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Two methods for the resolution of 10,10′-dihydroxy-9,9′-biphenanthryl

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Abstract

Two methods for the resolution of 10,10′-dihydroxy-9,9′-biphenanthryl were developed. The first involved salt formation with (−)-strychnine via its cyclic diester with phosphoric acid. The second method involved the formation of diastereomers (R)- and (S)-9,9′-biphenanthryl-10,10′-diyl N-((−)-α-methylbenzyl)phosphoroamidates.

1. Introduction

Chiral biaryl units are present in a wide range of compounds both natural and synthetic. Current research focuses on the 1,1′-binaphthlyl system, shown in many cases to be a successful inducer in asymmetric synthesis giving high enantioselectivity.[1] Since the synthesis of a racemic compound is often easier than the enantioselective synthesis, optical resolution still plays a very important role in the preparation of axially chiral biaryl compounds. Therefore, numerous efficient methods of resolution of 1,1′-binaphthlene-2,2′-diol **1** have been developed during the past decade. These methods include the resolution by crystallization of the salt of a racemic phosphoric ester of **1** with chiral amines;[2] resolution with chiral phosphoramidates as the resolving agent prepared from (S)-α-methylbenzylamine;[3] resolution by formation of inclusion complexes with chiral hosts;[4] and enzymatic resolution.[5] Buono[6] reported a good method of resolution with menthyl phosphorodichlorides as the chiral resolving agent; however, this reagent is very sensitive to moisture.

Although much research work has been carried out on the resolution and applications of 1,1′-binaphthlene-2,2′-diol **1**, 10,10′-dihydroxy-9,9′-biphenanthryl **2** has received much less attention. One reason for this may be that the studies of this compound as the chiral ligand in asymmetric synthesis have not revealed any significant advantage over the 1,1′-binaphthol **1**, though **2** contains both 1,1′-binaphthol and 2,2′-binaphthol units.[7] On the other hand, the optical rotation power of 9,9′-biphenanthol **2** is twice

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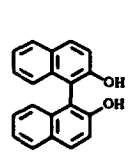
as much as that of 1,1′-binaphthol **1**. In our study towards the color pixelization of cholesteric reflective displays,[8] compounds with high optical rotation power are needed.



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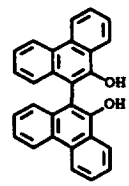

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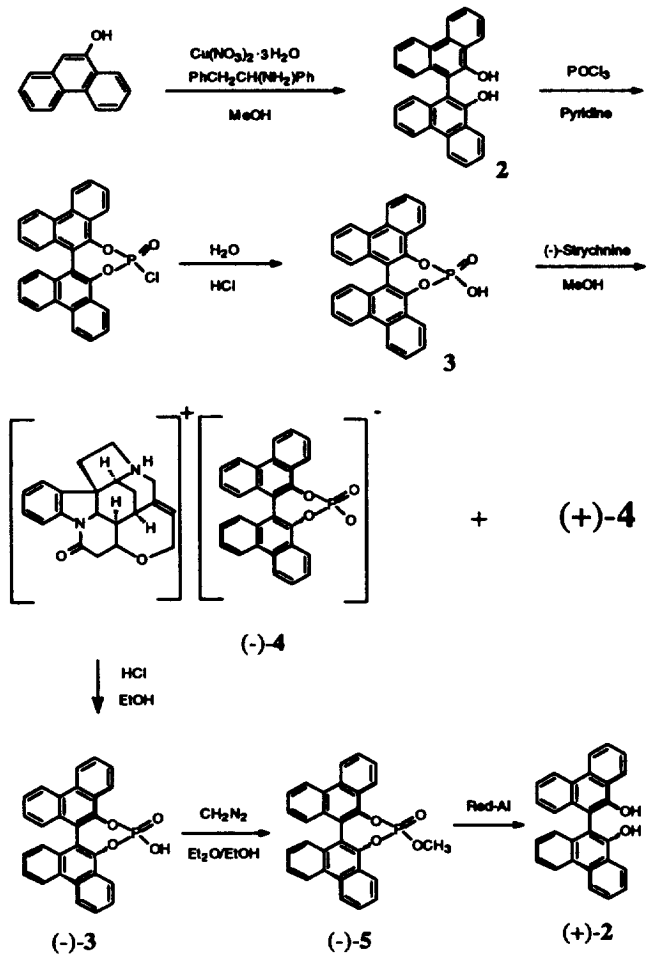
Toda[9] reported the resolution of 9,9′-biphenanthrol by inclusion with N-butylcinchonidinum bromide or a derivative from tartaric acid. However, only one of the two enantiomers was obtained in the optically pure form. A practical method of obtaining optically active **2** by enantioselective coupling of 9-hydroxyphenanthrene in the presence of optically active 1,2-diphenylethylamine has also been reported.[7] However, when we tried to repeat this reaction, we could get only an almost racemic mixture. Though 9,9′-biphenanthol is structurally similar to 1,1′-binaphthol, it is not always true that the same procedure for the resolution of the latter can be applied for the former. We wish to report herein the two methods for the resolution of 9,9′-biphenanthol in both enantiomeric pure forms.

