

SYNTHESIS OF NEW ATROPISOMERS DERIVED FROM METHOXYCHLOROACRIDINE. PREPARATION OF ENANTIOMERICALLY PURE (*aR*)-(-)-2,2'-DIHYDROXY-9,9'-BIACRIDINE

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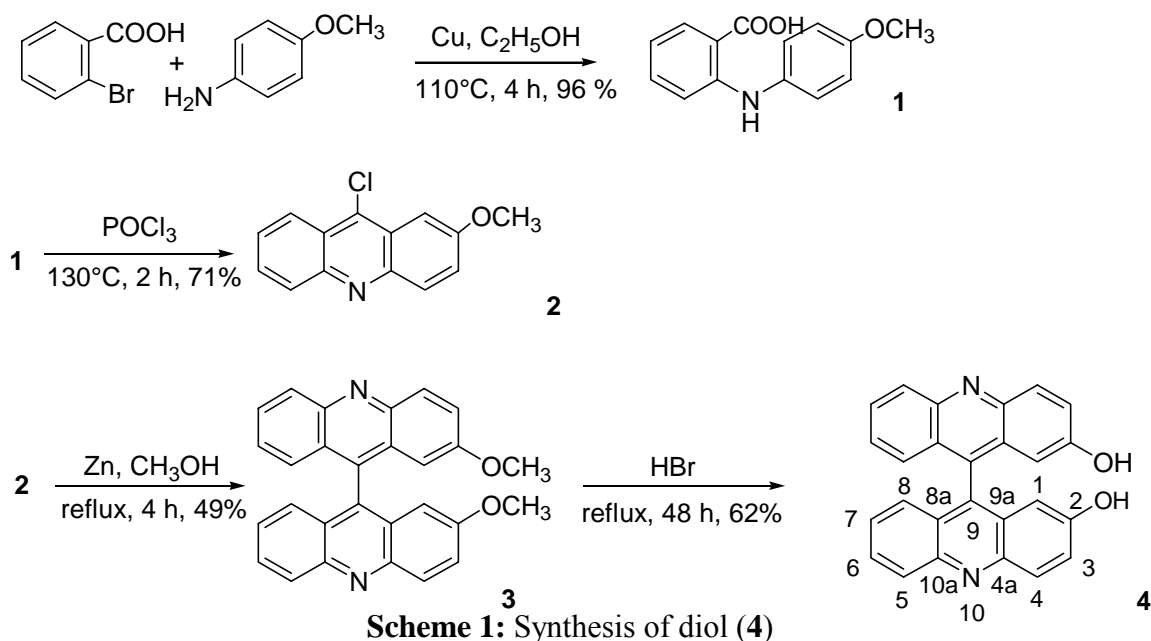
Abstract - New biacridinyl atropisomers were obtained from symmetric ligand 2,2'-dihydroxy-9,9'-biacridine (**4**), prepared from 9-chloro-2-methoxyacridine. Alternative *O*-acylation and alkylation led to different polycycles and to a biacridinyl crown ether. The molecular structures of 2,2'-di(*p*-chlorobenzoyloxy)-9,9'-biacridinyl (**5**) and (9,9'-bisacridinyl)-2,2'-dihydroxy-bis-(camphanate) ester (**13**) were solved by X-Ray crystallography, showing a 'scissor-like' host conformation and guest inclusion of chloroform and acetonitrile. The determination of X-Ray structure of one diastereomer (**13**) allows to assign the absolute configuration of enantiomerically recovered (*aR*)-(-)-2,2'-dihydroxy-9,9'-biacridinyl.

INTRODUCTION

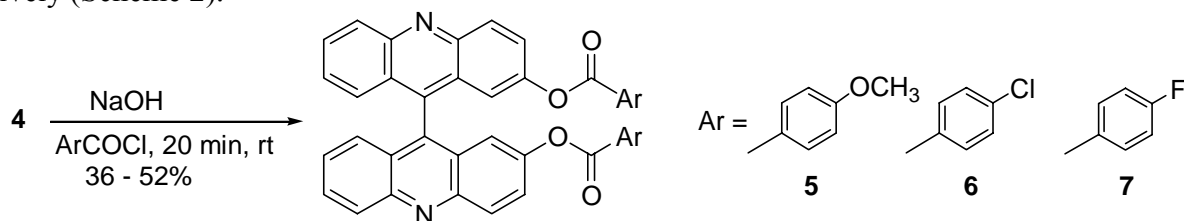
Among the numerous C₂-symmetry derivatives prepared in the literature,¹ binaphthyl and especially the chiral bidentate ligand 2,2'-dihydroxy-1,1'-binaphthyl has been widely used in asymmetric synthesis² and is known as a good host in optical resolution of chiral guest species. In connection with our experience in the synthesis of acridinic derivatives, well known for their therapeutic effects,³ we got involved in the preparation of symmetrical heterocyclic host compounds related to bianthryl but using 9,9'-biacridinyl.⁴ Dimethoxy atropisomers were also prepared; the corresponding 2,2'-dimethoxy-9,9'-biacridine has proved useful in molecular recognition with chloroform inclusion in its crystalline structure.⁵ We report now the synthesis and characterization of new atropisomers obtained using 2,2'-dihydroxy-9,9'-biacridine (**4**) as starting material.

