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Tripodal Ligands Possessing Six Convergent Hydroxyl Groups A Novel Family of Iron Sequestering Agents Based on o,o'-dihydroxybiphenyl Subunits

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Abstract : A new family of iron(III) sequestering agents has been designed. Tripodal ligands possessing six convergent hydroxyl groups have been prepared by condensation of an appropriate o, o'-biaryl building block and a spacer. The preparations of building blocks and of simple bidentate ligands designed for comparative studies are described : several methods have been used for ortho functionalisation and for 3,3'-difunctionalisation of 2,2'-dihydroxybiphenyl. Sulfonation of the ligands led to water soluble agents. These ligands offer an alternative to synthetic hydroxamate or catecholate siderophores. The hexamethoxylated tripodal precursors and their complexing ability towards alkali cations are also described. The complexing abilities of hexahydroxylated sequestering agents towards iron(III) are comparable to those of hydroxamate siderophores but are lower than those of catecholate siderophores.

INTRODUCTION

Interest in natural or synthetic iron(III) sequestering agents includes iron transport in microorganisms or plants[1], DNA cleavage[2] and iron enzymes mimics[3]. Some of these compounds are of therapeutical interest[4] : treatment of iron overload (hemosiderosis, Cooley anemia), antioxidant therapy (preventing Fenton chemistry), anticancer agents (sequence specific DNA cleavage), NMR contrast agents and imaging of organs. Others are promising catalysts.

An iron(III) sequestering agent implies a strong and selective complexing ability towards iron(III) (no exchangeable ligand) and the iron complex has to be difficult to reduce (a too easily reducible complex can induce the loss of iron and/or Fenton chemistry). An iron carrier is a solubilizing and chelating agent, adapted to a mechanism of release. In living organisms this mechanism usually implies a reducing step. The search for effective ferric ion chelating agents has been originally centered on desferrioxamine, an hydroxamate siderophore, but its use suffers limitations that are probably inherent to all hydroxamate

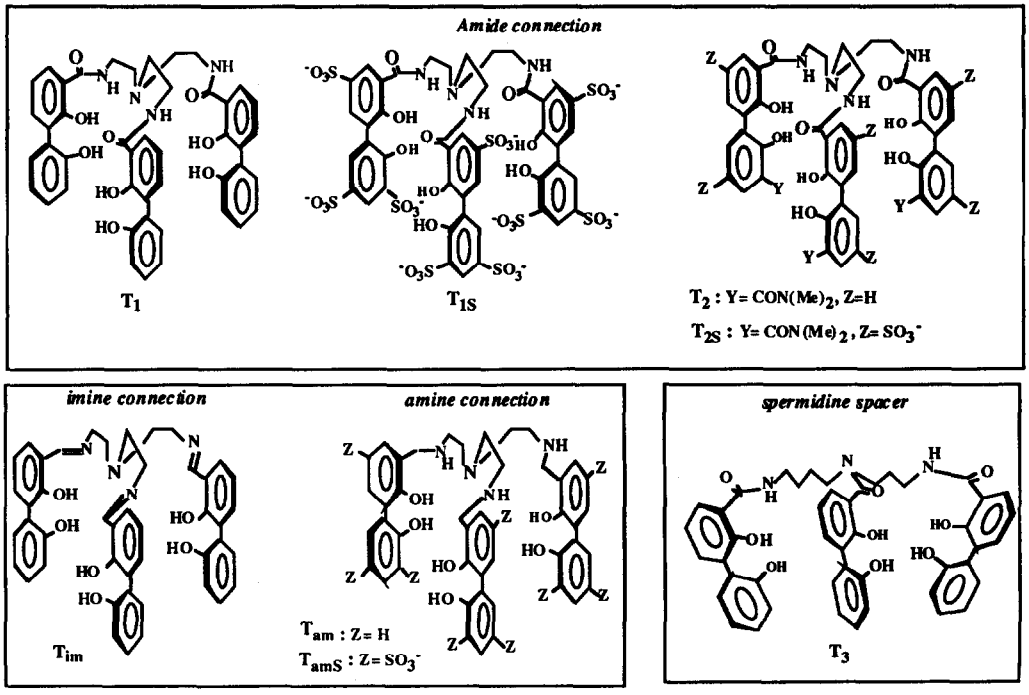
chelating agents. The pionnering work of K.N.Raymond has been focused in mimics of catecholate siderophores[1b]. Catechol-based ligands are the most powerful known siderophores, but catechol subunits are somewhat air-sensitive. This stimulated us to investigate different structures built upon o,o'-dihydroxybiaryl units. Besides the required thermodynamical features, the properties desired are : water solubility, good hydrolytic stability and stability towards oxidation.

The tripodal precursors of our target molecules imply six convergent methoxy groups. They present an interesting alternative to polypodal open chain crown-ethers[5,6] and can also be considered as "open chain spherands"[7] which can afford comparative data about the complexation of alkaline cations .

RESULTS

Tripodal target molecules (Scheme 1)

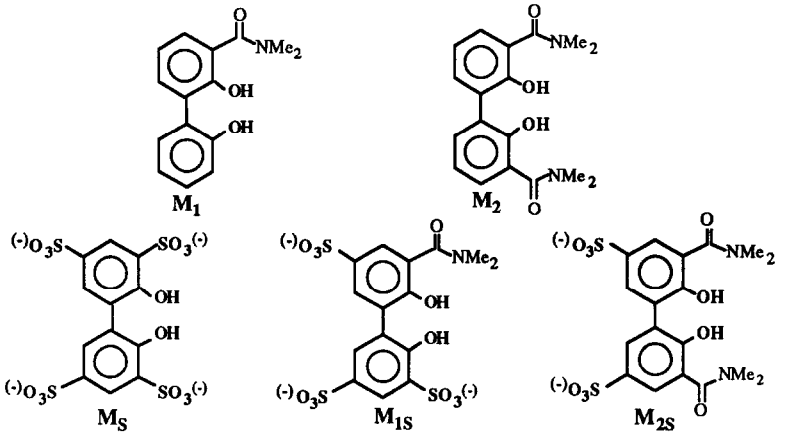
The synthesis of the tripodal ligands involved the condensation of three equivalents of the appropriate building block with a spacer (we essentially used tris (2-aminoethyl)amine = TREN). The building block was either a carboxylic acid (or derivative), leading to amide connections, or an aldehyde, leading to imine connections. The imine functions could be reduced, leading to amine connections. Sulfonation of the tripodal ligands afforded water-soluble products.



Scheme 1 : Tripodal ligands

Simple bidentate ligands.

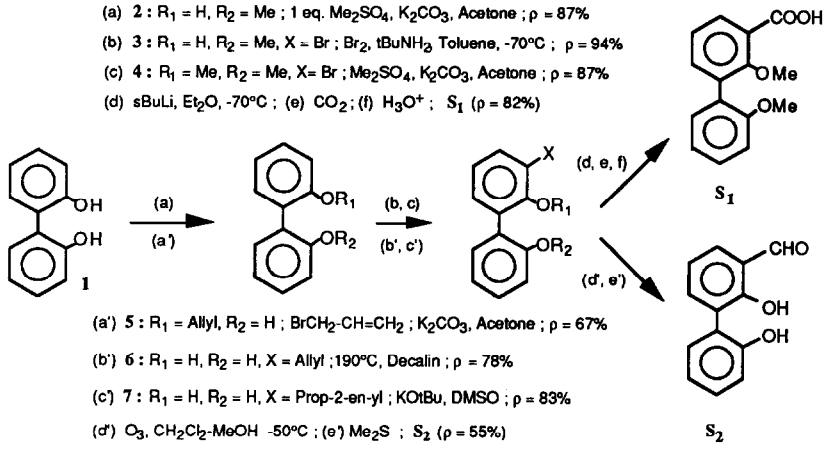
For comparative complexation studies, we have prepared the simple bidentate ligands depicted in Scheme 2. They have been obtained from compounds involved in the syntheses of tripodal targets. M_S was prepared (90%) by sulfonation of commercial biphenyl-2,2'-diol, using H_2SO_4 oleum .



Scheme 2 : Simple bidentate ligands for comparative complexation studies

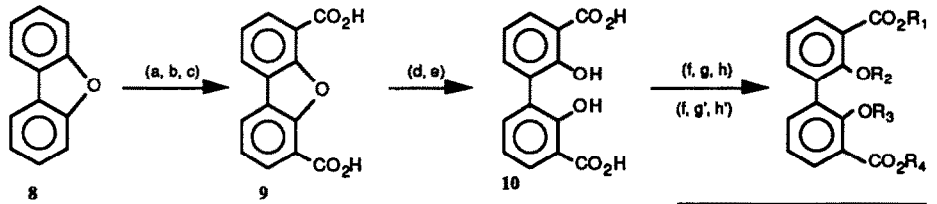
Reaction sequences.

The reaction sequences leading to the precursors S_1 to S_4 (derivatives of biphenyl-2,2'-diol **1**) are described in Schemes 3 and 4. The syntheses of the tripodal molecules T_1 and their simple analogs M_1 are described in Schemes 5 to 7. The analytical data are given in the Experimental Part.



Scheme 3 : the 3-substituted precursors S_1 and S_2

The strategy of the Claisen transposition for ortho functionalisation of biphenyl-2,2'-diol had been previously used[9,10] with the bisallyl derivative, leading to the corresponding dialdehyde[11]. This procedure is regiospecific ; the method of ortho lithiation (cf scheme 4) gave lower yields in this case.



(a) sBuLi , Et_2O , TMEDA, -70°C ; (b) CO_2 ; (c) H_3O^+ ; **9** (ρ = 89%)

(d) NaOH, KOH , fusion ; (e) H_3O^+; **10** (ρ = 73%)

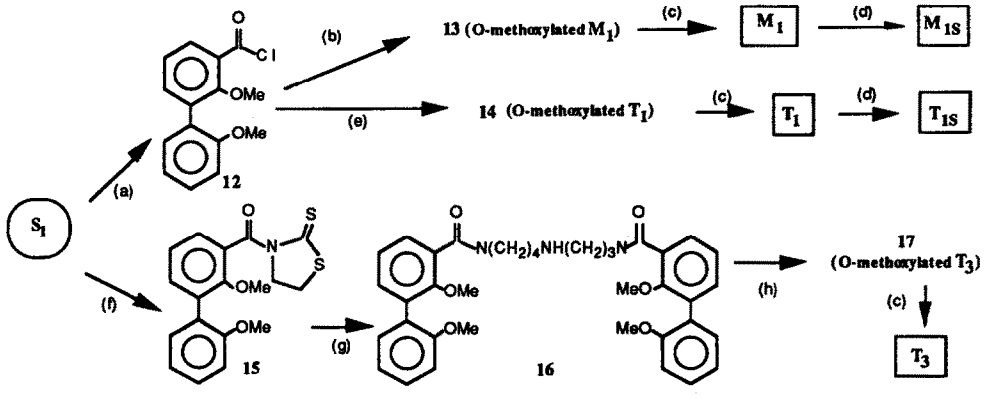
(f) Me_2SO_4 , K_2CO_3, Acetone ; **11** (ρ = 72%)

(g) NaOH, MeOH ; (h) H_3O^+ ; S_3 (quant.)