2. Results

2.1. Resolution of 10,10′-dihydroxy-9,9′-biphenanthryl by crystallization of strychnine salt of its diester with cyclic phosphoric acid

At the beginning of our approach, we employed the following method to resolve racemic compound **2** (Scheme 1). This is the conventional preparation of optically pure compound **1** which has been utilized by several groups; to the best of our knowledge, however, no report has been published on the resolution of racemic **2** by crystallization of the strychnine salt of its diester with phosphoric acid. Oxidative coupling of 9-hydroxyphenanthrene with $Cu(NO_3)_2 \cdot 3H_2O$ in the presence of 1,2-diphenylethylamine in CH_3OH gave the racemic **2**, which was treated with oxophosphoryl chloride in pyridine to afford the racemic cyclic diester **3**. Resolution of racemic **3** by the formation of its salt with (−)-strychnine was achieved by recrystallization from methanol. Thus, upon cooling the mixture, a pure crystalline compound (−)-**4** was obtained in 41% yield based on the racemic mixture. Treating (−)-**4** with boiling excess HCl/EtOH (6 N) solution, the optically pure (−)-**3** precipitated out in 95% yield. Evaporation of the mother liquor from the above crystallization gave the diastereomeric salt **4**, enriched in (+)-**4** in 46% yield based on the racemic mixture. This enriched mixture was then treated with hydrochloric acid/ethanol as above to give the precipitate of enantiomeric acid **3**, enriched with (+)-**3**, in 96% yield. Reaction of diazomethane with optically pure (−)-**3** yielded (−)-**5**. Optically pure (+)-**2** was obtained in 91% by the reduction of (−)-**5** with Red-Al. In a similar way, the addition of diazomethane to the enantiomeric acid **3** enriched with (+)-**3** gave the enantiomeric ester **5** enriched with (+)-**5**, which was reduced with Red-Al to yield enantiomeric **2** enriched with (−)-**2**. Optically pure (−)-**2** was obtained in 76% based on the enriched mixture by recrystallization from THF/hexanes.

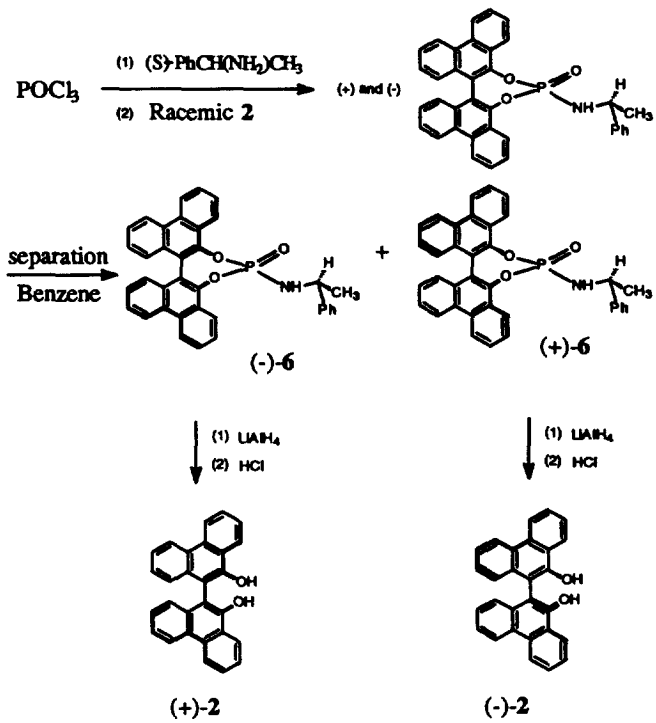


Scheme 1.