RESULTS AND DISCUSSION

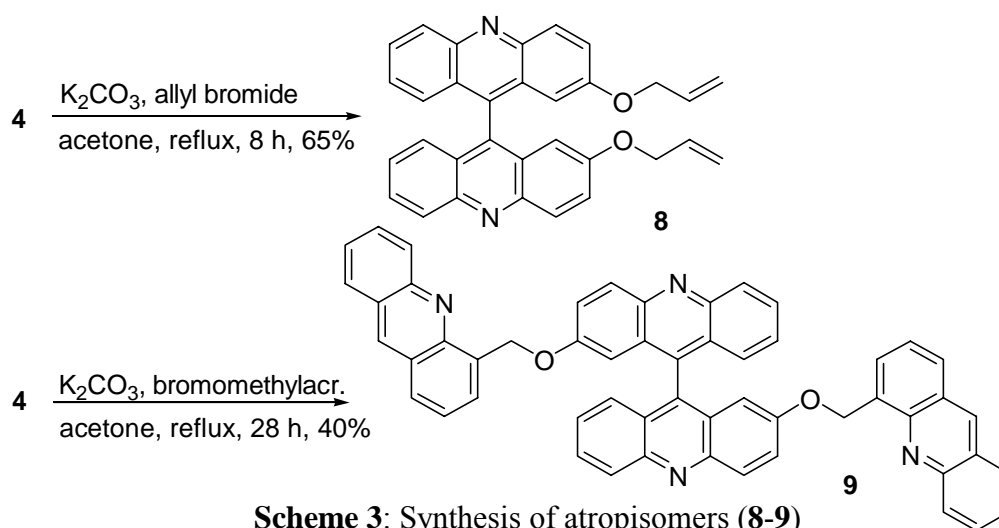
In the first pathway of the synthesis, attention was placed on the preparation of *O*-acyl derivatives. First, 4'-methoxyphenylanthranilic acid (**1**) was prepared by Ullmann's reaction between *o*-bromobenzoic acid and *p*-methoxyaniline.⁶ Cyclization of this anthranilic acid in the presence of POCl₃ led to 2-methoxy-9-chloroacridine (**2**).⁷ Homocoupling of **2** with zinc powder in anhydrous methanol under nitrogen afforded 2,2'-dimethoxy-9,9'-biacridine (**3**) with 49 % yield.⁸ The 2,2'-dihydroxy-9,9'-biacridine (**4**) was obtained by demethylation of **3** with 48 % hydrobromic acid (Scheme 1).



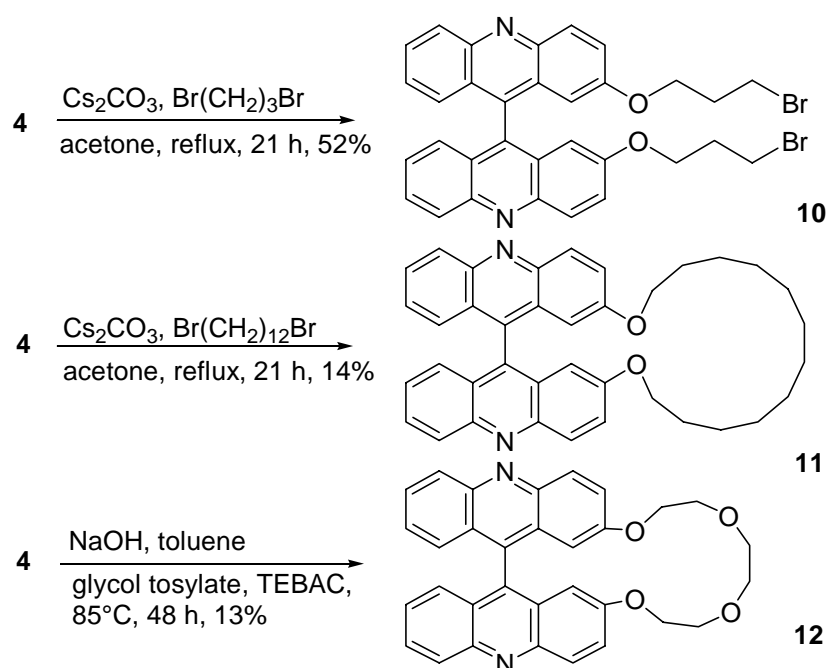
Next, reaction of **4** with *p*-methoxybenzoyl chloride in anhydrous dichloromethane led to the 2,2'-bis[*p*-methoxybenzoyloxy]-9,9'-biacridine (**5**) (36 %); *p*-chlorobenzoyl chloride and *p*-fluorobenzoyl chloride provided the corresponding 2,2'-bis(acyloxy)-9,9'-biacridines (**6**) and (**7**) in 52 and 48 % yields respectively (Scheme 2).



We also focused on the preparation of *O*-alkyl atropisomers. For example allyl groups were introduced on diol (**4**) by reaction with allyl bromide, leading to 2,2'-bis(allyloxy)-9,9'-biacridine (**8**) in 65 % yield. Moreover tetraacridinic polycycles can also be obtained using bromomethylacridine, previously prepared in the laboratory.⁹ Polyacridine (**9**) was obtained with 40 % yield with potassium carbonate in acetone (Scheme 3).



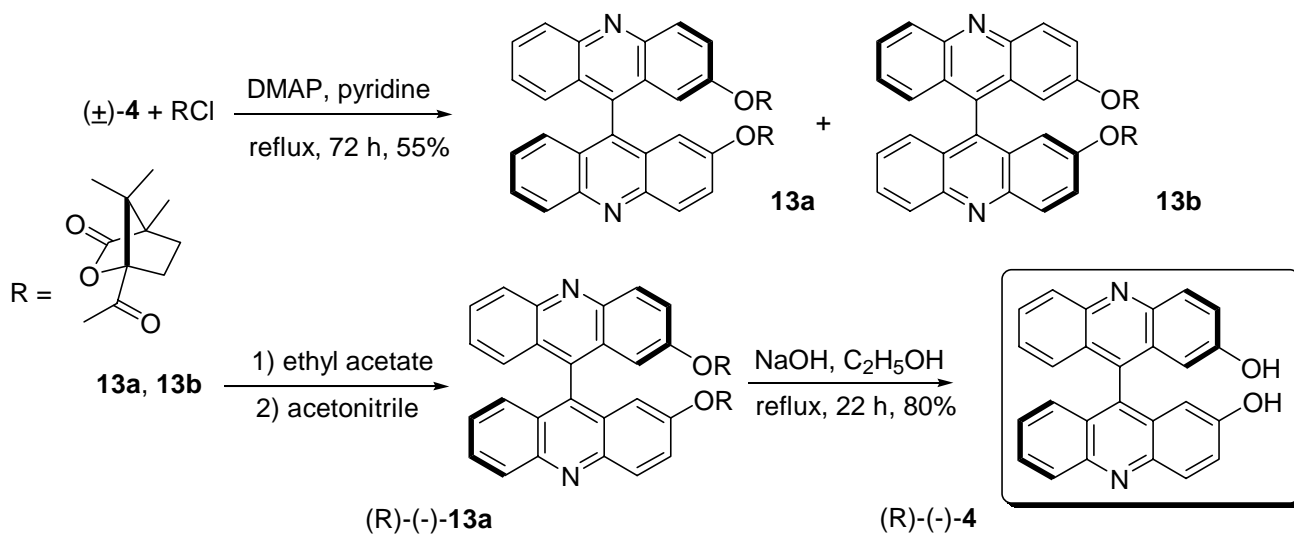
We were also interested in the preparation of macrocycles derived from an acridine moiety. Host macrocycles like crown ethers are much studied host compounds.¹⁰ Among them, one class is the crown ethers containing heterocyclic subunits such as the proton ionizable pyridin-4-one derivatives of Bradshaw.¹¹ These polyether-diester ligands serve to study the influence of the crown ether on the tautomerism of the heterocycle¹² and on their complexing properties. Moreover, Cram has described numerous crown ethers obtained from 2,2'-dihydroxy-1,1'-binaphthyl and usable for structural recognition of chemical substrates by molecular complexation,¹³ for example with cations.¹⁴ Lehn has reported the preparation of macrocyclic cyclo-bis-intercaland receptors containing two acridine units,¹⁵ and we previously obtained crown ethers from 2,7- and 2,3-dihydroxyacridan-9-ones.¹⁶