(g') NaOH 1 eq., MeOH ; (h') H_3O^+ ; S_4 (ρ = 44%)

Scheme 4 : the 3, 3'-disubstituted precursors S_3 and S_4

The regioselective conversion of dibenzofuran **8** by organolithium reagent into its monometallated derivative in position 4 has been described by Gilman[12]. The twofold lithiation in positions 4 and 6 could be performed with secButyllithium (scheme 4). The monosaponification (step g') is the key step in the preparation of S_4 and the 44% yield is optimized.

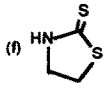


(a) $SOCl_2$; **12** (ρ = 98%) ; (b) Me_2NH ; Et_3N ; CH_2Cl_2 ; **13** (ρ = 75%)

(c) BBr_3 ; CH_2Cl_2 ; M_1 (ρ = 82%) ; T_1 (ρ = 80%) ; T_3 (ρ = 87%)

(d) H_2SO_4, oleum ; M_{1S} (ρ = 84%) ; T_{1S} (ρ = 91%);

(e) TREN ; THF ; Et_3N ; **14** (ρ = 87%)

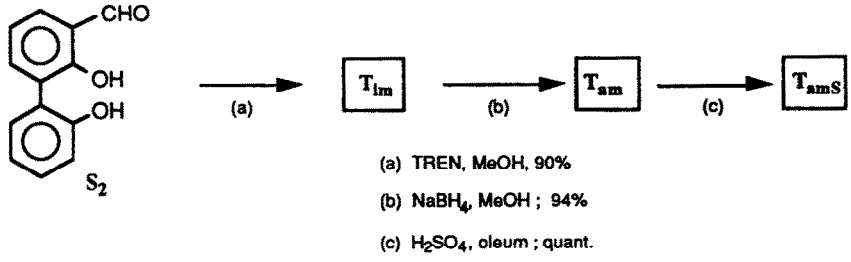
(f)  CH_2Cl_2, DCC, DMAP ; **15** (r = 80%)

(g) SPERMIDINE ; CH_2Cl_2 ; **16** (ρ = 91%)

(h) **12** ; THF ; Et_3N ; **17** (ρ = 70%)

Scheme 5 : podands and models from S_1

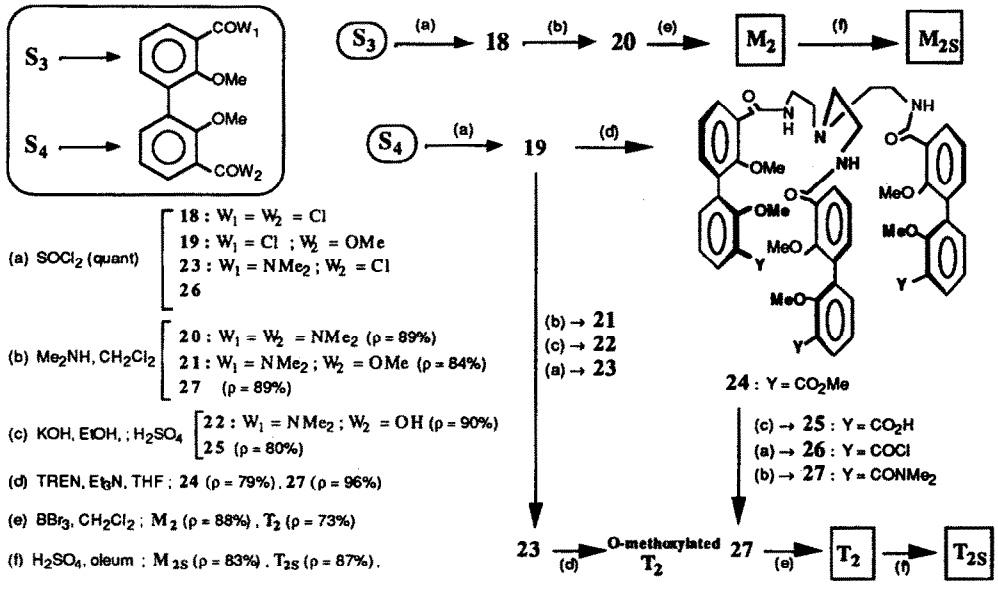
The synthesis of the spermidine based podand T_3 was performed in two steps : monitored aminolysis[8] of **15** with spermidine followed by condensation of bipodand **16** and acid chloride **12**. To obtain the hydrosoluble podand T_{1S}, the phenolic tripodal molecule T_1 (prepared by condensation of TREN and **12** followed by demethylation of the six methoxyl groups with BBr_3) was treated with oleum at 90°C in order to sulfonate all the positions 3, 5 and 5' and to prevent formation of mixtures.



Scheme 6 : podands derived from S_2

In the case of the imine connection, the coupling reaction (a) is catalysed by the phenol group when using S_2 instead of methoxylated-S_2.

Two reaction sequences have been used in the conversion of **19** to the tripodal intermediate **27**. The methoxylated podand **24**, directly obtained from **19** (Scheme 7), could not be demethylated without concomitant hydrolysis of the ester functions. The sequence (**19** → **24** → **25** → **26** → **27**) in Scheme 7 revealed less efficient (overall yield 56%) than the sequence (**19** → **21** → **22** → **23** → **27**) (overall yield 73%).



Scheme 7 : podands and models from S_3 and S_4

Hexamethoxylated podands and alkaline ions complexations studies in acetonitrile.

Open chain ligands containing potentially convergent methoxyaryl groups are of interest as "open chain spherands". We have previously described the complexing abilities of the methoxylated precursors of podands $\mathbf{T_1}$ and $\mathbf{T_3}$ towards alkaline cations[6]. Studies have been carried out by ^{7}Li, ^{23}Na and ^{133}Cs NMR, using alkali picrates in acetonitrile. Lithium cation is complexed by the two podands and by methoxylated-$\mathbf{M_1}$, while sodium cation is complexed only by methoxylated-$\mathbf{T_1}$; caesium cation is complexed by none of the ligands. When complexation is detected, only one population average resonance is observed in the temperature range from -30 to + 50° C, which shows that the cation exchange between the bulk solution and the complex is faster than the NMR time scale. The variation of the metal resonance frequency, mesured as a function of the [ligand]/[M^+] mole ratio, indicates the formation of a 1: 1 complex of the cation with the ligands. The association constants of the complexes have been determined from the metal NMR studies, by a Benesi-Hildebrand type treatment. They are reported in Table 1.

Table 1 : Association constants of alkaline ions with methoxylated ligands

{K (M^{-1}) = [Ligand-M^+]/[Ligand] [M^+]}

	Li^+	Na^+
14 : Methoxylated-$\mathbf{T_1}$	153 ± 6	16 ± 0.6
17 : Methoxylated-$\mathbf{T_3}$	65 ± 3	too weak
13: Methoxylated-$\mathbf{M_1}$	7 ± 3	too weak

The stronger binding of lithium compared to that of sodium or caesium is probably due to the harder character of the lithium cation. The low values of the association constants suggest that there is a major contribution from the solvent reorganization that occurs during the complexation.

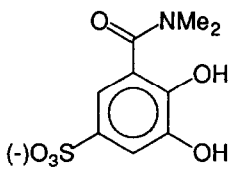
Ferric iron complexation studies in water.

In a preliminary report, we have described the pKa determinations for the simple bidentates models[13]. Iron complexation studies are in progress and the detailed physico-chemical measurements will be reported elsewhere. Only preliminary and typical data are given in this paper. Solely the sulfonated derivatives are enough water soluble to allow easily reproducible studies. Spectrophotometric titrations at 25°C gave the pKa values reported in Table 2. The pKa_2 of the ligands are lower (from 4 to 6) than for catechols (about 9) but the pKa_1 are high (from 11 to 12). Formation constants of the ferric complexes were determined by spectrophotometric measurements in acidic medium using excess of iron (ferric perchlorate) and in neutral medium using excess of ligand. Two modes of coordination were evidenced for the ligand possessing amide(s) group (s) : the "salicylate mode" (in acidic medium) and the "dihydroxylate mode" (as the pH increased, deprotonation of salicylate complexes induced a change from a salicylate to a dihydroxylate mode of coordination). The same is true for catechol ligands[14,15] These two modes of

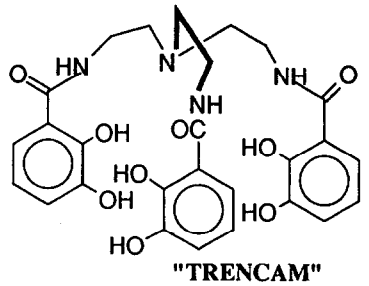
coordination have been confirmed by proton NMR chemical shifts of Ga(III)-ligands complexes[16] The values of the formation constants (non reported here) show that the simple bidentate ligands have a greater effectiveness than catechol derivatives as iron(III) chelating agents in acidic media, but a lower one at neutral pH. The pFe values are reported in Table 2 ; these data allow comparative considerations at physiological pH, of the complexing abilities of our ligands and of the siderophores described in the literature[1].

Table 2 : Thermodynamic Data

	M_{1S}	M_{2S}	Tiron[17]	Desferal[1b]
pKa	4.93 11.09	4.16 11.62	8.42 12.10	
pFe	12.7	11.6	19.2	23.6
	T_{1S}	T_{2S}	T_{amS}	TRENCAM[18]
pKa	3.8, 4.77, 5.8 8.7, 9.74, 10.7	3.1, 4.06, 5.1 9.6, 10.58, 11.6	3.9, 4.95, 5.9 10.0, 11.05, 12.0	5.88, 6.71, 8.61 8.75, 11.26, 12.1 12.9
($^+$NH) ($^+NH_2$)	7.1	7.1	4.35 9.2, 10.2, 11.2	
pFe	22.8	-	22.1	27.8



"Tiron"



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The pFe values clearly evidence that our ligands are poorer potential agents for iron chelation therapy than are the catechol type podands of K.N.Raymond. Nethertheless they are comparable to hydroxamates ligands and the pFe values are in the range of human transferrin (pFe : 23.6). It must be emphasized that, at physiological pH, the complexes derived from the hexaphenate complexation mode is the predominent species in the cases of T_{1S} and T_{2S}. An explanation of the higher complexing abilities shown by catecholate derivatives lies in the marked preference for five membered chelate rings versus seven membered chelate rings.

CONCLUSION

We have described the syntheses of several podands and tripodands containing the o,o'-dihydroxybiphenyl subunit. The key step of these syntheses is the ortho functionalisation of biphenyl-2,2'-diol or the o,o'-difunctionalisation of dibenzofuran. Several methods have been investigated for monofunctionalisation : the direct ortholithiation procedures have shown to be deceptive and the procedures described in this paper have always shown more successful. The strategy of Claisen transposition implies numerous steps, but it is a very clean procedure. In the case of bifunctionalisation, the old procedure described in 1958 revealed to be the most elegant.

Hexamethoxylated podands are a novel family of alkaline ions complexing agents : they show poor complexing abilities and their interest lies only for comparative considerations.