2.2. *Resolution of 10,10′-dihydroxy-9,9′-biphenanthryl by the formation of diastereomers with chiral phosphoramides*

Since the resolution by the above described method requires many steps, we sought another method. The second method we developed uses (S)-(−)-(α)-methylbenzylamine as the resolving agent (Scheme 2). Reaction of racemic diol **2** with equimolar quantities of oxophosphoryl chloride and (S)-(−)-(α)-methylbenzylamine in pyridine gave the diastereomers **6** in 81% yield. The enantiopure form of (+)-**6** was obtained in 40% yield based on the racemic **6** by single recrystallization of the diastereomers from hot benzene. Evaporation of benzene gave the diastereomers enriched with (−)-**6**, which was recrystallized in benzene:hexane (1:1 in v/v) to give optically pure (−)-**6** in 36% based on the racemic mixture **6**. Reduction of (+)-**6** with $LiAlH_4$ gave (−)-**2** in almost quantitative yield and reduction of (−)-**6** led to (+)-**2**. This scheme represents a simple method for the resolution of racemic **2**.

The two resolution methods described above seem complementary. In the first method, the salt of (−)-strychnine and (−)-9,9′-biphenanthryl-10,10′-diyl hydrogen phosphate crystallized out first; from it (+)-10,10′-dihydroxy-9,9′-biphenanthryl was obtained in the subsequential reactions. In the second method,



Scheme 2.

(+)-9,9′-biphenanthryl-10,10′-diyl-N-(α-(S)-methylbenzyl)phosphor-amide crystallized out first; it was reduced to give (−)-10,10′-dihydroxy-9,9′-biphenanthryl.

3. Experimental

3.1. General methods

All reagents and solvents were obtained from commercial sources and used as received, unless otherwise specified. ^{1}H NMR spectra were obtained on a Varian 200 MHz spectrometer in $CDCl_3$ using TMS as an internal standard, unless otherwise stated. Chemical shifts are reported in parts per million (ppm) downfield from TMS. Coupling constants are given in hertz, and the spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). ^{1}H NMR data are reported as follows: number of protons, multiplicity, coupling constants. Infrared spectra were measured with a Nicolet Magna FT-IR spectrometer 550. The optical activity was measured using an AA-10 Automatic Polarimeter. Elemental analyses were performed at Oneida Research Services, Inc. Melting points are uncorrected and were determined on a Thomas–Hoover melting point apparatus.

3.2. Synthesis of racemic 10,10′-dihydroxy-9,9′-biphenanthryl 2

The starting compound 9-hydroxyphenanthryl was purchased from Aldrich as tech grade (mp: 139–140°C) and purified by column chromatography using 2:1 hexanes:EtOAc as the eluent, mp 150–152°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 5.31 (1H, s), 6.98 (1H, s), 7.43–7.58 (2H, m), 7.59–7.73

(3H, m), 8.28–8.33 (1H, m), 8.56–8.69 (2H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 106.09, 122.33, 122.58, 122.70, 124.29, 125.52, 126.42, 126.72, 126.95, 127.22, 130.53, 131.53, 132.64, 149.46.

Into a 100 mL round-bottomed flask were placed 30 mL of methanol, 14.66 g (74.3 mmol) of 1,2-diphenylethylamine, 5.96 g (24.7 mmol) of copper(II) nitrate trihydrate. The solution was cooled in an ice bath. To the above mixture was added under a nitrogen atmosphere a solution of 2.2 g (11.3 mmol) of 9-hydroxyphenanthryl in 10 mL of methanol. After stirring at 0°C for 5 h, the reaction mixture was quenched with 2 N HCl and the product was extracted with diethyl ether four times (100 mL each). Evaporation of ether provided 1.9 g of crude 10,10′-dihydroxy-9,9′-biphenanthryl, which was recrystallized from acetone/hexanes, 1.6 g (73%), mp 232–234°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 5.51 (1H, s), 7.19–7.35 (2H, m), 7.49 (1H, ddd, J=8.2, 6.4, 1.8 Hz), 7.64–7.82 (2H, m), 8.44 (1H, dd, J=7.8, 1.5 Hz), 8.70 (1H, d, J=8.2 Hz), 8.76 (1H, d, J=7.8 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 107.07, 122.66, 122.89, 123.51, 124.77, 125.07, 126.84, 127.05, 127.65, 128.14, 131.65, 131.96, 149.37.