Coupling 1,3-dibromopropane with **4** in acetone with cesium carbonate led us to obtain the symmetrical bis-bromopropyl compound (**10**) with 52 % yield; only the monomeric macrocycle (**11**) was obtained using 1,12-dibromododecane (14 % yield). Phase transfer catalysis¹⁷ was used to prepare the bisacridinyl crown (**12**) by reaction of diol **4** in alkaline toluene during two days with triethyleneglycol ditosylate. Only one monomeric crown ether was recovered with 14 % yield, (Scheme 4).

All compounds were characterized by NMR spectroscopy. For monomers (**11**) and (**12**), no further information could be gained from the simplified ¹H and ¹³C NMR spectra; HR MS spectrometry confirmed the propose structure of a single monomeric biacridine.

The resolution of racemic 2,2'-dihydroxy-9,9'-biacridine (**4**) was performed by the crystallization of a mixture of diastereomers (**13**) obtained by derivatization of precursor (**4**) with (*1S*)-(-)-camphanic acid chloride. Because of the poor solubility of **4** we used a modified procedure of esterification in a mixture of pyridine¹⁸ and 4-dimethylaminopyridine¹⁹ to prepare the bis(camphanate)esters (**13**). After 3 days under reflux a mixture of diesters (**13**) was recovered (55 % yield). First recrystallization from ethyl acetate gave two fractions: an insoluble fraction enriched with one diastereomer (**13a**) (de 75 %) and a filtrate with the ester (**13b**) (de 60 %). Then, all attempts to improve the diastereomeric purification of **13a** and **13b** failed and we decided to use acetonitrile as recrystallization solvent. In this case only compound (**13a**) was recovered diastereomerically pure ($[\alpha]_D^{20} = -100^\circ$, $c = 0.08 \text{ CHCl}_3$); it provided crystals suitable for X-Ray crystallography. From the crystallographic structure, we determined the absolute configuration of the biacridinyl moiety of ester (**13a**) as (*aR*), (see the ORTEP drawing of diester (**13a**) represented in Figure 2). Then (*aR*)-(-)-**13a** was saponified in EtOH²⁰ to yield enantiomerically pure (*R*)-(-)-diol (**4**) ($[\alpha]_D^{20} = -120^\circ$, $c = 0.025 \text{ MeOH}$). (Scheme 5).



Scheme 5: Enantioselective separation of the axially chiral biacridine (**(R)-(-)-4**) by crystallization in acetonitrile.

The X-Ray structures of 9,9'-bianthryl- and 10,10'-biacridinyl-9,9'-diones have been reported.^{4,21} The averaged torsion angles between the anthracene or acridinone rings were 74.2(3)° and 85.3(3)° respectively but no guest inclusion was observed. We turned to dimethoxy and dihydroxy derivatives and obtained a crystal structure of racemic dimethoxy-9,9'-biacridinyl that showed a CHCl₃ 1:1 inclusion. Because racemic diol (**4**) is poorly soluble we did not obtain crystals suitable for an X-Ray study, but after derivatization we obtained the structure of **6** with one molecule of CHCl₃ included. The torsion between the two acridine moieties is 97.2(8)° and 85.8(1)° for compounds (**6**) and (**13a**) respectively. The two *p*-chlorophenyl rings have a dihedral angle of 117.8(7)° and 79.3(8)° relative to the acridine moiety of **6**, and the camphoric groups have 104.8(9)° and 99.5(8)° for compound (**13a**). Selected geometrical parameters of **6** and **13a** are gathered in Table 1 according to the numbering scheme displayed in Figure 1 and Figure 2.

Table 1. Data collection and processing parameters for derivatives (**6**) and (**13a**)

Compound	6	13a
Empirical formula	C ₄₁ H ₂₃ N ₂ O ₄ Cl ₅	C ₁₁₀ H ₁₀₇ N ₁₆ O ₁₃
Molecular mass	784.91	1861.12
Crystal system	Orthorhombic	Triclinic
Space group	P bcn	P ₁
<i>a</i> [Å]	14.8574(9)	13.1169(7)
<i>b</i> [Å]	17.732(2)	14.334(1)
<i>c</i> [Å]	27.494(3)	14.452(1)
α [deg]	90.00 (1)	85.692 (3)
β [deg]	90.00 (1)	74.197 (3)
γ [deg]	90.00 (1)	79.549 (3)
<i>V</i> [Å ³]	7243.1(2)	2570.2(3)
<i>Z</i>	8	1
Crystal size [mm]	0.2x0.2x0.1	0.4x0.3x0.05
<i>d</i> calcd [g.cm ⁻³]	1.44	1.202
μ (MoKα), cm ⁻¹	2.21	0.080
θ range [°]	4-21	7-26
Reflexions collected	4415	9482
<i>R</i>	0.088 (2616 refl.>3 σ(<i>F</i>))	0.097 (6463 refl.>4 σ(<i>F</i>))
<i>R_w</i>	0.092	0.148