Complexation of ferric iron in water is a more promising area : the significative pFe value is, for podands, in the range of the values of the hydroxamate siderophores ; it is lower than for catecholate siderophores. The syntheses of macrocyclic and macrobicyclic ligands are in progress in our laboratory, with the hope of complexing abilities of the same order as for catecholate derivatives. On an another hand, biochemical studies have just started (removal of iron from transferrin ; inhibition of Haber-Weiss reaction) and will be described in the future.

EXPERIMENTAL SECTION

Materials and Equipment

Solvents were purified by usual techniques. Thionyl chloride was distilled from triphenylphosphite. Boron tribromide (Aldrich) was vacuum distilled and stored under Argon. The amine TREN was distilled from sodium. All other compounds used were of reagent grade and were not further purified.

Spectra were collected on custom built 80 or 200 or 300 MHz FT Brucker spectrometers (NMR), a Perkin Elmer spectrometer (IR) and NERMAG R 10 10 C (Mass spectra).

Microanalyses were performed by the Analytical Services Laboratory, CNRS, Solaise.

Melting points were taken on a Büchi apparatus and are uncorrected.

Physical measurements

The procedures and apparatus used for pKa and pFe determinations will be described elsewhere in detail. Briefly, ligand deprotonation constants and complexation constants for Fe(III) were determined spectrophotometrically in the UV-Vis. region (ligand concentration in aqueous solutions in 5.10^{-5} -5.10^{-4} M range, ionic strength adjusted with $NaClO_4$ 0.1M). ; the stock solutions of Fe(III) were prepared by dissolving ferric perchlorate nonahydrate in standardized $HClO_4$ and $NaClO_4$ solutions. For NMR studies, the solutions were prepared by dissolving appropriate amounts of the ligands (about 0.01M) and the metal salt (alkali picrate, gallium nitrate) (ca. 0.005-0.01M) in ^2H_2O ; spectra were recorded using a 5mm probe and sodium 3-trimethylsilyl-propane-1-sulfonate as internal reference.

2'-methoxybiphenyl-2-ol (2)

Under nitrogen, a mixture of biphenyl-2,2'-diol **1** (15 g, 80 mmol) , potassium carbonate (12 g) and dimethylsulfate (7.6 mL, 80 mmol), in 300 mL of dry acetone was heated under reflux until no starting material was detectable by TLC (CH_2Cl_2/hexane (50:50)). Aqueous ammonia (70 mL) was added and the reaction left to stir at room temperature for 4 h. The mixture was extracted with CH_2Cl_2 to remove the dimethoxy derivative. Upon cooling, the aqueous phase was acidified with HCl (1N), concentrated, and then extracted with CH_2Cl_2. The combined organic phases were washed twice with brine, dried over $MgSO_4$, filtered and evaporated to afford the essentially pure monomethoxy derivative as an oil.

The product (14.2 g, 87%) crystallized on standing in heptane ; mp 78°C

^{1}H NMR (300 MHz, $CDCl_3$) : δ 3.9 (3H, s, OMe), 6.3 (1H, br s, OH), 7.02 - 7.17 (4H, m, ArH 3,3',5,5'), 7.28 - 7.45 (4H, m, $ArH_{4,4',6,6'}$)

^{13}C NMR (200 MHz, $CDCl_3$) : δ 56.1 (OMe), 111.6, 117.3, 120.9, 122.1, 126.2, 127.0, 129.1, 129.3, 131.2, 132.4, 153.7, 155.5 (Ar)

3-bromo-2'-methoxybiphenyl-2-ol (3)

In a 1L. three-necked flask fitted with a mechanical stirrer, low-temperature thermometer, and addition funnel protected with a drying tube was mixed 500 mL of dry toluene and 9.98 g of t-butylamine (137 mmol). The contents were cooled to -30°C and bromine (11.2g, 70 mmol) was added dropwise. The solution was then cooled to -70°C and 2 (13.67g, 68 mmol) dissolved in CH_2Cl_2 was added over a period of 10 min. The reaction mixture was then allowed to warm to room temperature, and washed with 250 mL of water in a separatory funnel. The organic phase was extracted 3 times with 10% aqueous sodium hydroxyde ; the combined alkaline extracts were cooled and acidified with HCl 30%. The white precipitate which separated was extracted with CH_2Cl_2 ; the extracts were dried over Na_2SO_4, filtered, concentrated. The bromophenol 3 was further purified by recrystallization from hexane (17.8 g, 94%) ; mp 89-90°C

^{1}H NMR (200 MHz, $CDCl_3$) : δ 3.86 (3H, s, OMe), 6.37 (1H, br s, OH), 6.86 (1H, t, J = 7.8 Hz, H_5), 7.03 (1H, dd, J = 0.8 , 8.3 Hz, $H_{3'}$), 7.08 (1H, ddd, J = 0.8, 7.4, 7.6 Hz, $H_{5'}$), 7.19 (1H, dd, J = 7.8, 1.6 Hz, H_4), 7.28 (1H, dd, J = 1.8, 7.6 Hz, $H_{6'}$), 7.39 (1H, ddd, J = 1.8, 7.4, 8.3 Hz, $H_{4'}$), 7.52 (1H, dd, J = 1.6, 7.8 Hz, H_6)

^{13}C NMR (300 MHz, $CDCl_3$) : δ 56,0 (OMe), 111.4, 121.6, 121.7, 126.3, 127.5, 129.7, 130.8, 132.1, 132.2, 133.2, 150.3, 155.7 (Ar)

3-bromo-2,2'-dimethoxybiphenyl (4)

The same procedure was followed as reported for the preparation of the monomethoxybiphenol 2 [3 (14.1 g, 50 mmol), dimethylsulfate (4.7 mL), K_2CO_3 (7g), acetone (200 mL)] , yielding, upon recrystallization from methanol, 13.02 g (87%) of pure dimethoxy derivative 4 ; mp 79°C

^{1}H NMR (200 MHz, $CDCl_3$) : δ 3.48 (3H, s, OMe), 3.78 (3H, s, OMe), 6.96 - 7.04 (3H, m, $H_{3',5,5'}$), 7.18 - 7.27 (2H, m, $H_{4,6'}$), 7.37 (1H, ddd, J = 1.8, 7.4, 7.7 Hz, $H_{4'}$), 7.53 (1H, dd, J = 1.7, 7.9 Hz, H_6)

^{13}C NMR (200 MHz, $CDCl_3$) : δ 55.6, 60.5 (OMe), 110.9, 117.4, 120.3, 124.6, 126.8, 129.2, 131.2 (2), 132.5, 133.9, 155.0, 156.7 (Ar)

2,2'-dimethoxybiphenyl-3-carboxylic acid (S_1)

To a solution of 4 (3 g, 10 mmol) in 100 mL of freshly distilled (dry) ether at -40°C was added, under nitrogen, 15 mL of secButyllithium 1N in hexane. The mixture was stirred for 20 min and dry ice was added. The suspension was stirred for 3 h and allowed to warm slowly to ambient temperature. The mixture was concentrated under reduced pressure ; the residue was treated with NaOH 1N and extracted with CH_2Cl_2 to remove unreacted bromide and then poured at 0°C into aqueous 5% sulfuric acid. The acidic mixture was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered and evaporated. The residue was crystallized from $CHCl_3$/pentane to give the dimethoxyacid S_1 (2.16 g , 82%) as a white solid. ; mp 113°C ; IR (cm^{-1}) 1675-1688 (C=O), 2450-3450 (OH)

^{1}H NMR (300 MHz, $CDCl_3$) : δ 3.52 (3H, s, OMe), 3.80 (3H, s, OMe), 7.02 (1H, dd, J = 1.8, 8.2 Hz, $H_{3'}$), 7.05 (1H, m, J = 1.8, 7.6, 7.8 Hz, $H_{5'}$), 7.28 (1H, dd, J = 1.7, 7.6 Hz, $H_{6'}$), 7.30 (1H, dd, J = 7.2, 8.0 Hz, H_5), 7.41 (1H, m, J = 1.7, 7.8, 8.2 Hz, $H_{4'}$), 7.53 (1H, dd, J = 1.8, 7.2 Hz, H_6), 8.16 (1H, dd, J = 1.8, 8.0 Hz, H_4), 11.1 (1H, br s, COOH)

^{13}C NMR (200 MHz, $CDCl_3$) : δ 55.6, 62.0 (OMe) ; 111.53, 120.8, 124.3, 129.87, 131.1, 132.1, 137.8 (Csec.); 121.9, 126.0, 131.5 (Cquat.) ; 156.8, 157.3 (C-O) ; 166.0 (C=O)

Anal. : Calcd for $C_{15}H_{14}O_4$: C, 69.6 ; H, 5.46 ; Found : C, 69.60 ; H, 5.27

2'-allyloxybiphenyl-2-ol (5)

Under nitrogen, a mixture of 1 (10 g, 54 mmol) , potassium carbonate (12 g) and allyl bromide (7.9 g, 65 mmol), in 300 mL of dry acetone was heated under reflux until no starting material was detectable by TLC (ethyl acetate/hexane (50:50)). The same work-up was followed as described above for the preparation of 2.

The oily product (8.15 g, 67%) was used without further purification.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.4 - 4.5 (2H, dt, $=CH_2$), 5.0 - 5.3 (2H, m, OCH_2), 5.6 - 6.1 (1H, m, =CH), 6.4 (1H, br s, OH), 6.8 - 7.4 (8H, m, ArH)

^{13}C NMR (200 MHz, $CDCl_3$) : δ 69.9 (OCH_2), 113.5 (=CH), 118.0 ($=CH_2$), 117.4, 120.8, 122.4, 129.1, 129.2, 131.3, 132.3, 132.4 (CH) ; 126.3, 127.8 (C quat) ; 153.8, 154.6 (C-O)

3-allylbiphenyl-2,2'-diol (6)

Under argon, a solution of monoallylether (4.3 g, 19 mmol) in dry decalin (250mL) was heated under reflux (189°C) for 30 h. Upon cooling the product crystallized off, the solide was washed with pentane (3.35 g, 78%) and was used without further purification. ; mp 75°C

^{1}H NMR (200 MHz, $CDCl_3$) : δ 3.48 (2H, d, J = 6.5, CH_2), 5.10 - 5.22 (2H, m, $=CH_2$), 5.48 (2H, br s, OH), 5.95 - 6.15 (1H, m, =CH), 6.95 - 7.36 (7H, m, ArH)

^{13}C NMR (200 MHz, $CDCl_3$) : δ 34.6 (CH_2), 115.8 ($=CH_2$), 116.3 (=CH), 121.1, 121.2, 129.2, 129.4, 130.0, 131.5, 136.5 (CH) 124.4, 124.7, 127.7(C quat) ; 151.0, 152.6 (C-O)

3-(propen-1-yl)biphenyl-2,2'-diol (7)

Under nitrogen, to a solution of **6** (2.5 g, 11mmol) in 50mL of freshly dried and distilled DMSO, was added 5 g of potassium t-butylate. The mixture was stirred for 18h at 60°C. A solution of 5% sulfuric acid was slowly added to the cold (0°C) solution. The aqueous residue was extracted with $CHCl_3$. The combined extracts were washed with water, and evaporated. The residue was crystallized from methanol/water 80:20) (2.08 g, 83%) ; mp = 129°C