3.3. Synthesis of racemic 9,9′-biphenanthryl-10,10′-diyl hydrogen phosphate 3

Under anhydrous conditions, 2.7 g (7.0 mmol) of racemic 10,10′-dihydroxy-9,9′-biphenanthryl and 10 mL of pyridine were placed in a three-necked flask equipped with a reflux condenser, a thermometer, and an addition funnel. The funnel was charged with 1.5 mL (16.1 mmol) of $POCl_3$. At room temperature, the $POCl_3$ was added to the pyridine solution slowly and with stirring. The temperature soon reached 65°C. After the addition, the reaction mixture was heated at 100°C overnight. Upon cooling, the mixture was poured into a boiling solution of 6 N HCl (60 mL) and the mixture was kept boiling for 30 min. The precipitated acid was collected and washed with water several times and air dried, 2.20 g (70.3%), mp greater than 300°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ:7.28–7.44 (2H, m), 7.62–7.69 (1H, m), 7.78–7.92 (2H, m), 8.35–8.39 (1H, m), 8.94–9.02 (2H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 118.99, 123.19, 123.35, 123.64, 126.34, 126.95, 127.41, 127.58, 128.02, 128.37, 130.27, 131.26, 144.84, 145.03.

3.4. Resolution of racemic 9,9′-biphenanthryl-10,10′-diyl hydrogen phosphate

In a 1000 mL flask were placed 2.88 g (6.41 mmol) of racemic 9,9′-biphenanthryl-10,10′-diyl hydrogen phosphate, 2.14 g (6.41 mmol) of (−)-strychnine, and 600 mL of methanol. The solution was heated to boiling until all of the solid material dissolved. Upon cooling and leaving overnight, white crystals were collected and washed with methanol and dried, 2.01 g (41%), mp 275–278°C, $[\alpha]_D^{25}=-361$ (EtOH, c=0.38).

The above salt of (−)-strychnine and 9,9′-biphenanthryl-10,10′-diyl hydrogen phosphate was dissolved in about 400 mL of EtOH. Complete dissolution was achieved by heating the mixture to reflux, and then 160 mL of 6 N hydrochloric acid was added slowly and with stirring. The temperature was maintained between 85–90°C during the addition and another 30 min after the addition. Partial evaporation of the EtOH led to the precipitation of the acid. The solid contaminated by a small amount of strychnine was redissolved in a minimum amount of EtOH by heating to reflux, and 100 ml of 6 N HCl was added with vigorous stirring. The acid began to precipitate during the addition. After the addition, the solution was allowed to cool to room temperature. The solid was collected, washed with water, and air-dried to give 1.08 g (95%) of (−)-9,9′-biphenanthryl-10,10′-diyl hydrogen phosphate, $[\alpha]_D^{25}=-575$ (EtOH, c=0.46). The ^{1}H- and ^{13}C NMR spectra of this acid are the same as those of racemic 9,9′-biphenanthryl-10,10′-diyl hydrogen phosphate.

3.5. (−)-5, (−)-9,9′-Biphenanthryl-10,10′-diyl methyl phosphate

In a round-bottomed flask, 1.08 g (2.41 mmol) of (−)-9,9′-biphenanthryl-10,10′-diyl hydrogen phosphate was dissolved in 50 mL of EtOH. The solution was then treated with an excess of diazomethane in ether. After stirring at RT for 4 h, the excess of CH_2N_2 was decomposed by the addition of acetic acid to the ether solution. The ether was then evaporated and the (−)-9,9′-biphenanthryl-10,10′-diyl methyl phosphate began to precipitate. The solution was cooled and the solid was collected, washed with EtOH, and air-dried to afford 1.06 g (96%) of the product, $[\alpha]_D^{25}=-609$ (THF, c=0.37), mp 275–277°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.98 (3H, d, J=11.5 Hz), 7.25–7.47 (4H, m), 7.57–7.67 (2H, m), 7.74–7.88 (4H, m), 8.40–8.51 (2H, m), 8.74–8.84 (4H, m).

