.

The CD-spectra reveal that obviously the couplet around 270 nm is significant for the axial chirality.

Since the relative configurations of the planar and axial chiralities of **6a** are known from the crystal structure (Fig. 1), the correlations described allow also the assignment of the absolute chiralities: the dextrorotatory enantiomer of **6a** (eluted first from silicagel) therefore has the absolute chirality (+)-$(R)_p(R)_a(R)_p$. The dextrorotatory rotamer obtained by isomerization (and eluted as the third fraction on silica gel in toluene, *vide supra*) – consequently has the chirality (+)-$(R)_p(S)_a(R)_p$-**6b**.

Optical resolution by enantioselective chromatography (on *CTA* in ethanol) of the chiral 1,6-methano[10]annulenes **4** and **6** obtained from the racemic bromo derivative **3** provided the following results: 3-Methoxy-1,6-methano[10]annulene (**4**) was quantitatively resolved in one run, with the dextrorotatory enantiomer eluted first ($[\alpha]_D$ + 700°, ethanol). For its CD-spectrum, see Fig. 4.

Both rotamers of the biannulenyl **6** (**a** and **b**) could also easily be resolved by chromatography on *CTA*; here, too, the dextrorotatory enantiomers ($[\alpha]_D$ = +1550 and +830°, resp.) are less strongly adsorbed and eluted first. Their CD-spectra are identical with those shown in Fig. 3.

According to the results for the separation of the rotamers of racem. **6** (into **a** and **b**, *vide supra*), it could be expected that for **6c** (*meso*-**6**) the rotational barrier was also high enough to allow a separation into stable enantiomers. Indeed, **6c** could be quantitatively resolved on *CTA* (in ethanol) in one run ($\alpha = 2.09$) with the

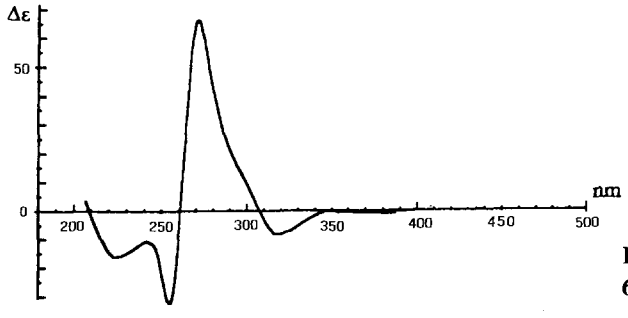


Fig. 5. CD-spectrum of (+)-$(R)_p(S)_a(S)_p$-**6c** (optically active *meso*-form) in ethanol

laevorotatory enantiomer being eluted first ($[\alpha]_D = -200°$ (ethanol); see Fig. 5 for the CD-spectrum of (+)-**6c**).

The *Cotton* effect at 270 nm was used to study the kinetics of racemization revealing an energy barrier of $\Delta G^{\#}$ of $118 \pm 1\ kJ \cdot mol^{-1}$ (at 78 and 90°C). Here, too, as for the rotamers **6a** and **6b** (*vide supra*), the increase of the barrier with regard to the *meso*-10,10′-dibromo derivative ($58\ kJ \cdot mol^{-1}$ [2]) is considerable. From a comparison of the CD-spectra (Figs. 3 and 5), the chirality $(R)_p(S)_a(S)_p$ can be deduced for (+)-**6c**.

Experimental

The NMR spectra (see Fig. 1) were recorded on a Bruker AM 300 spectrometer at 300 MHz in CD_2Cl_2. Optical rotations: Perkin–Elmer 241 polarimeter. CD: Dichrograph Mark III (Jobin Yvon). UV: Perkin–Elmer, Lambda 7 UV-Vis-spectrophotometer. Microcrystalline *CTA* (Merck, 15–25 μm) was used for enantioselective chromatography (column 63 × 690 mm, UV-detector).