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.91 (3H, dd, CH_3), 5.5 (2H, br s, OH), 5.8 - 6.4 (1H, dq, CH=), 6.9 - 7.4 (8H, m, CH=, ArH) : complex spectrum, mixture Z/E

^{13}C NMR (200 MHz, $CDCl_3$) : δ 18.8 (CH_3) ; 116.5, 121.2 (CH=) ; 121.4, 125.5, 127.0, 127.8, 129.5, 129.8, 131.4 (CH) ; 123.7, 124.2, 126.7 (Cquat) ; 149.8, 152.9 (C-O)

2,2'-dihydroxybiphenyl-3-carboxaldehyde (S_2)

Ozone was bubbled through a solution of alkene **7** (1 g, 4.4 mmol) in 50mL CH_2Cl_2/methanol (50:50, v/v) at -50°C until no starting material was detectable by TLC(CH_2Cl_2). Excess of ozone was removed with a stream of nitrogen and dimethyl sulfide was added at -50°C. The solvents were evaporated off. The residue was diluted with CH_2Cl_2, washed with brine, dried and concentrated. The product was purified by recrystallization from methanol-water (70:30) (0.52g, 55%) ; mp = 136°C

^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.28 (1H br s, OH) ; 7.00 - 7.16 (2H, m, $H_{3',5'}$) ; 7.20 - 7.38 (3H, m, $H_{4',6',5}$) ; 7.63 - 7.67 (2H, m, $H_{4,6}$) ; 9.97 (1H, br s, CHO) ; 12.1 (1H, br s, OH)

^{13}C NMR (200 MHz, $CDCl_3$) : δ 117.7, 120.7, 120.9, 129.6, 131.1, 133.4, 139.3 (CH) ; 124.4, 127.4 , 141.7 (Cquat) ; 153.7, 157.4 (C-O) ; 196.9 (CHO)

Dibenzofuran-1,4-dicarboxylic acid (9)

At room temperature, under Argon, 60 mL of secButyllithium 1.35M in hexane (81 mmol) was added to a solution of dibenzofuran **8** (6g, 36 mmol) and TMEDA (12 mL) in 330 mL of dry ether. The orange colored solution was stirred overnight. Upon cooling at -78°C, a stream of CO_2 was passed into the solution for 1h.. The resulting mixture was allowed to warm gradually to room temperature and was stirred for 2 h, whereupon it was carefully quenched with 10% aqueous HCl. The precipitate that separated contained the diacid practically pure ; the ether extract contained a mixture of mono and diacid (traces). The precipitate of diacid **9** was successively washed with ether then water, and dried under vacuum (8.2g, 89%)

^{1}H NMR (200 MHz, DMSO) : δ 7.53 (2H, t, J = 7.5 Hz, H_2), 8.06 (2H, dd, J = 1.0, 7.5 Hz, H_1), 8.46 (2H, dd, J = 1.0, 7.5 Hz, H_3)

^{13}C NMR (200 MHz, DMSO) : δ 123.3, 125.8, 129.9 ($C_{1,2,3}$sec) ; 116.4 (Cquat) ; 124.5 (C_4) ; 154.2 (C_1 O) ; 165.3 (C=O)

2,2'-dihydroxybiphenyl-3,3'-dicarboxylic acid (10)

A mixture of KOH (50 g) and NaOH (35 g) was heated to 200°C in a beaker made of inox ; then the diacid **9** (5.37g, 21 mmol) and again KOH (50 g) and NaOH (35 g) were added. The mixture was heated to 300°C and stirred for 30 min. with a glass rod. After cooling, ice was added with precaution, and the mixture was treated by sulphuric acid (CAUTION!!). The diacid **10** was separated by filtration, washed with cold water and dried under vacuum. The pure product was obtained by recrystallization in methanol-water (4.2g, 73%) ; mp = 230°C (dec)

IR (cm^{-1}) 1675-1689 (C=O), 2450-3350 (OH)

^{1}H NMR (200 MHz, DMSO) : δ 6.96 (2H, t, J = 7.5 Hz, H_2), 7.46 (2H, dd, J = 1.6, 7.5 Hz, H_1), 7.83 (2H, dd, J = 1.6, 7.5 Hz, H_3)

^{13}C NMR (200 MHz, DMSO) : δ 118.5, 129.7, 135.5 ($C_{1,2,3}$sec) ; 112.7 (Cquat) ; 125.7 (C_4) ; 159.0 (C_1-O) ; 172.4 (C=O)

MS : 274, 238, 210, 154, 126

Anal. : Calcd for $C_{14}H_{10}O_6$: C, 61.32 ; H, 3.68 ; Found : C, 60.77 ; H, 3.49

2,2'-dimethoxybiphenyl-3,3'-dicarboxylic acid dimethyl ester (**11**)

A mixture of diacid **10** (2.51g, 9 mmol), dissolved in dry acetone (100mL), and K_2CO_3 (12,5g) was stirred, under N_2, for 4h . Dimethyl sulphate (8.6 mL, 90 mmol) was added and the mixture was refluxed for 12 h. Upon cooling, ammonia (10mL) was added and the mixture was stirred for 4 h. The solid was removed by filtration and the solution was concentrated. The residue was taken up with CH_2Cl_2, washed with brine and dried on Na_2SQ. Evaporation gave crystals (2.17g, 72%) ; mp 73°C

^1H NMR (300 MHz, $CDCl_3$) : δ 3.54 (6H, s, OCH_3) ; 3.93 (6H, s, OCH_3) ; 7.20 (2H, t, J = 7.7 Hz, H_5), 7.52 (2H, dd, J = 1.7, 7.7 Hz, H_6), 7.81 (2H, dd, J = 1.7, 7.7 Hz, H_4)

^{13}C NMR (200 MHz, $CDCl_3$) : δ 52.2, 61.7 (OCH_3) ; 123.3, 131.0, 135.4 (Csec) ; 125.2, 132.5 (Cquat) ; 157.4 (C-O) 166.7 (C=O)

MS : 330, 299, 283, 267, 253, 239, 225, 209

Anal. : Calcd for $C_{18}H_{18}O_6$: C, 65.45 ; H, 5.49 ; Found : C, 65.75 ; H, 5.48

2,2'-dimethoxybiphenyl-3,3'-dicarboxylic acid (S_3)

The diester **11** (2.2g, 6.7 mmol) was refluxed with methanolic sodium hydroxide (excess) for 12h. The mixture was evaporated, 10% HCl was added The precipitate was filtered, washed with water, dried under vacuum to give S_3 (2,0g, quant.) ; mp = 210°C

^1H NMR (300 MHz, Acetone) : δ 3.59 (6H, s, OCH_3) ; 7.30 (2H, t, J = 7.7 Hz, H_5), 7.55 (2H, dd, J = 1.7, 7.7 Hz, H_6), 7.89 (2H, dd, J = 1.7, 7.7 Hz, H_4) ; 11.2 (2H, br s, OH)

^{13}C NMR (200 MHz, $CDCl_3$, DMSO) : δ 60.3 (OCH_3) ; 121.8, 129.6, 133.6 (Csec) ; 124.6, 131.2 (Cquat) ; 155.9 (C-O) ; 166.4 (C=O)

Anal. : Calcd for $C_{16}H_{14}O_6$: C, 63.57 ; H, 4.67 ; Found : C, 63.49 ; H, 4.59

2,2'-dimethoxy-3'-methoxycarbonylbiphenyl-3-carboxylic acid (S_4)

The diester **11** (2.2g, 6.7 mmol) was dissolved in methanol ; sodium hydroxide (267mg in 2ml water) was added and the mixture was refluxed. The reaction was monitored by CCM. The mixture was concentrated and acetone (50 mL) was added. The precipitate of the sodium salt of diacid S_4 (35 mg) was filtered off. The filtrate was concentrated, the residue was treated with 10% HCl, filtered, washed with water, dried under vacuum to give pure S_4 (0.92g, 44%) ; mp = 110°C

^1H NMR (200 MHz, $CDCl_3$) : δ 3.56 (6H, s, OCH_3) ; 3.95 (3H, s, CO_2CH_3) ;7.26 (1H, t, J = 7.7 Hz, H_5), 7.35 (1H, t, J = 7.7 Hz, $H_{5'}$), 7.53 (1H, dd, J = 1.7, 7.7 Hz, H_6), 7.59 (1H, dd, J = 1.7, 7.7 Hz, $H_{6'}$), 7.88 (1H, dd, J = 1.7, 7.7 Hz, H_4) , 8.21 (1H, dd, J =1.7, 7.7 Hz, $H_{4'}$)

^{13}C NMR (200 MHz, $CDCl_3$) : δ 52.4, 61.9, 62.2 (OCH_3) ; 123.8, 124.6, 131.8, 132.6, 135.0, 137.1 (Csec) ; 122.3, 125.4, 131.4, 131.9 (Cquat) ; 157.1, 157.3 (C-O) ; 166.5 (C=O)

MS (CI, NH_3, isobutane) : 334, 317

Anal. : Calcd for $C_{17}H_{16}O_6$, 0.25 H_2O: C, 63.65; H, 5.17; Found : C, 63.58 ; H, 4.83

2,2'-dimethoxybiphenyl-3-carbonyl chloride (**12**)

Heating S_1 (0.5 g, 19 mmol.) in 15 mL of $SOCl_2$ under reflux for 12 h. gave a solution which was then concentrated. The red insoluble residue taken up with hexane and evaporated afforded the acid chloride essentially pure as a pink oil (0.530 g, 98%) ; IR (cm^{-1}) 1775 (C=O)

^1H NMR (200 MHz, $CDCl_3$) : δ 3.47 (3H, s, OMe), 3.78 (3H, s, OMe), 6.97 - 7.06 (2H, m, $H_{3',5'}$), 7.20 - 7.39 (2H, m, $H_{5,6'}$), 7.41 (1H, m, $H_{4'}$), 7.54 (1H, dd, J = 1.8, 7.6 Hz, H_6), 8.01 (1H, dd, J = 1.8, 8.0 Hz, H_4)

^{13}C NMR (200 MHz, $CDCl_3$) : δ 55.6, 61.5 (OMe), 110.9, 120.5, 123.2, 129.5, 131.1, 132.4, 138.3 (Csec.); 123.2, 128.0, 133.8 (Cquat.) ; 156.6, 157.9 (C-O) ; 164.9 (C=O)

N,N-dimethyl-2,2'-dimethoxybiphenyl-3-carboxamide (**13**)

At 0°C a solution of **12** (0.45 g, 16 mmol) and Et_3N (0.3 mL) in CH_2Cl_2 (30 mL) was treated with excess Me_2NH (1 mL in 40 mL CH_2Cl_2). The mixture was successively washed with 10% HCl, 10% NaOH and brine. The organic phase was dried (Na_2SO_4), filtered and evaporated. The residue taken up, with pentane-ether afforded **6** as a white powder (0.348 g, 75%) ; mp 96°C

^1H NMR (200 MHz, $CDCl_3$) : δ 2.93 (3H, s, NMe), 3.13 (3H, s, NMe), 3.46 (3H, s, OMe), 3.74 (3H, s, OMe), 6.94 - 7.03 (2H, m, $H_{3',5'}$), 7.10 - 7.39 (5H, m, $H_{4,4',5,6,6'}$)