3.6. (+)-3, (+)-9,9′-Biphenanthryl-10,10′-diyl hydrogen phosphate

The filtrate from the initial crystallization of the strychnine salt was evaporated to dryness to give 2.8 g of diastereomeric salts, enriched in (−)-strychnine of (+)-9,9′-biphenanthryl-10,10′-diyl hydrogen phosphate. To free the acid from the strychnine, the salt was dissolved in EtOH and treated twice with 6 N HCl, in the way described above, to give 1.4 g of an enantiomeric mixture of hydrogen phosphate, enriched in (+)-9,9′-biphenanthryl-10,10′-diyl hydrogen phosphate, $[\alpha]_D^{25}=+470$ (EtOH, c=0.48).

3.7. (+)-5, (+)-9,9′-Biphenanthryl-10,10′-diyl methyl phosphate

The (+)-9,9′-biphenanthryl-10,10′-diyl methyl phosphate was obtained by treatment of the (+)-9,9′-biphenanthryl-10,10′-diyl hydrogen phosphate with diazomethane as described above, $[\alpha]_D^{25}=+523$ (THF, c=0.50).

3.8. (+)-2, (+)-10,10′-Dihydroxy-9,9′-biphenanthryl

A 100 mL, three-necked flask equipped with a dropping funnel, thermometer, and drying tube was charged with 0.51 g (1.10 mmol) of (−)-9,9′-biphenanthryl-10,10′-diyl methyl phosphate and 30 ml of dry toluene. The mixture was stirred under nitrogen and heated with a water bath until all material dissolved. The solution was then cooled in an ice–water bath to 5–10°C. To this solution, a solution of 4 mL of Red-Al in 5 mL of toluene was added from the dropping funnel slowly. After the addition, the mixture was stirred at room temperature for an additional hour.

The reaction mixture was poured into 100 mL of 4 N hydrochloric acid. The organic layer was separated and washed with 80 mL of 4 N HCl. After further washing with 40 mL of brine and 50 mL of water, all aqueous layers were combined and extracted with three 60 mL portions of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and filtered. The solvent was removed on a rotary evaporater under reduced pressure to give 0.45 g (91%) of product, $[\alpha]_D^{25}=+69.1$ (THF, c=0.138). The product was recrystallized from THF/hexanes to give colorless crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 5.51 (1H, s), 7.19–7.35 (2H, m), 7.49 (1H, ddd, J=8.2, 6.4, 1.8 Hz), 7.64–7.82 (2H, m), 8.44 (1H, dd, J=7.8, 1.5 Hz), 8.70 (1H, d, J=8.2 Hz), 8.76 (1H, d, J=7.8 Hz). Anal. Calcd for $C_{28}H_{18}O_2$: C, 87.02; H, 4.70. Found: C, 86.25; H, 4.59.

3.9. (−)-2, (−)-10,10′-Dihydroxy-9,9′-biphenanthryl

(−)-10,10′-Dihydroxy-9,9′-biphenanthryl was obtained by treatment of (−)-9,9′-biphenanthryl-10,10′-diyl methyl phosphate with Red-Al as described above, $[\alpha]_D^{25}=-60.5$ (THF, c=0.31), which was recrystallized twice from THF/hexanes to give an enantiopure compound, $[\alpha]_D^{25}=-70.1$ (THF, c=0.156), Anal. Calcd for $C_{28}H_{18}O_2$: C, 87.02; H, 4.70. Found: C, 86.58; H, 4.66.

3.10. (R,S)-9,9′-Biphenanthryl-10,10′-diyl-N-(α-(S)-methylbenzyl)phosphoramide 6

To an ice-cooled solution of phosphoryl chloride (1.01 g, 6.59 mmol) in 10 mL dry pyridine was added a solution of (S)-(−)-α-methylbenzylamine (0.80 g, 6.60 mmol) in 10 mL dry pyridine dropwise under the N_2 condition. The mixture was stirred at 0°C for 3 h and an additional 4 h at room temperature. Then racemic 10,10′-dihydroxy-9,9′-biphenanthryl (1.70 g, 4.4 mmol) was added to the above solution and the mixture was refluxed overnight. Upon cooling, 25 mL of 10% H_2SO_4 was added. After stirring the solution for 10 min, 30 mL of water was added. The mixture was then extracted with three portions of 40 mL of $CHCl_3$. The combined $CHCl_3$ layer was dried over Na_2SO_4. Removal of $CHCl_3$ gave diastereomers **6** as a white solid, 1.96 g (81%).