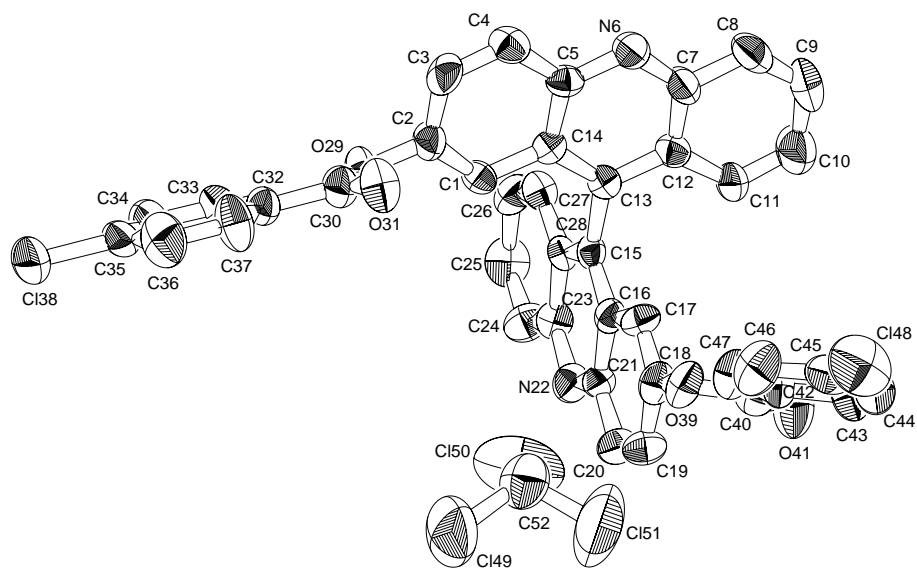


Figure 1 Perspective view of **6** showing the numbering system and chloroform inclusion

Table 2 Selected bond lengths (Å) for derivatives (**6**) and (**13a**)

Compounds	6		13a
C(2)-O(29)	1.40(8)	O(43)-C(18)	1.416(9)
O(29)-C(30)	1.38(8)	O(43)-C(44)	1.328(1)
C(30)-C(32)	1.487(7)	C(44)-C(46)	1.516(1)
C(13)-C(15)	1.495(7)	C(13)-C(15)	1.490(1)
C(18)-O(39)	1.42(7)	O(29)-C(2)	1.395(9)
O(39)-C(40)	1.492(7)	O(29)-C(30)	1.359(1)
C(40)-C(42)	1.50(2)	C(30)-C(32)	1.512(1)

Table 3 Selected bond and torsion angles (Å, °) for derivatives (**6**) and (**13a**)

Compounds	6		13a
C(2)-O(29)-C(30)	114.9(5)	C(18)-O(43)-C(44)	116.5(6)
C(32)-C(30)-O(29)	110.9(3)	O(43)-C(44)-C(46)	113.2(7)
C(18)-O(39)-C(40)	116.3(4)	C(30)-O(29)-C(2)	116.1(6)
C(16)-C(15)-C(13)-C(14)	97.2(8)	C(14)-C(13)-C(15)-C(16)	85.8(1)
C(1)-C(2)-O(29)-O(30)	117.8(7)	C(17)-C(18)-O(43)-C(44)	104.8(9)
C(19)-C(18)-O(39)-C(40)	79.3(8)	C(30)-O(29)-C(2)-C(3)	99.5(8)

The absolute configuration of saponified diol (**4**) was determined using the X-Ray data of structure (**13a**).

The latter was obtained after recrystallization in ethyl acetate and acetonitrile of **13**, leading to only one diastereomer (**13a**). The structure of **13a** consists of two independent units packed with nine molecules of acetonitrile. Only one diastereomer without solvent molecules is shown in Figure 2.

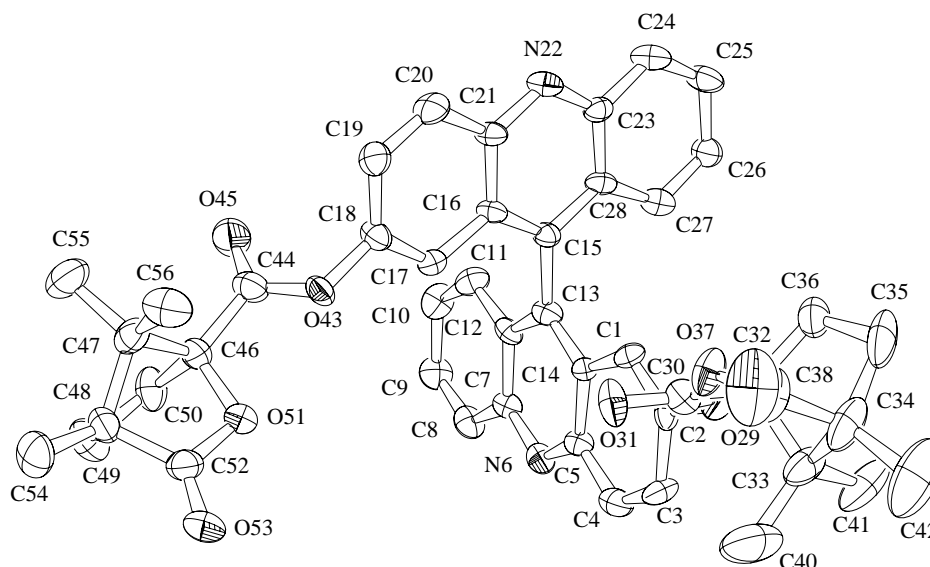


Figure 2 ORTEP drawing of diester ((*aR*)-(-)-**13a**). Only one unit is represented without acetonitrile inclusion.

CONCLUSION

We synthesized new biacridinic derivatives by using the racemic 9,9'-biacridinyl-2,2'-diol; the (*aR*)-(-)-9,9'-biacridinyl-2,2'-diol obtained was enantiomerically pure. Further studies on the use of such compounds as chiral ligands in asymmetric synthesis are in progress.

EXPERIMENTAL

Solvents or reagents were grade quality and were used without further purification, except methanol. Melting points were measured on an Electrothermal IA 9300 apparatus and were uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum sheets pre-coated with silica gel (Merck Kieselgel, 60 F₂₅₄, layer thickness 0.25 mm). Column chromatography was performed on silica gel (Merck Kieselgel, 230-240 mesh). ¹H NMR and ¹³C NMR spectra were recorded on BRUKER AM 200 and AMX 400 spectrometers. Spectra were referenced to the residual solvent peak. Optical rotations were obtained on a Perkin-Elmer 141 polarimeter at 589 nm (sodium D line) using 1.0 dm cells. Specific rotations, [α]_D are reported in degrees per decimeter at 25 °C, and the concentration (*c*) is given in grams per 100 mL.