^{13}C NMR (200 MHz, $CDCl_3$) : δ 34.7, 38.4 (NMe), 55.6, 61.5 (OMe), 110.9, 120.4, 123.6, 127.0, 129.0, 131.0, 132.6 (Csec.) ; 129.1, 130.5, 132.2 (Cquat.) ; 154.0, 156.8 (C-O) ; 169.7 (C=O)

Anal. : Calcd for $C_{17}H_{19}NO_3$. 0.35 H_2O : C, 70.08 ; H, 6.80 ; N, 4.81 ; Found : C, 70.01; H, 6.81 ; N, 5.17

N,N-dimethyl-2,2'-dihydroxy-[1,1'-biphenyl] -3-carboxamide (M_1)

In 40 mL of CH_2Cl_2 was dissolved **13** (0.7 g, 2.4 mmol). After the apparatus was placed under nitrogen, 20 mL of BBr_3 (1M in CH_2Cl_2, 20 mmol.) was added carefully at 0°C. The mixture was then stirred for 12h at room temperature. Methanol (40 mL) was added dropwise and the reddish mixture was stirred vigorously for 4 h at 40°C and then evaporated. This procedure of heating with methanol, followed by evaporation was repeated several times in order to remove volatile boron species. The residue was then treated with dilute aqueous NaOH and stirred overnight. Upon acidification at O°C with HCl a precipitate was obtained. Recrystallization from ethyl acetate-ether - hexane gave pure M_1 as a white powder (0,52 g, 82%). ; mp 146°C

^1H NMR (200 MHz, $CDCl_3$) : δ 3.18 (6H, s, NMe), 6.94 - 7.12 (3H, m, $H_{3',5,5'}$), 7.20 - 7.42 (4H, m, $H_{4,4',6,6'}$), 7.6 (2H, bs, OH)

^1H NMR (200 MHz, D_2O - NaOD) : δ 2.72 (3H, s, NMe), 2.86 (3H, s, NMe), 6.59 - 6.75 (3H, m, $H_{3',5,5'}$), 6.90 (1H, dd, H_4), 7.04 (1H, dt, $H_{4'}$), 7.20 - 7.27 (2H, m, $H_{6,6'}$) ; a complete study of the variation of the chemical shifts of M_1 with pH was reported in ref. 13

^{13}C NMR (200 MHz, $CDCl_3$) : δ 38.3 (NMe), 118.0, 119.6, 121.0, 127.8, 129.4, 131.2, 134.7 (Csec.) ; 118.4, 125.8, 128.1 (Cquat.) ; 153.8, 154.3 (C-O) ; 172.0 (C=O)

MS : 257, 212, 195, 151

Anal. : Calcd for $C_{15}H_{15}NO_3$. 0.25 H_2O : C, 68.82 ; H, 5.97 ; N, 5.35 ; Found : C, 68.86; H, 6.01; N, 5.51

2,2'-dimethoxy-3-(N,N-dimethylaminocarbonyl)biphenyl-5,5'-disulfonic acid disodium salt (M_{1S})

In portions, M_1 (0.5 g, 1.9 mmol) was added to oleum SO_3-H_2SO_4 (15 mL) while stirring vigorously with a magnetic stir bar. The reaction solution was heated at 90°C for 3 h. The mixture was then carefully poured on to ice. Careful dropwise addition of 5N NaOH with vigorous stirring and cooling, gave a pH 4 mixture. Addition of 1 volume of methanol precipitated the inorganic salt which was removed by filtration, washed well with methanol - water (1:1, v/v), then discarded. The combined filtrate and wash were evaporated, taken up again with methanol - water. This procedure of filtration-washing repeated several times afforded the trisulfonated derivative M_{1S} as a powder (0.9 g, 84%)

^1H NMR (200 MHz, D_2O) : δ 2.92 (6H, bs, NMe_2), 7.59 and 7.67 (2H, AB, J = 2.3, $H_{4',6'}$), 7.75 and 8.04 (2H, AB, J = 2.3, $H_{4,6}$); (200 MHz, D_2O - NaOD) : δ 2.92 (3H, s, NMe), 2.97 (3H, s, NMe)

^{13}C NMR (200 MHz, D_2O) : δ 35.0, 38.7 (NMe_2), 125.6, 125.8, 128.4, 130.3, 132.3, 134.4, 135.0 (CH and CS) ; 124.7, 126.2, 127.0 (Cquat.) ; 152.7, 153.6 (C-O) ; 170.1 (C=O)

MS (FAB - NBA) : 564, 542, 519

14 (O-methoxylated T_1)

Under argon, at 0°C, acid chloride **12** (1.39 g, 5 mmol) in dry THF (30 mL) was added to a solution of TREN (0.24 g, 1.6 mmol) and 0.5 mL of Et_3N in THF (20 mL). The solution was stirred overnight at room temperature. The precipitate of hydrochlorides was removed by filtration, and washed with THF. The combined extracts were concentrated under vacuum. The residue was dissolved in $CHCl_3$ and the solution was washed successively with aqueous 5% HCl, 10% NaOH and brine, then dried over Na_2SO_4. Evaporation of the solution afforded an oil (1.26 g, 87%) which crystallized in white solid. ; mp 85°C (dec.)

^1H NMR (300 MHz, $CDCl_3$) : δ 2.88 (6H, t, J = 6.5 Hz, NCH_2) ; 3.37 (9H, s, OCH_3) ; 3.57 (6H, q, J = 6.5 Hz, NCH_2) 3.71 (9H, s, OCH_3) ; 6.93-6.97 (6H, m, $H_{3',5'}$), 7.11-7.22 (6H, m, $H_{5,6'}$), 7.29-7.35 (6H, m, $H_{4',6}$), 7.96 (3H, dd, J = 1.9, 7.8 Hz, H_4) ; 8.03 (3H, m, NH)

^{13}C NMR (300 MHz, $CDCl_3$) : δ 38.1, 53.9 (NCH_2) ; 55.9, 61.3 (OCH_3) ; 111.4, 120.6, 123.8, 129.2, 130.7, 131.4, 135.3 (Csec) ; 126.6, 127.1, 132.5 (Cquat) ; 156.4, 156.9 (C-O) ; 165.9 (C=O)

MS-CI : 869, 612, 598

Anal. : Calcd for $C_{51}H_{54}N_4O_9$: C, 70.65 ; H, 6.28 ; N, 6.46 ; Found : C, 70.28 ; H, 6.29 ; N, 6.38

Podand (T_1)

To a solution of **14** (0.37g, 0.42 mmol) in CH_2Cl_2 (10mL) under N_2 at O°C was added BBr_3 (20 mL of a 1M solution in CH_2Cl_2). The reaction mixture containing a yellow precipitate was allowed to warm to ambient temperature and stirred for 24h. Water (30 mL) was added carefully and the mixture was stirred for 3h. The white precipitate.that formed was washed with water then dried in vacuo, affording pure T_1 as a powder (0.27 g, 80%).

mp = 210°C

MS (FAB+, NBA) : 783 ; MS-CI: 784, 528, 256

^{1}H NMR (300 MHz, $CDCl_3$-Acetone-d_6) : δ 3.80 (6H, m, NCH_2) ; 4.02 (6H, m, NCH_2) ; 6.87-6.97 (9H, m, $H_{5,3',5'}$), 7.17-7.23 (9H, m, $H_{6,4',6'}$), 7.42 (3H, dd, J = 1.5, 7.5 Hz, H_4) ; 8.02 (3H, m, NH) ; 9.24 (br s OH)

^{13}C NMR (200 MHz, $CDCl_3$-Acetone-d_6) : δ 35.3, 55.1 (NCH_2) ; 117.3, 119.4, 120.4, 127.4, 129.4, 131.9, 136.9 (Csec) ; 114.8, 125.9, 128.6 (Cquat) ; 155.1, 158.9 (C-O) ; 171.8 (C=O)

Anal. : Calcd for $C_{45}H_{42}N_4O_9$, HBr : C, 62.57 ; H, 5.02 ; N, 6.49 ; Found : C, 62.68 ; H, 5.24 ; N, 6.30

Podand (T_{1S})

T_1 (0.54 g, 0.7 mmol) was added to oleum SO_3-H_2SO_4 (20 mL) while stirring vigorously with a magnetic stir bar. The reaction solution was heated for 3 h. at 90°C. The mixture was then carefully poured onto ice. Dropwise addition of 5N NaOH with vigorous stirring and cooling, gave a pH 4 mixture. The mixture was concentrated to 200mL. Addition of 1 volume of methanol precipitated the inorganic salt which was removed by filtration, washed well with methanol-water (1:1, v/v), then discarded. The combined filtrate and wash were evaporated, taken up again with methanol-water. This procedure of filtration-washing repeated several times afforded the trisulfonated derivative T_{1S} as a beige powder. (1.25 g, 91%)

^{1}H NMR (200 MHz, D_2O) : δ 3.50 (6H, m, NCH_2) ; 3.77 (6H, m, NCH_2) ; 8.09 + 8.36 (6H, AB, J = 2.3 Hz, $H_{6',4'}$) ; 8.15 + 8.52 (6H, AB, J = 2.4 Hz, $H_{6,4}$)

^{13}C NMR (200 MHz, D_2O) : δ 39.5, 55.5 (NCH_2) ; 127.9, 130.5, 132.4, 134.5 (Csec) ; 122.8, 133.5, 133.8, 134.0, 134.2, 134.4 (Cquat) ; 161.7, 166.6 (C-O) ; 171.9(C=O)

3-(2,2'-dimethoxybiphenyl)-3-carbonyl-1,3-thiazolidine-2-thione (15)

A solution of DMAP (25mg) and DCC (1.215 g, 57 mmol) in CH_2Cl_2 (30 mL) was added dropwise, at O°C under nitrogen, to a solution of S_1 (1.4 g, 54 mmol) and thiazolidine-2-thione (0.712 g, 6 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at ambient temperature for 12 h ; the precipitate was filtered off and washed with CH_2Cl_2. The filtrate was evaporated and the residue taken up with ether afforded pure **15** as a yellow powder (1.62 g, 80%).

mp = 140°C

^{1}H NMR (200 MHz, $CDCl_3$) : δ 3.57 (2H, t, CH_2), 3.61 (3H, s, OMe), 3.78 (3H, s, OMe), 4.63 (2H, t, CH_2), 6.89 - 7.02 (2H, m, $H_{3',5'}$), 7.10 - 7.43 (5H, m, $H_{4,5,6,4',6'}$)

^{13}C NMR (200 MHz, $CDCl_3$, DEPT 120) : δ 29.0 (CH_2), 55.6 (CH_2), 55.6 (CH_3), 61.4 (CH_3), 111.0, 120.4, 123.2, 128.0, 129.1, 131.1, 134.9 (Csec.) ; 126.7, 128.7, 131.5 (Cquat.) ; 155.1, 156.6 (C-O) ; 168.4 (C=O); 200.7 (C=S)

Podand (16)