3.11. Separation of diastereomers 6

The diastereomers were dissolved in the refluxed benzene. After staying at room temperature overnight, the solution yielded a crystalline solid, which was collected to give (+)-**6**, 0.78 g (40%), mp 227–229°C; $[\alpha]_D^{25}=+545$ (c=0.72, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.44 (3H, d, J=6.7 Hz), 3.25 (1H, dd, J=11.3 and 9.6 Hz), 4.44–4.65 (1H, m), 6.98–7.85 (15H, m), 8.36–8.46 (2H, m), 8.73–8.80 (4H, m). IR (KBr disk, cm^{-1}): 3200, 3070, 1594, 1489. Anal. Calcd for $C_{36}H_{26}NO_3P$: C, 78.39; H, 4.75; N, 2.54. Found: C, 77.92; H, 4.70; N, 2.65.

The mother liquor of benzene solution was evaporated to dryness and the residue was recrystallized from a mixture of benzene/hexane solution. After 48 h at RT, a white crystalline solid precipitated out from the solution. The solid was collected to give 0.71 g (36%) of (−)-**6**, mp 245–247°C; $[\alpha]^{25}{}_D=-532$ (c=0.12, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.29 (3H, dd, J=6.9 and 1.0 Hz), 3.48 (1H, dd, J=11.4 and 9.6 Hz), 4.35–4.54 (1H, m), 7.07–7.839 (15H, m), 8.20–8.24 (1H, m), 8.40–8.45 (1H, m), 8.71–8.79 (4H, m). IR (KBr disk): 3187, 3065, 1595, 1489. Anal. Calcd for $C_{36}H_{26}NO_3P$: C, 78.39; H, 4.75; N, 2.54. Found: C, 78.34; H, 4.78; N, 2.65.

3.12. Reduction of (+)-6

A solution of (+)-**6** (0.78 g, 1.42 mmol) in 20 mL of dry THF was cooled in a ice-bath. Lithium alminum hydride (0.45 g, 11.8 mmol) was added in portions with stirring. The reaction mixture was worked up after 3 h by the addition of H_2O and dilute HCl until the solution was slightly acidic. The solution was extracted with $CHCl_3$ (3×40 mL). The combined $CHCl_3$ layers were dried over Na_2SO_4. Evaporation of the solvent gave (−)-10,10′-dihydroxy-9,9′-biphenanthryl as a white solid, 0.50 g (93%), mp 232–234°C (lit. 234–236°C), $[\alpha]_D^{25}=-69.8$ (THF, C=0.132; lit. −71°C). Phenylethylamine was recovered in 90% yield without significant loss of its optical purity.

3.13. Reduction of (−)-6

(+)-10,10′-Dihydroxy-9,9′-biphenanthryl was obtained in a similar way by the reduction of (−)-**6** with $LiAlH_4$ in THF as white solid: mp 232–234°C; $[\alpha]_D^{25}$=+69.1 (THF, c=0.173).

Acknowledgements

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References

1. Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, D., *Synthesis*, **1992**, 503.
2. (a) Jacques, J.; Fouqeuey, C., *Org. Synth.*, **1988**, *67*, 1. (b) Tamai, T.; Heung, P.; Iizuka, K.; Okamura, A.; Miyano, S., *Synthesis*, **1990**, 222, and references cited in.
3. (a) Gong, B. Q.; Chen, N. Y.; Hu, B. F., *J. Org. Chem.*, **1991**, *56*, 423. (b) Fabbri, D.; Delogu, G.; De Lucchi, O., *J. Org. Chem.*, **1993**, *58*, 1748.
4. Hu, Q. S.; Vitharana, D.; Pu, L., *Tetrahedron: Asymmetry*, **1995**, *6(9)*, 2123, and references cited in.
5. Miyano, S.; Kawahara, Y.; Inoue, Y.; Hashimoto, H., *Chem Lett.*, **1987**, 355.
6. Brunel, J.; Buono, G., *J. Org. Chem.*, **1993**, *58*, 7313.
7. Yamoto, K.; Fukushima, H.; Nakazaki, M., *J. Chem. Soc. Che. Commun.*, **1984**, 1490.
8. Chien, L.-C.; Muller, U.; Vincentini, F.; Lin, Y., *Polymer Preprints*, **1997**, *38*, 359.
9. Toda, F.; Tanaka, K.; Stein, Z.; Goldberg, I., *J. Org. Chem.*, **1994**, *59*, 5748.