4'-Methoxy-*N*-phenylanthranilic acid (**1**)

A mixture of *p*-anisidine (12.4 g, 0.1 mol), *o*-bromobenzoic acid (24.3 g, 0.1 mol), copper (1 g, 16 mmol) and ethanol (200 mL) was heated at 110°C for 4 h. After evaporation of the solvent, the residue was

dissolved in hot water (350 mL) and filtered. After cooling, the pH was adjusted to 3 with 6N HCl. The precipitate obtained was washed with water and dried to yield 23.5 g (96 %) of **1**; mp 187°C (from ethanol), (lit.,⁴ 186°C). TLC/R_f: 0.4 (CH₂Cl₂/EtOH, 6/4). ¹H NMR (DMSO-d₆): δ = 3.76 (s, 3H), 6.69 (t, 1H, *J* = 7.1 Hz), 6.93 (d, 1H, *J* = 8.0 Hz), 6.96 (d, 2H, *J* = 9.0 Hz), 7.19 (d, 2H, *J* = 9.0 Hz), 7.31 (ddd, 1H, *J* = 1.4, 7.1 and 8.5 Hz), 7.88 (d, 1H, *J* = 7.8 Hz), 9.45 (s, 2H). ¹³C NMR (DMSO-d₆): δ = 55.33, 111.43, 112.86, 114.84 (2C), 116.34, 125.12 (2C), 131.86, 133.04, 134.23, 148.88, 156.15, 170.15.

2-Methoxy-9-chloroacridine (2)

A mixture of 4-methoxyphenylanthranilic acid (**1**) (8.33 g, 34 mmol) and phosphorous oxychloride (33 mL, 0.36 mmol) was heated at 90°C for 15 min, and then for 2 h at 130°C. After evaporation of the solvent, the residue was dissolved in chloroform (100 mL) and washed successively with aqueous 2N ammonia and water. The organic layer was dried over MgSO₄ and evaporated. The residue was recrystallized from ethanol to yield 5.94 g (71 %) of **2** as yellow needles; mp 152°C (from ethanol), (lit.,²² 152-153°C). TLC/R_f: 0.6 (Et₂O/hexane, 8/2). ¹H NMR (CDCl₃): δ = 3.99 (s, 3H), 7.43 (dd, 1H, *J* = 2.1, 10.1 Hz), 7.45 (d, 1H, *J* = 2.5 Hz), 7.58 (td, 1H, *J* = 2.1, 7.2 Hz), 7.73 (td, 1H, *J* = 2.2, 7.1 Hz), 8.08 (d, 1H, *J* = 10.1 Hz), 8.17 (d, 1H, *J* = 8.1 Hz), 8.36 (d, 1H, *J* = 6.2 Hz). ¹³C (CDCl₃): δ = 55.99, 99.75, 124.10, 124.42, 125.23, 125.86, 126.98, 129.30, 129.73, 131.43, 138.16, 146.05, 147.14, 158.14.

2,2'-Dimethoxy-9,9'-biacridine (3)

A mixture of 2-methoxy-9-chloroacridine (**2**) (2 g, 8 mmol) and zinc powder (0.6 g, 9 mmol) was refluxed in anhydrous methanol (60 mL) under nitrogen for 4 h. After filtration of the hot solution, the residue obtained was dissolved in hot chloroform (120 mL), and the zinc was eliminated by filtration. The organic phase was dried over MgSO₄ and concentrated to give a crude compound which was recrystallized from chloroform to yield a yellow powder (**3**) (1.68 g, 49 %); mp 264°C (from chloroform). TLC/R_f: 0.60 (AcOEt/CH₂Cl₂, 1/1). ¹H NMR (DMSO-d₆): δ = 3.33 (s, 6H), 6.18 (d, 2H, *J* = 2.5 Hz), 6.92 (br d, 2H, *J* = 8.5 Hz), 7.35 (br dd, 2H, *J* = 7.8 and 8.5 Hz), 7.59 (dd, 2H, *J* = 2.5 and 9.4 Hz), 7.79 (br dd, 2H, *J* = 7.8 and 8.5 Hz), 8.29 (d, 2H, *J* = 9.4 Hz), 8.31 (br d, 2H, *J* = 8.5 Hz). ¹³C NMR (DMSO-d₆): δ = 56.02, 101.13, 125.14, 125.28, 125.28 (2C), 127.18, 129.40, 129.80, 131.76, 137.52, 145.19, 146.61, 157.35. *Anal.* Calcd. for C₄₂H₂₈N₂O₆: C, 76.82; H, 4.30; N, 4.27. Found: C, 76.60; H, 4.55; N, 4.42. *Anal.* Calcd for C₂₈H₂₀N₂O₂: C, 80.75; H, 4.84; N, 6.73. Found: C, 80.59; H, 4.61; N, 6.97.

2,2'-Dihydroxy-9,9'-biacridine (4)

A mixture of 2,2'-dimethoxy-9,9'-biacridine (**3**) (1.3 g, 3.12 mmol) and 48 % hydrobromic acid (80 mL) was heated under reflux for 48 h. After cooling, the solution was poured into ice and the pH was adjusted

to **7** by addition of 5N ammonia. The precipitate obtained was filtered and dried to yield after recrystallization from methanol (40 mL) a yellow powder (**4**) (0.75 g, 62 %); mp >300°C (from methanol). TLC/R_f: 0.40 (AcOEt/CH₂Cl₂, 1/1). ¹H NMR (DMSO-d₆): δ = 6.17 (d, 2H, *J* = 2.5 Hz), 6.95 (br d, 2H, *J* = 8.3 Hz), 7.33 (ddd, 2H, *J* = 1.2, 6.7 and 8.2 Hz), 7.48 (dd, 2H, *J* = 2.5 and 9.4 Hz), 7.76 (ddd, 2H, *J* = 1.3, 6.7 and 8.5 Hz), 8.24 (d, 2H, *J* = 9.4 Hz), 8.29 (br d, 2H, *J* = 8.7 Hz), 9.95 (s, 2H). ¹³C NMR (DMSO-d₆): δ = 103.93, 125.26, 125.33, 125.88, 126.56, 127.07, 129.10, 129.88, 131.76, 137.04, 145.07, 146.38, 155.75. *Anal.* Calcd for C₂₆H₁₆N₂O₂: C, 80.40; H, 4.15; N, 7.21. Found: C, 80.59; H, 4.37; N, 6.92.

General procedure for synthesis of esters (**5-7**).