A solution of spermidine (0.4 g, 2.7 mmol) in CH_2Cl_2 (20 mL) was added to a yellow solution of **15** (1.354 g, 3.7 mmol) in CH_2Cl_2 (35 mL). After beeing stirred at room temperature under N_2 for 12 h, the mixture was washed with 2% NaOH solution to remove thiazolidine-2-thione excess. The organic phase washed with brine, then dried and evaporated under reduced pressure afforded the amide **16** as a colorless oil (1.067 g, 91%). This product was used without further purification.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.7-1.9 (7H, m, C-CH_2+ NH), 2.7.(4H, m, N-CH_2), 3.2 (6H, s, OMe), 3.5.(4H, m, CH_2NCO), 3.8 (6H, s, OMe), 6.9 - 7.1 (4H, m, $H_{3',5'}$), 7.2 - 7.4 (8H, m, $H_{5,6,4',6'}$), 8.0 - 8.2 (4H, m, H_4+ NHCO)

^{13}C NMR (200 MHz, $CDCl_3$) : δ 24.9, 27.6, 29.8 (C-CH_2), 33.8, 37.6(N-CH_2), 47.1, 49.6 (CONHCH$_2$), 55.6 (OCH_3), 61.3 (OCH_3), 111.1, 120.4, 123.9, 129.1, 130.7, 131.2, 135.2 (Csec.) ; 126.4, 126.7, 132.5 (Cquat.) ; 156.0, 156..7 (C—O) ; 165.6 (C=O)

Podand (17) (O-methoxylated T_3)

Under N_2, in a 250 mL flask protected with a drying tube, was mixed **16** (1.06 g, 1.7 mmol) and triethylamine (0.3 mL) in freshly distilled (on benzophenone ketyl) THF (80mL). Acid chloride **12** (0.53 g, 1.9 mmol) in THF (40mL) was added dropwise and the reaction was left to stir at room temperature for 24h. The mixture was concentrated under reduced pressure, washed with 10% NaOH and extracted with $CHCl_3$. The combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was chromatographed on a silica gel column first with CH_2Cl_2/iPrNH_2 (98:2), second with CH_2Cl_2/MeOH (95:5) to afford compound **9** (1.04g, 70%)

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.8-1.9 (6H, m, C-CH_2), 3.2-3.5 (15H, m, OMe+CH_2), 3.65-3.8 (11H, m, OMe+CH_2), 6.9-7.4 (18H, m, H_{Ar}), 7.95 (1H, dd, H_4), 8.05 (2H, dd, H_4), 8.2 (2H, m, NHCO)

^{13}C NMR (200 MHz, $CDCl_3$; DEPT 120) : δ 25.8, 27.6, 29.9 (C-CH_2), 36.6, 41.8, 46.4, 47.8 (NCH_2), 55.6 (OCH_3), 59.1 (OCH_3), 61.3 (OCH_3), 111.1, 120.4, 123.7, 123.9, 126.6, 126.9, 129.1, 130.6, 131.0, 131.2, 131.4, 132.4, 132.7, 135.3 (Csec.) ; 155.3, 156.0, 156.4, 156.7 (C-O) ; 165.7, 169.5, 170.1(C=O)

MS- CI : 866, 608, 314, 241, 195

Podand (T_3)

To a solution of 17 (0.58g, 0.67 mmol) in CH_2Cl_2 (30mL) under N_2 at O°C was added BBr_3 (7mL of a 1M solution in CH_2Cl_2). The reaction mixture was allowed to warm to ambient temperature and stirred for 24h. Methanol (15mL) was added carefully and the mixture was stirred for 3h. The solvent was evaporated, then the residue was combined with another 20 mL of MeOH and the solution was heated. The procedure of addition of methanol, heating, followed by evaporation was repeated several times. The yellowish powder obtained was chromatographed (silicagel,CH_2Cl_2/ $PrNH_2$, 99:1) to afford pure T_3 (0.46g, 87%)

^1H NMR (300 MHz, DMSO-d_6) : δ 1.4-1.9 (6H, m, C-CH_2), 3.2-3.6 (8H, m, N-CH_2), 6.6-6.9 (9H, m, H_{Ar}), 7.0-7.4 (12H, m, H_{Ar}), 7.9 (CONH)

^{13}C NMR (200 MHz, D_2O-NaOD ; DEPT 120) : δ 23.2, 24.9, 25.8 (C-CH_2), 34.7, 42.6, 43.0, 42.6 (NCH_2), 113.7, 115.4, 115.6, 116.3, 116.7, 118.0, 123.5, 124.2, 126.5, 127.3, 128.6, 128.9, 129.5, 133.0 (Csec.) ; 153.6, 155.7 (C-O) ; 161.2, 168.0, 171.5 (C=O) . MS-CI : 782, 570

Podand (T_{Im})

Under argon, in a solution of the aldehyde S_2 (2g, 9.3 mmol) in 80 mL of dry methanol TREN (tris-(2-aminoethyl)amine ; 0.55mL, 3.9mmol) was added dropwise under reflux and the mixture was stirred for 1 h. The yellow precipitate of imine which separated was filtered, washed with cold methanol and dried (2.07g, 90%)

mp : 145°C ; IR (cm^{-1}) 1650 (C=N)

^1H NMR (200 MHz, $DMSOd_6$) : δ 2.90 (6H, br s, N-CH_2), 3.67 (6H, br s, =N-CH_2), 6.62 (3H, t, H_5), 6.81 (6H, m, $H_{4',6'}$), 7.01 (3H, m, $H_{3'}$), 7.13 (3H, m, $H_{5'}$) 7.18 (3H, m, H_3), 7.41 (3H, m, H_4), 8.30 (3H, br s, CH=N), 10.5 (3H, br s, OH), 13.7 (3H, br s, $^+$NH)

^{13}C NMR (200 MHz, $DMSOd_6$) : δ 52.4, 54.0 (CH_2) ; 115.6, 116.2, 117.2, 119.0, 126.5, 130.1, 130.7 (CH) ; 128.2, 132.8, 136.5 (Cquat) ; 155.9 (C=N) ; 167.1, 167.5 (C-O)

Podand (T_{am})

$NaBH_4$ (0.52g, 135mmol) was added to a suspension of imine T_{Im} (2.2g, 3mmol) in dry methanol (80mL). After stirring under argon for 1h, hydrochloric was added and the solvent was evaporated. The white powder was treated with sodium hydroxide and then neutralized to pH 7. The resulting precipitate was continuously extracted with chloroform, the solvent was then evaporated, affording a white powder (2.08g, 94%).

FABMS : 741, 543, 345

^1H NMR (300 MHz, $DMSOd_6$) : δ 2.62 (6H, t, N-CH_2), 2.86 (6H, t, N-CH_2), 3.88 (6H, s, N-CH_2Ar), 5.70 (3H, s, NH), 6.57 (3H, t, J = 7.5Hz, H_5), 6.81 (6H, m, $H_{4',6'}$), 6.91 (6H, m, $H_{3'}$), 7.13 (3H, m, $H_{5'}$), 7.25 (6H, m, H_4), 9.55 (6H, br s, HO)

(80 MHz, D_2O-NaOD) : δ 2.59 (12H,br s, N-CH_2), 3.74 (6H, s, N-CH_2Ar), 6.80 - 7.47 (21H, m, ArH)

^{13}C NMR (200 MHz, $DMSOd_6$) : δ 42.8, 48.9, 49.3 (CH_2) ; 114.7, 118.0, 118.3, 120.0, 127.6, 128.5, 128.6, 128.9, 130.1, 131.1 (Ar) ; 157.9, 161.8 (C-O)

Anal. : Calcd for $C_{45}H_{48}N_4O_6$, 4HCl : C, 60.95 ; H, 5.91 ; N, 6.32 ; Found : C, 61.79 ; H, 5.85 ; N, 6.30

Podand (T_{amS})

A mixture of T_{am} (1.2g, 1.6mmol), and H_2SO_4-SO_3 oleum (30mL) was heated at 90°C for 3h. After cooling, the solution was poured into ice and the pH was adjusted to 4. Methanol was added to precipitate Na_2SO_4 ; the solid was filtered off, washed with water-methanol and the solution was concentrated under vacuum.The combined filtrate and wash were evaporated, taken up again with methanol - water. This procedure of filtration-washing repeated several times afforded, after drying, the trisulfonated derivative T_{amS} as a powder (2.6g, quant.).

^1H NMR (200 MHz, D_2O) : δ 2.85 (6H, br s, N-CH_2), 3.13 (6H, br s, N-CH_2), 4.28 (6H, br s, N-CH_2Ar) ; 7.64-7.78 (12H, m, ArH)

^{13}C NMR (200 MHz, D_2O, DEPT120) : δ 43.7, 46.9, 48.5 (CH_2) ; 116.4, 126.0, 128.1, 129.2, 129.4, 129.6, 130.7, 130.8, 132.5 (Ar) ; 155.4, 157.7 (C-O)

2,2'-dimethoxybiphenyl-3,3'-dicarbonyl chloride (**18**)

Under argon, a mixture of diacid S_4 (1.4 g, 4.6 mmol) and freshly distilled $SOCl_2$ (35 ml) was heated to reflux for 3 h. Excess of $SOCl_2$ was removed by vacuum distillation. The residue was treated by hexane and concentrated ; this procedure, repeated several times, afforded white crystals of practically pure acid chloride (1.52 g, 97%)

^1H NMR (200 MHz, $CDCl_3$) : δ 3.57 (6H, s, OCH_3) ; 7.30 (2H, t, J = 7.8 Hz, H_5), 7.63 (2H, dd, J = 1.7, 7.8 Hz, H_6), 8.08 (2H, dd, J = 1.9, 7.8 Hz, H_4) ; 11.2 (2H, br s, OH)

^{13}C NMR (200 MHz, $CDCl_3$) : δ 62.1 (OCH_3) ; 123.8, 133.4, 137.6 (Csec) ; 128.4, 132.1 (Cquat) ; 157.5 (C-O) ; 164.8 (C=O)

N,N,N',N'-tetramethyl-2,2'-dimethoxybiphenyl-3,3'-dicarboxamide (**20**)

Under nitrogen, in a 100 mL flask containing 25mL of CH_2Cl_2 cooled to -10°C, were dissolved 2.7 mL of triethylamine, 3 mL of dimethylamine (excess). A solution of acid chloride **18** (1.5 g, 4.4 mmol) in 20 mL of CH_2Cl_2 was added dropwise. The mixture was allowed to warm to room temperature overnight. The precipitate of hydrochlorides was removed by filtration, and washed with CH_2Cl_2. The combined extracts were concentrated under vacuum. Flash chromatography (silica, CH_2Cl_2-MeOH 95:5) afforded the pure product as a white powder (1.4 g, 89%) mp 100°C

^{1}H NMR (200 MHz, $CDCl_3$) : δ 2.91 (6H, s, NCH_3) ; 3.12 (6H, s, NCH_3) ; 3.51 (6H, s, OCH_3) ; 7.12 - 7.35 (6H, m, $H_{4,5,6}$)
^{13}C NMR (200 MHz, $CDCl_3$) : δ 34.8, 38.3 (NCH_3) ; 61.4 (OCH_3) ; 123.9, 127.7, 132.3 (Csec) ; 130.8, 131.7 (Cquat) 153.8 (C-O) ; 169.4 (C=O)