3,3′-Dimethoxy-2,2′-bi(1,6-methano[10]annulenyl)s (**6a**–**6c**)

A solution of 1.7 g (10 mmol) of 3-methoxy-1,6-methano[10]annulene (**4**) [8] in 45 ml of dry ether was treated at 0 °C under argon dropwise with 12 mmol of *n*-butyl lithium in dry ether. After warming to room temperature and 4 h of stirring (colour change from bright yellow to deep brown), the lithium derivative **5** was added slowly to a cold (−78 °C) suspension of 1.6 g (12 mmol) dry copper(II) chloride in dry ether (under argon). After stirring at this temperature and warming up overnight, water was added, the organic phase separated and aqu. ammonia added until a clear blue solution resulted. This was extracted with ether (3 × 100 ml), the ether layer washed with water, dried over sodium sulfate and evaporated. The residue was chromatographed with toluene on a 80 × 2 cm silicagel column to give the following fractions: **6a** (yellow with greenish fluoroscence), 232 mg (13%), mp. 126–129 °C; **6c** (yellow), 272 mg (16%), mp. 79–80 °C and **6b** (yellow), 86 mg (5%), mp. 105–107 °C (all crystallizations from ether/pentane).

6a: $C_{24}H_{22}O_2$ (342.42); calcd. C 84.18, H 6.48; found C 83.96, H 6.52. Mass spectrum: m/e (% intensity): 342 (M^+, 3), 327 (M^+–Me, 4), 311 (M^+–OMe, 8), 171 ($M^+/2$, 59), 57 (100). UV [cyclohexane, λ_{max} (ε_{max})]: 395 (sh, 3600), 335 (sh, 8800), 275 (sh, 45200), 257 (57800). For the ^1H NMR spectra of **6a**–**6c** (in CD_2Cl_2) see Fig. 1. ^{13}C NMR (δ (ppm); 75.5 MHz, CD_2Cl_2): 158.78 (C3, C3′), 129.40 (C5, C5′), 128.97 (C7, C7′), 128.40 (C10, C10′), 127.20 (C9, C9′), 125.68 (C8, C8′), 125.59 (C2, C2′), 116.69 (C4, C4′), 116.4 (C1, C1′), 115.41 (C6, C6′), 59.34 (C3a, C3a′), 36.12 (C11, C11′); $^1J_{CH} = 141.2$–161.2 Hz). X-ray crystal structure of **6a** (crystallization from pentane): crystals ortho-rhombic, space group $P2_12_12_1$, $Z = 4$; lattice constants: $a = 9.487$, $b = 10.270$, $c = 19.050$ Å, $\alpha = \beta = \gamma = 90°$, $\rho = 1.225\ g \cdot cm^{-3}$; number of reflexes: 1417; $R = 0.049$, $R_w = 0.045$; intensity measurements on a Stoe four-cycle diffractometer (See Fig. 2).

The reaction sequence described above, if started from (+)$(R)_p$-**4**, $[\alpha]_D = +700 \pm 10°$ in ethanol) gave a pure mixture of **6a** and **6b** with no detectable amount of **6c** which is a proof for the enantiomeric purity of the starting material. (+)-**4** is accessible either from (−)(*S*)-**3** [6] – as described for racemic **4** [8] – or by enantioselective chromatography of the latter on *CTA* in ethanol ($\alpha = 1.34$, with the dextrorotatory rotatory enantiomer eluted first). Both rotamers were separated by chromatography as described above for the racemates and are dextrorotatory: $[\alpha]_D = +1550 \pm 15°$ and $+830 \pm 10°$, resp., in ethanol. They were also accessible from the racemates (*vide supra*) by enantioselective chromatography on *CTA* in ethanol. ($\alpha = 1.64$ and 1.13, resp.); in the latter case, the recycling technique [9] had to be applied for a complete separation of the enantiomers; both for **6a** and **6b** the dextrorotatory enantiomers are eluted first. From the three stereoisomers, **6c** has the highest

separation factor ($\alpha = 2.09$) on *CTA* in ethanol. Here the laevorotatory enantiomer is less strongly adsorbed. $[\alpha]_D = -200 \pm 10°$ ($c = 0.065$ in ethanol). For the CD-spectra (in ethanol) see Figs. 3 and 5.

Equilibration of (+)-**6a** with (+)-**6b** was performed by refluxing in toluene for 2 h. After evaporation, the residue was separated by preparative thin-layer chromatography on silicagel (KG-60), the layers eluted with CH_2Cl_2 and their CD-spectra recorded; they were identical with those of (+)-**6a** and (+)-**6b**, resp., obtained by chromatography on *CTA* (see Fig. 3).

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