2,2'-Bis[*p*-methoxybenzoyloxy]-9,9'-biacridine (**5**)

To a solution of diol (**4**) (100 mg, 0.25 mmol) dissolved in a 2 % NaOH solution (6 mL) was added *p*-anisoyl chloride (132 mg, 0.77 mmol). The mixture was shaken vigorously for 20 min at rt. The solid product obtained was filtered and washed thoroughly with water. The residue was dissolved in dichloromethane (80 mL), dried over MgSO₄, filtered, and concentrated to yield 75 mg of crude ester. Flash column chromatography (silica gel, CH₂Cl₂/AcOEt 12/1) yielded pure ester (**5**) (60 mg, 36%); mp 263°C (from dichloromethane). TLC/R_f: 0.30 (CH₂Cl₂/AcOEt, 12/1). ¹H NMR (CDCl₃): δ = 3.81 (s, 6H), 6.81 (d, 2H, *J* = 2.4 Hz), 6.85 (d, 4H, *J* = 8.9 Hz), 7.06 (br d, 2H, *J* = 8.5 Hz), 7.31 (ddd, 2H, *J* = 1.0, 6.7 and 8.4 Hz), 7.72 (dd, 2H, *J* = 2.4 and 9.2 Hz), 7.80 (ddd, 2H, *J* = 1.1, 6.6 and 8.4 Hz), 7.98 (d, 4H, *J* = 8.9 Hz), 8.38 (br d, 2H, *J* = 8.5 Hz), 8.43 (d, 2H, *J* = 9.3 Hz). ¹³C NMR (CDCl₃): δ = 55.56, 113.87, 115.88, 121.15, 125.85, 125.97, 126.06, 127.42, 127.53, 130.15, 130.59, 131.56, 132.45, 140.26, 147.02, 148.57, 149.29, 164.11, 164.64. *Anal.* Calcd for C₄₂H₂₈N₂O₆: C, 76.82; H, 4.30; N, 4.27. Found: C, 76.60; H, 4.55; N, 4.42.

2,2'-Bis[*p*-chlorobenzoyloxy]-9,9'-biacridine (**6**)

As described for **5** but with diol (**4**) (100 mg, 0.25 mmol) and *p*-chlorobenzoyl chloride (135 mg, 0.77 mmol). After work up, recrystallization from ethanol (30 mL) yielded compound (**6**) (85 mg, 52%); mp 287°C (from ethanol). TLC/R_f: 0.80 (CH₂Cl₂/AcOEt, 9/1). ¹H NMR (CDCl₃): δ = 6.86 (d, 2H, *J* = 2.1 Hz), 7.12 (d, 2H, *J* = 8.6 Hz), 7.38 (d, 4H, *J* = 8.5 Hz), 7.47 (t, 2H, *J* = 7.6 Hz), 7.89 (dd, 2H, *J* = 2.1 and 9.4 Hz), 7.95 (d, 4H, *J* = 8.5 Hz), 7.97 (t, 2H, *J* = 7.6 Hz), 8.75 (d, 2H, *J* = 8.8 Hz), 8.82 (d, 2H, *J* = 9.5 Hz). ¹³C NMR (CDCl₃): δ = 115.85, 125.79 (2C), 125.80, 126.85, 127.35, 127.39, 128.90, 129.11 (2C), 129.66, 129.66, 131.68 (2C), 133.26, 140.85, 143.54, 145.19, 149.90, 163.80. *Anal.* Calcd for C₄₀H₂₂N₂O₄Cl₂: C, 72.19; H, 3.33; N, 4.27. Found: C, 72.52; H, 3.10; N, 4.04.

2,2'-Bis(*p*-fluorobenzoyloxy)-9,9'-biacridine (7)

As described for **5** but with diol (**4**) (100 mg, 0.25 mmol) and *p*-fluorobenzoyl chloride (122 mg, 0.77 mmol). After work up the obtained powder was triturated in hot ethanol (30 mL), filtered, and dried; this provided ester (**6**) (75 mg, 48%); mp 273 °C (from dichloromethane). TLC/R_f: 0.70 (CH₂Cl₂/AcOEt, 9/1). ¹H NMR (CDCl₃): δ = 6.82 (d, 2H, *J* = 2.4 Hz), 7.06 (t, 4H, *J* = 8.4 Hz), 7.08 (d, 2H, *J* = 8.5 Hz), 7.34 (t, 2H, *J* = 7.4 Hz), 7.73 (dd, 2H, *J* = 2.5 and 9.4 Hz), 7.76 (t, 2H, *J* = 7.4 Hz), 8.05 (dd, 4H, *J* = 5.3 and 8.8 Hz), 8.43 (d, 2H, *J* = 8.7 Hz), 8.49 (d, 2H, *J* = 9.4 Hz). ¹³C NMR (CDCl₃): δ = 115.84 (d, *J*_{CF} = 22 Hz), 115.84, 125.04 (d, *J*_{CF} = 2 Hz), 125.77, 125.93 (2C), 127.41, 127.62, 129.82, 130.95, 131.40, 132.89 (d, *J*_{CF} = 10 Hz), 140.54, 146.58, 148.23, 149.03, 162.40, 165.16 (d, *J*_{CF} = 245 Hz). *Anal.* Calcd for C₄₀H₂₂N₂O₄F₂: C, 75.94; H, 3.51; N, 4.43. Found: C, 76.26; H, 3.84; N, 4.20.

2,2'-Bis(vinyloxy)-9,9'-biacridine (8)

A mixture of diol (**4**) (250 mg, 0.65 mmol), allyl bromide (158 mg, 1.31 mmol), anhydrous cesium carbonate (181 mg, 1.31 mmol), and dry acetone (50 mL) was refluxed for 8 h under stirring. After cooling, the mixture was filtered and the precipitate washed with chloroform (60 mL). The organic phases were recovered, dried over MgSO₄, and filtrated to yield a green powder which was recrystallized from chloroform to yield compound (**8**) (201 mg, 65 %); mp 177 °C (from chloroform). TLC/R_f: 0.72 (CH₂Cl₂/AcOEt 1/1). ¹H NMR (CDCl₃): δ = 4.02 (br d, 4H, *J* = 5.5 Hz), 4.88 (dq, 2H, *J* = 1.1 and 17.2 Hz), 4.92 (dq, 2H, *J* = 1.1 and 17.2 Hz), 5.68 (ddd, 2H, *J* = 5.4, 9.8 and 17.0 Hz), 6.18 (d, 2H, *J* = 2.6 Hz), 7.03 (br d, 2H, *J* = 8.6 Hz), 7.24 (br t, 2H, *J* = 8.0 Hz), 7.48 (dd, 2H, *J* = 2.6 and 9.5 Hz), 7.71 (ddd, 2H, *J* = 1.2, 6.7 and 8.6 Hz), 8.28 (d, 2H, *J* = 9.5 Hz), 8.34 (d br, 2H, *J* = 8.8 Hz). ¹³C NMR (CDCl₃): δ = 68.93, 102.84, 118.31, 125.86 (2C), 126.54, 126.81 (2C), 129.39, 129.96, 131.62, 132.15, 138.63, 146.05, 147.27, 156.56. *Anal.* Calcd for C₃₂H₂₄N₂O₂F₂: C, 82.03; H, 5.16; N, 5.98. Found: C, 81.81; H, 5.33; N, 4.27.