N,N,N',N'-tetramethyl-2,2'-dihydroxybiphenyl-3,3'-dicarboxamide (**M_2**)

a) Diamide **20** (1 g, 2.8 mmol) was dissolved in 40 mL of CH_2Cl_2 at 0°C under nitrogen and BBr_3 (10 mL of 1M solution in CH_2Cl_2, excess) was added dropwise, causing a yellow precipitate. After stirring overnight at room temperature, the reaction mixture was cooled to 0°C and treated with 30 mL of MeOH and 20mL of water. After 4 h the mixture was concentrated and then repeatedly evaporated with MeOH to remove the borates. Drying in vacuo yielded a slightly pink powder (0.898 g, 88%) ; mp = 185°C

b) Diamide **20** (0.712 g, 2 mmol) was placed in a 100 mL flask. A freshly prepared 1M solution in THF of Ph_2PLi (20 mL) was added. The mixture was stirred at room temperature for 6 h whereupon it was quenched with aqueous HCl and extracted with CH_2Cl_2. The extract was washed 3 times with 1M NaOH and the combined washings containing the phenate were acidified with HCl. The biphenol was extracted with CH_2Cl_2 and dried over Na_2SO_4. The product was purified by recrystallization (pentane-ether) (0.60 g, 92%)

^{1}H NMR (200 MHz, $CDCl_3$) : δ 3.13 (12H, s, NCH_3) ; 6.95 (2H, t, J = 7.7 Hz, H_5) 7.24 - 7.39 (4H, m, $H_{4,6}$)
^{1}H NMR (200 MHz, D_2O-NaOD) : δ 2.98 (6H, s, NCH_3) ; 3.13 (6H, s, NCH_3) ; 6.99 (2H, t, J = 7.7 Hz, H_5) ; 7.22 (2H, dd, J = 7.7, 1.4 Hz, H_6) ; 7.60 (2H, dd, J = 7.7, 1.4 Hz, H_4)
^{13}C NMR (200 MHz, $CDCl_3$) : δ 38.1 (NCH_3) ; 118.9, 128.2, 134.0 (Csec) ; 119.2, 126.9 (Cquat) ; 154.9 (C-O) ; 171.5 (C=O)
^{13}C NMR (200 MHz, D_2O-NaOD) : δ 32.9, 36.7 (NCH_3) ; 116.4, 124.6, 130.2 (Csec ; DEPT 120) ; 124.7, 127.8 (Cquat) ; 153.3 (C-O) ; 171.5 (C=O)
MS (FAB+, NBA) : 329, 284, 255, 239

2,2'-dihydroxy-3,3'-dimethylaminocarbonylbiphenyl-5,5'-disulfonic acid disodium salt (**M_{2S}**)

In portions, **M_2** (0.6 g, 1.8 mmol) was added to oleum SO_3-H_2SO_4 (30 mL) while stirring vigorously with a magnetic stir bar. The reaction solution was stirred overnight at room temperature. The mixture was then carefully poured on to ice. Dropwise addition of 5N NaOH with vigorous stirring and cooling, gave a pH 4 mixture. The mixture was concentrated to a volume of 200 mL. Addition of 1 volume of methanol precipitated the inorganic salt which was removed by filtration, washed well with methanol-water (1:1, v/v), then discarded. The combined filtrate and wash were evaporated, taken up again with methanol-water. This procedure of filtration-washing repeated several times afforded the trisulfonated derivative **M_{2S}** as a beige powder. (0.8 g, 83%)

^{1}H NMR (200 MHz, D_2O) : δ 2.92 (6H, s, NMe_2) ; 3.07 (6H, s, NMe_2) ; 7.59 (2H, AB, J = 2.3 Hz, $H_{6,6'}$), 7.95 (2H, AB, J = 2.3 Hz, $H_{4,4'}$)
^{13}C NMR (200 MHz, D_2O) : δ 34.6, 38.2 (NMe_2), 124.1, 126.5, 129.1, 131.9 (CH and CS) ; 128.7 (Cquat.) ; 157.8 (C-O) ; 171.4 (C=O)
MS (FAB+, NBA) : 531, 509, 487, 464, 305

2,2'-dimethoxy-3'-methoxycarbonylbiphenyl-3-carbonyl chloride (**19**)

Under argon, a mixture of monoacid **S_4** (3.85 g, 12.2 mmol) and freshly distilled $SOCl_2$ (40 ml) was heated to reflux for 3 h. Excess of $SOCl_2$ was removed in vacuo. The residue was treated by hexane and concentrated ; this procedure, repeated several times, afforded practically pure acid chloride as a white powder (4.05 g, quant.).
IR (cm^{-1}) 1770, 1730 (C=O)
^{1}H NMR (300 MHz, $CDCl_3$) : δ 3.56 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), 3.94 (3H, s, OCH_3) ; 7.23 (2H, t, J = 7.8 Hz, $H_{5'}$), 7.29 (2H, t, J = 7.8 Hz, H_5), 7.51 (2H, dd, J = 1.8, 7.8 Hz, $H_{6'}$), 7.63 (2H, dd, J = 1.8, 7.8 Hz, H_6), 7.85 (2H, dd, J = 1.8, 7.8 Hz, $H_{4'}$), 8.05 (2H, dd, J = 1.8, 7.8 Hz, H_4)
^{13}C NMR (300 MHz, $CDCl_3$) : δ 52.3, 61.9, 62.1 (OCH_3) ; 123.5, 123.7, 131.3, 133.4, 134.9, 137.6 (Csec) ; 125.3, 128.2, 128.4, 131.9 (Cquat) ; 157.4, 157.6 (C-O) ; 164.8, 166.6 (C=O)

N,N-dimethyl-2,2'-dimethoxy-3'-methoxycarbonylbiphenyl3-carboxamide (21)

Acid chloride **19** (2.28 g,) in 80 mL of CH_2Cl_2 was added at 0°C to a solutionof Et_3N (0.68 g), Me_2NH (2 mL, excess). The mixture was allowed to warm to room temperature overnight. After filtration, washing with successively aqueous HCl and NaCl, then drying over Na_2SO_4, and evaporation of the solution afforded a white powder (1.97 g , 84%) ; mp 107°C. ; IR (cm^{-1}) : 1708 ; 1700 , 1600

^1H NMR (200 MHz, $CDCl_3$) : δ 2.94 (3H, s, NCH_3) ; 3.14 (3H, s, NCH_3) ; 3.51 (3H, s, OCH_3) ; 3.54 (3H, s, OCH_3) ; 3.92 (3H, s, OCH_3) ; 7.15 - 7.51 (5H,m , $H_{5,6,4',5',6'}$) ; 7.80 (1H, dd, J = 7.7, 1.8 Hz, H_4)

^{13}C NMR (200 MHz, $CDCl_3$, DEPT) : δ 34.8, 38.1 (NCH_3) ; 52.2 (CO_2CH_3) ; 61.5, 61.7 (OCH_3) ; 123.4, 123.9, 127.7, 130.9, 132.3, 135.2 (Csec) ; 125.3, 131.2, 133.0 (Cquat) ; 131.0, 153.7, 157.4 (C-O) ; 166.7, 169.4 (C=O)

N,N-dimethyl-2,2'-dimethoxy-3'-carboxybiphenyl-3-carboxamide (22)

A solution of monoester **21** (1.9 g, 5.5 mmol), KOH (1 g, excess) in EtOH (100 mL) was stirred at reflux for 4 h. The solvent was evaporated, the residue was treated with aqueous HCl and extracted with $CHCl_3$. The extracts were washed with brine and dried over Na_2SO_4. The crude solid triturated in pentane-ether afforded the pure product as a yellow powder (1.65g, 90%). ; mp 215°C ; IR (cm^{-1}) : 3500-2500, 1711 ; 1638

^1H NMR (200 MHz, $CDCl_3$) : δ 2.95 (3H, s, NCH_3) ; 3.17 (3H, s, NCH_3) ; 3.55 (3H, s, OCH_3) ; 3.56 (3H, s, OCH_3) ; 7.20 - 7.43 (4H,m , $H_{5,6,5',6'}$) ; 7.56 (1H, dd, J = 7.8, 1.8 Hz, $H_{4'}$) ; 8.12 (1H, dd, J = 7.8, 1.8 Hz, H_4)

^{13}C NMR (200 MHz, $CDCl_3$) : δ 34.9, 38.3 (NCH_3) ; 52.2 (CO_2CH_3) ; 61.5, 62.0 (OCH_3) ; 124.2, 124.6, 128.4, 132.1, 132.4, 136.9 (Csec) ; 122.6, 130.5, 130.9, 131.7 (Cquat) ; 153.6, 157.1 (C-O) ; 166.4, 169.3 (C=O).

MS (CI, NH_3 + isobutane) : 330, 312, 298, 285

N,N-dimethyl-2,2'-dimethoxy-3'-chlorocarbonylbiphenyl-3-carboxamide (23)

Under argon, a mixture of monoacid **22** (0.65 g, 2 mmol) and freshly distilled $SOCl_2$ (20 ml) was heated to reflux for 3 h. Excess of $SOCl_2$ was removed in vacuo. The residue was treated by benzene and concentrated ; this procedure, repeated 3 times, afforded practically pure acid chloride as a white powder (0.67 g, quant.).

^1H NMR (200 MHz, $CDCl_3$) : δ 2.95 (3H, br s, NCH_3) ; 3.17 (6H, br s, NCH_3) ; 3.52 (3H, s, OCH_3) ; 3.55 (3H, s, OCH_3) ; 7.18 - 7.41 (4H,m , $H_{5,6,5',6'}$) ; 7.59 (1H, dd, J = 7.9, 1.5 Hz, $H_{4'}$) ; 8.05 (1H, dd, J = 7.9, 1.5 Hz, H_4)

^{13}C NMR (200 MHz, $CDCl_3$) : δ 35.1, 38.4 (NCH_3) ; 52.2 (CO_2CH_3) ; 61.7, 61.9 (OCH_3) ; 123.7, 124.1, 128.3, 132.3, 132.9, 137.6 (Csec, DEPT 120) ; 130.2, 130.4, 133.2 (Cquat) ; 153.7, 157.6 (C-O) ; 164.8, 169.6 (C=O)

Podand (24) Y = CO_2Me

Under nitrogen, a solution of acid chloride **19** (2.2g, 6.6 mmol) in dry THF (50 mL) was added dropwise to a solution of tris (2-aminoethyl) amine (TREN) (0.320g, 2.2 mmol), Et_3N (1.2 mL) in 100 mL of THF. The mixture was stirred for 12 h at room temperature. The precipitate of hydrochlorides was removed by filtration, and washed with THF. The combined extracts were concentrated under vacuum. The residue was dissolved in CH_2Cl_2 and the solution was washed successively with aqueous 5% HCl, 10% NaOH, NaCl then dried over Na_2SO_4. Flash chromatography (silica, CH_2Cl_2-$iPrNH_2$ 98:2) afforded an oil (1.82 g, 79%) which crystallized. ;mp 70°C

^1H NMR (300 MHz, $CDCl_3$) : δ 2.86 (6H, t, J = 6.4 Hz, NCH_2), 3.56 (6H, q, J = 6.4 Hz, NCH_2) ; 3.47 (9H, s, OCH_3), 3.51 (9H, s, OCH_3), 3.93 (9H, s, OCH_3) ; 7.20 (3H, t, J = 7.8 Hz, H_5), 7.22 (3H, t, J = 7.8 Hz, $H_{5'}$), 7.44 (3H, dd, J = 1.8, 7.8 Hz, H_6), 7.46 (3H, dd, J = 1.8, 7.8 Hz, $H_{6'}$), 7.82 (3H, dd, J = 1.8, 7.8 Hz, $H_{4'}$), 8.01 (3H, dd, J = 1.8, 7.8 Hz, H_4) ; 8.08 (3H, m, NH)

^{13}C NMR (300 MHz, $CDCl_3$) : δ 37.8, 53.5 (NCH_2) ; 52.3, 61.5, 61.8 (OCH_3) ; 123.6, 124.3, 131.2, 131.3, 134.7, 135.3 (Csec) ; 125.4, 126.8, 131.5, 132.7 (Cquat) ; 155.8, 157.4 (C-O) ; 165.6, 166.7 (C=O)

MS (FAB - glycerol) : 1041, 342, 299

Anal. : Calcd for $C_{57}H_{60}N_4O_{15}$: C, 65.76 ; H, 5.81 ; N, 5.38 ; Found : C, 65.38 ; H, 5.81 ; N, 5.23

Podand (25) Y = CO_2H

A solution of ester **24** (1.0 g, 0;96 mmol), KOH (0.7 g, excess) in EtOH (50 mL) was stirred at reflux for 3 h. The solvent was evaporated, the residue was treated with aqueous H_2SO_4. The white precipitate of the hydrogenosulfate derivative of **25** was filtered, washed with water and dried in vacuo (0.843 g, 80%) ; mp 144°C (dec)

IR (cm^{-1}) 3600-2800 (OH) ; 1730, 1650 (C=O ; MS (FAB, NBA) : 997, 981

^1H NMR (300 MHz, $CDCl_3$-DMSO) : δ 3.46 (9H, s, OCH_3) ; 3.54 (9H, s, OCH_3) ; 3.64 (6H, s, NCH_2) ; 3.92 (6H, s, NCH_2) ; 7.17 (3H, t, J = 7.8 Hz, H_5), 7.20 (3H, t, J = 7.8 Hz, $H_{5'}$), 7.45 (6H, m, $H_{6,6'}$), 7.73 (3H, dd, J = 1.8, 7.8 Hz, $H_{4'}$), 7.84 (3H, dd, J = 1.8, 7.8 Hz, H_4) ; 8.74 (3H, m, NH)

^{13}C NMR (300 MHz, $CDCl_3$-DMSO) : δ 33.9, 52.7 (NCH_2) ; 60.4, 60.6 (OCH_3) ; 122.2, 122.7, 129.4, 130.3, 132.4, 133.7(2) (Csec) ; 124.9, 125.8, 130.8, 131.7 (Cquat) ; 155.0, 156.2 (C-O); 165.9, 166.6 (C=O)

Anal.: Calcd for $C_{54}H_{56}N_4O_{19}S$, 0.5 H_2O: C, 58.64 ; H, 5.19 ; N, 5.07 ; Found : C, 58.65 ; H, 5.36 ; N,,4.96

Podand (**26**) Y = COCl

Under argon, a mixture of acid **25** (0.83 g, 0.83 mmol) and freshly distilled $SOCl_2$ (30 ml) was stirred at room temperature for 3 h. Excess of $SOCl_2$ was removed in vacuo. The residue was treated by benzene and concentrated ; this procedure, repeated 3 times, afforded practically pure acid chloride **25** (hydrochloride) as a white powder (0.9 g, quant.) ; IR (cm^{-1}) 1778, 1715, 1650 (C=O)

^1H NMR (300 MHz, $CDCl_3$-DMSO) : δ 3.38 (9H, s, OCH_3) ; 3.45 (9H, s, OCH_3) ; 3.54 (6H, s, NCH_2) ; 3.86 (6H, s, NCH_2) ; 7.09 (3H, t, J = 7.8 Hz, H_5), 7.11 (3H, t, J = 7.8 Hz, $H_{5'}$), 7.35 (6H, m, $H_{6,6'}$), 7.68 (3H, dd, J = 1.8, 7.8 Hz, $H_{4'}$), 7.73 (3H, dd, J = 1.8, 7.8 Hz, H_4) ; 8.58 (3H, m, NH)

^{13}C NMR (300 MHz, $CDCl_3$) : δ 35.0, 53.9 (NCH_2) ; 61.4, 61.6 (OCH_3) ; 123.4, 123.7, 127.9, 130.6, 131.5, 134.9(2) (Csec) ; 125.0, 125.8, 131.3, 131.8 (Cquat) ; 155.9, 157.0 (C-O); 166.7, 167.2 (C=O)

Podand (**27**) Y = $CONMe_2$ (**O-methoxylated T_2**)

a) Upon cooling at 0°C, acid chloride **26** (0.9 g, 0.82 mmol) in $CHCl_3$ (50mL) was added dropwise to a solution of Me_2NH (2 mL, excess) and 0.4 g of Et_3N in 50 mL of $CHCl_3$. The red coloured solution was allowed to warm to room temperature and stirred overnight. After filtration, washing with successively aqueous HCl and NaCl ; then drying over Na_2SO_4, and evaporation of the solution afforded the hydrochloride of **27** as a yellowish powder which was purified (0.77 g, 89%) by chromatography (silica, CH_2Cl_2-$iPrNH_2$ 98:2) ;mp 120°C (dec.)

^1H NMR (200 MHz, $CDCl_3$-DMSO) : δ 2.87 (6H, t, NCH_2) ; 2.93 (9H, s, NCH_3) ; 3.44 (9H, s, NCH_3) ; 3.44 (9H, s, OCH_3) ; 3.50 (9H, s, OCH_3) ; 3.58 (6H, q, NCH_2) ; 7.13-7.45 (15H, m, $H_{4',5,5',6,6'}$), 8.01 (3H, dd, J = 1.9, 7.8 Hz, H_4) 8.08 (3H, m, NH)

^{13}C NMR (200 MHz, $CDCl_3$, DEPT) : δ 34.8, 38.4 (NCH_3) ; 37.9, 53.5 (NCH_2) ; 61.4, 61.5 (OCH_3) ; 124.1, 124.3, 127.9, 131.2, 132.3, 134.8 (Csec) ; 131.0, 126.7, 131.1, 131.8 (Cquat) ; 153.6, 155.8 (C-O); 165.6, 169.3 (C=O)

Anal. : Calcd for $C_{60}H_{73}N_7O_{14}$, HCl : C, 62.51 ; H, 6.47 ; N, 8.50 ; Found : C, 62.50 ; H, 6.44 ; N, 8.04

b) Upon cooling at 0°C, acid chloride **23** (1.69 g, 4.8 mmol) in CH_2Cl_2 (60mL) was added dropwise to a solution of TREN (0.24 g, 1.6 mmol) and 0.5 g of Et_3N in 100 mL of CH_2Cl_2. The solution was allowed to warm to room temperature and stirred overnight. The same work-up procedure as above afforded the pure hydrochloride **27,HCl** as yellow crystals (1.6 g, 96%)

Podand (T_2)

Podand **27** (1.60 g, 1.32 mmol) was dissolved in 100 mL of CH_2Cl_2 at 0°C under argon and BBr_3 (14 mL of 1M solution in CH_2Cl_2, excess) was added dropwise. After stirring overnight at room temperature, the reaction mixture containing a white precipitate was cooled to 0°C and treated with 80 mL of MeOH. After 4 h the yellow mixture was concentrated and then repeatedly evaporated with MeOH to remove the borates. Treatement of the residue by 10% NaOH, extraction with CH_2Cl_2 and acidification with HBr afforded a white precipitate which was filtered, washed with ether and dryed in vacuo (1.046 g, 73%) ; CCM (silica, CH_2Cl_2-EtOH 70:30, dying reagent : $FeCl_3$/alcohol) gave one spot at Rf = 0.45. ; mp 180°(dec)

^1H NMR (300 MHz, D_2O-NaOD, pD dependent) : δ 2.81 (9H, s, NCH_3) ; 2.93 (9H, s, NCH_3) ; 2.85 (6H, m, NCH_2) ; 3.49 (6H, m, NCH_3) ; 6.70 (3H, t, J = 8 Hz, H_5) ; 6.83 (3H, t, J = 8 Hz, $H_{5'}$) ; 7.05 (3H, dd, J = 8, 1.4 Hz, H_6) ; 7.32 (3H, dd, J = 8, 1.4 Hz, $H_{6'}$) ; 7.41 (3H, dd, J = 8, 1.4 Hz, H_4) ; 7.71 (3H, dd, J = 8, 1.4 Hz, $H_{4'}$)

^{13}C NMR (200 MHz, D_2O-NaOD) : δ 35.2, 37.4 (NCH_3) ; 37.3, 53.1 (NCH_2) ; 115.7, 117.6, 126.6, 129.5, 132.9, 135.7 (Csec ; DEPT) ; 120.2, 126.7, 130.1, 132.1 (Cquat) ; 156.1, 164.0 (C-O) ; 170.9, 174.0 (C=O)

MS (FAB+, NBA) : 996

Anal. : Calcd for $C_{54}H_{57}N_7O_{12}$, HBr: C, 60.22 ; H, 5.43 ; Found : C, 60.41 ; H, 5.77

Podand (T_{2S})

In portions, T_2 (0.5 g, 0.5 mmol) was added to oleum SO_3-H_2SO_4 (20 mL) while stirring vigorously with a magnetic stir bar. The reaction solution was stirred overnight at room temperature. The mixture was then carefully poured on to ice. Dropwise addition of 5N NaOH with vigorous stirring and cooling, gave a pH 4 mixture. The mixture was concentrated to 200mL. Addition of 1 volume of methanol precipitated the inorganic salt which was removed by filtration, washed well with methanol-water (1:1, v/v), then discarded. The combined filtrate and wash were evaporated, taken up again with methanol-water. This procedure of filtration-washing repeated several times afforded the trisulfonated derivative T_{2S} as a beige powder. (0.744 g, 87%)

^1H NMR (300 MHz, D_2O) : δ 2.75 (9H, s, NCH_3) ; 2.90 (9H, s, NCH_3) ; 3.50 (6H, m, NCH_2) ; 3.77 (6H, m, NCH_2) ; 7.51 + 7.81 (6H, AB, J = 2.1 Hz, $H_{6,4}$) ; 7.85 + 8.19 (6H, AB, J = 2.3 Hz, $H_{6',4'}$)

^{13}C NMR (200 MHz, D_2O, DEPT) : δ 37.2, 40.8 (NCH_3) ; 37.1, 55.7 (NCH_2) ; 126.6, 130.1, 132.0, 134.5 (Csec) ; 121.5, 128.5, 131.4, 132.4, 132.8, 136.3 (Cquat) ; 157.7, 167.4 (C-O) ; 172.2, 173.3(C=O)

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