2,2'-Bis(4-acridylmethoxy)-9,9'-biacridine (9)

To a solution of 2,2'-dihydroxy-9,9'-biacridine (**4**) (100 mg, 0.25 mmol), anhydrous acetone (50 mL) and cesium carbonate (840 mg, 2.58 mmol) was added dropwise with stirring, under nitrogen, a solution of 4-bromomethylacridine (140 mg, 0.516 mmol) in anhydrous acetone (20 mL). The mixture was heated to reflux for 28 h and filtered hot, and the precipitate was washed with acetone (50 mL). The organic phase was recovered and concentrated. The residue was extracted with water/dichloromethane (1/1). The organic phase was separated, dried over MgSO₄, filtered, and evaporated. The obtained oil was triturated with hexane to yield a yellow powder which was recrystallized from dichloromethane to yield compound (**9**) (81 mg, 40 %); mp 164 °C (from dichloromethane). TLC/R_f: 0.65 (CH₂Cl₂/AcOEt, 9/1). ¹H NMR

(CDCl₃): δ = 5.51 (d, 2H, J = 14.1 Hz), 5.58 (d, 2H, J = 14.1 Hz), 6.09 (d, 2H, J = 2.7 Hz), 6.69 (br d, 2H, J = 8.2 Hz), 7.04 (ddd, 2H, J = 1.1, 6.6 and 8.3 Hz), 7.20 (dd, 2H, J = 7.0 and 8.3 Hz), 7.49 (dd, 2H, J = 2.7 and 9.5 Hz), 7.53 (ddd, 2H, J = 1.3, 6.5 and 8.5 Hz), 7.57 (dd, 2H, J = 1.1 and 8.1 Hz), 7.60 (ddd, 2H, J = 1.1, 6.5 and 8.1 Hz), 7.68 (br d, 2H, J = 7.6 Hz), 7.75 (ddd, 2H, J = 1.4, 6.5 and 7.9 Hz), 7.83 (br d, 2H, J = 8.1 Hz), 7.90 (d, 2H, J = 9.5 Hz), 7.99 (br d, 2H, J = 8.7 Hz), 8.04 (br d, 2H, J = 8.4 Hz), 8.62 (s, 2H). ¹³C NMR (CDCl₃): δ = 66.36, 103.94, 124.83, 125.44, 125.48, 125.48, 125.79, 125.95, 126.10, 126.17, 126.45, 127.39, 127.61, 128.11, 128.72, 129.71, 129.91, 130.08, 131.15, 133.87, 136.07, 138.18, 145.25, 145.90, 146.58, 148.15, 156.27. *Anal.* Calcd for C₅₄H₃₄N₄O₂: C, 84.14; H, 4.45; N, 7.27. Found: C, 84.36; H, 4.63; N, 7.02.

2,2'-Bis(3-bromopropoxy)-9,9'-biacridine (10)

To a solution of diol (**4**) (100 mg, 0.25 mmol) in anhydrous acetone (30 mL) was added cesium carbonate (406 mg, 1.25 mmol) and 1,3-dibromopropane (520 mg, 2.5 mmol). The mixture was refluxed in the dark for 21 h. After cooling, the cesium salts were removed by filtration and washed with acetone. The organic filtrate was evaporated and the residue was purified by column chromatography (silica gel, chloroform/acetone 15/1) to yield **10** (81 mg, 52 %); mp 146 °C (from chloroform). TLC/R_f: 0.70 (CH₂Cl₂/AcOEt 9/1). ¹H NMR (CDCl₃): δ = 2.05 (quint, 4H, J = 6.1 Hz), 3.38 (t, 4H, J = 6.8 Hz), 3.56 (td, 2H, J = 6.1 and 9.6 Hz), 3.61 (td, 2H, J = 6.1 and 9.5 Hz), 6.21 (d, 2H, J = 2.6 Hz), 7.01 (d, 2H, J = 8.7 Hz), 7.25 (ddd, 2H, J = 1.2, 6.6 and 8.7 Hz), 7.46 (dd, 2H, J = 2.7 and 9.5 Hz), 7.72 (ddd, 2H, J = 1.3, 6.6 and 8.0 Hz), 8.28 (d, 2H, J = 9.5 Hz), 8.34 (d, 2H, J = 8.4 Hz). ¹³C NMR (CDCl₃): δ = 29.51, 31.87, 65.38, 102.32, 125.74, 125.87, 126.54, 126.90 (2C), 129.46, 130.05, 131.85, 138.57, 146.19, 147.36, 156.80. *Anal.* Calcd for C₃₂H₂₆N₂O₂Br₂: C, 60.97; H, 4.16; N, 4.44. Found: C, 61.19; H, 4.31; N, 4.68.

9,9'-Bisacridinyl-22-crown-2 (11)

To a solution of diol (**4**) (100 mg, 0.25 mmol) in anhydrous acetone (30 mL) were added cesium carbonate (406 mg, 1.25 mmol) and 1,12-dibromododecane (84 mg, 0.26 mmol). The mixture was refluxed in the dark for 21 h. After cooling, the cesium salts were removed by filtration and the precipitate washed with acetone. The organic phase was dried over MgSO₄ and evaporated to obtain an oil, which was purified by flash column chromatography (silica gel, CH₂Cl₂/AcOEt 4/1) to yield ether (**11**) (20 mg, 14 %); mp 183 °C (from dichloromethane). TLC/R_f: 0.75 (CH₂Cl₂/AcOEt 4/1). ¹H (CDCl₃): δ = 1.22 (m, 20H), 3.39 (td, 2H, J = 3.9 and 9.7 Hz), 3.60 (td, 2H, J = 5.1 and 9.6 Hz), 6.25 (d, 2H, J = 2.0 Hz), 6.96 (d, 2H, J = 8.6 Hz), 7.22 (t, 2H, J = 7.5 Hz), 7.50 (dd, 2H, J = 2.2 and 9.5 Hz), 7.69 (t, 2H, J = 7.4 Hz), 8.29 (d, 2H, J = 9.4 Hz), 8.32 (d, 2H, J = 8.7 Hz). ¹³C NMR (CDCl₃): δ = 24.83, 27.06, 27.17, 27.57, 27.85, 67.36, 101.96, 125.85, 126.01, 126.27, 126.62, 126.81, 129.44, 129.65, 131.31, 138.74,

145.78, 146.91, 157.46. *Anal.* Calcd for C₃₈H₃₈N₂O₂: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.01; H, 7.19; N, 4.87. HR MS (FAB: measured on M+H⁺ peak); found: 554.

Bisacridinyl-18-crown-4 (12)

To a solution of diol (**4**) (158 mg, 0.40 mmol) dissolved in an alkaline solution (H₂O/NaOH, 9 mL, 30 mg, 0.8 mmol) were added under stirring toluene (30 mL) triethyleneglycol-di-*p*-tosylate (124 mg, 0.27 mmol) and tetrabutyl ammonium bromide (87 mg, 0.27 mmol). The mixture was stirred at 85 °C for 2 days. After cooling, toluene (50 mL) was added and the residue was washed with brine (3 x 50 mL). The aqueous phase was extracted with chloroform (3 x 50 mL), the organic phase was dried over MgSO₄, filtered and concentrated. Flash column chromatography of the residue (silica gel, chloroform/ethyl acetate 1/1) yielded crown ether (**12**) (18 mg, 14 %); mp 213 °C (from chloroform). TLC/R_f: 0.35 (light petroleum/AcOEt 7/3). ¹H (DMSO-d₆): δ = 3.42 (m, 8H), 3.89 (m, 4H), 6.36 (d, 2H, *J* = 2.4 Hz), 6.91 (d, 2H, *J* = 8.3 Hz), 7.32 (t, 2H, *J* = 7.5 Hz), 7.61 (dd, 2H, *J* = 2.5 and 9.5 Hz), 7.77 (t, 2H, *J* = 7.9 Hz), 8.28 (d, 2H, *J* = 9.4 Hz), 8.29 (d, 2H, *J* = 8.7 Hz). ¹³C NMR (200 MHz, CDCl₃): δ = 67.56, 67.94, 70.08 (2C), 102.87, 125.85, 125.93, 126.23, 126.28, 127.43, 129.13, 129.67, 131.64, 137.10, 145.21, 147.33, 156.15. *Anal.* Calcd for C₃₂H₂₆N₂O₄: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.65; H, 5.50; N, 5.36. HR MS (FAB: measured on M+H⁺ peak); found: 502.

(9,9'-Bisacridinyl)-2,2'-dihydroxybis(camphanate) esters (13a-b)

To a mixture of diol ((±)-**4**) (0.6 g, 1.5 mmol) and (1S)-(-)-camphanic acid chloride (3.3 g, 15.2 mmol) in dry pyridine (40 mL) was added 4-dimethylaminopyridine (60 mg, 0.49 mmol). The solution was refluxed for 72 h under nitrogen. The reaction mixture was extracted with ethyl acetate (3 x 60 mL). The organic phase was washed with water, dried over MgSO₄, and evaporated *in vacuo* to give bis(camphanate)ester diastereomers ((±)-**13**) (0.630 g, 55 %). This powder (**13**) was recrystallized from ethyl acetate (10 mL) to yield after filtration an insoluble fraction and a filtrate. Then, this insoluble compound was recrystallized from acetonitrile (5 mL) to yield after filtration one insoluble part of pure diastereomer (**13a**) and a mixture of non isolable esters (**13**) dissolved in the filtrate. (20 mg, 18 %). [α]_D²⁰ = -100° (c = 0.08 CHCl₃); mp 289°C (from acetonitrile). TLC/R_f: 0.37 (CHCl₃/acetonitrile 6/1). ¹H NMR (CDCl₃): δ = 0.93 (s, 6H), 1.00 (s, 6H), 1.06 (s, 6H), 1.66 (m, 2H), 1.90 (m, 2H), 2.02 (m, 2H), 2.39 (m, 2H), 6.75 (d, 2H, *J* = 2.6 Hz), 7.02 (br d, 2H, *J* = 8.4 Hz), 7.31 (dt, 2H, *J* = 1.0 and 7.6 Hz), 7.60 (dd, 2H, *J* = 2.5 and 9.4 Hz), 7.81 (dt, 2H, *J* = 1.4 and 7.6 Hz), 8.39 (br d, 2H, *J* = 8.5 Hz), 8.44 (d, 2H, *J* = 9.3 Hz). ¹³C NMR (DMSO-d₆): δ = 9.71, 16.89 (2C), 28.87, 28.87, 30.80, 54.88, 90.61, 115.84, 125.62, 125.95, 125.99, 126.38, 127.76, 130.23, 130.90, 132.09, 140.19, 147.00, 148.12, 148.93, 165.96, 177.60. *Anal.* Calcd for C₄₆H₄₀N₂O₈: C, 73.78; H, 5.38; N, 3.74. Found: C, 74.01; H, 5.14; N, 3.98.

(aR)-(-)-2,2'-Dihydroxy-9,9'-biacridine (4)

A mixture of recrystallized ester (**13a**), (-)-(9,9'-biacridinyl)-2,2'-diol bis-(camphanate) (10 mg, 0.013 mmol) and NaOH (3.2 mg, 0.08 mmol) in EtOH (4 mL) was refluxed for 22 h. The solvent was evaporated and the residue was dissolved in water (4 mL) and neutralized by 9 % HCl. The precipitate obtained was filtered to yield 43 mg (80%) of (aR)-(-)-2,2'-dihydroxy-9,9'-biacridine (**4**). $[\alpha]_D^{20} = -120^\circ$ (c = 0.025 MeOH); mp >300 °C (from methanol).

X-Ray Crystallographic Study²³

The X-Ray diffractions were measured at room temperature on an Enraf Nonius Kappa CCD diffractometer with monochromated MoK α ($\lambda = 0.71073 \text{ \AA}$) radiation. A set of 90 frames was measured for **6** and **13a** through a 180°C ϕ scan in the following conditions: 2° ϕ steps, 120 seconds per frame repeated two times. Lorentz polarization corrections were applied to the raw data, which were not corrected for absorption. The structures were solved by direct methods calculations using SIR.²⁴ All non hydrogen atoms were refined anisotropically through cycles of full-matrix least squares using Maxus²⁵ for **6** or SHELXL²⁶ for **13a**.

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