Polynucleating Open-Chain Systems with Imidazole and Proton-Ionizable 1,2,4-Triazole Structural Motifs

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Received October 11, 2000

A multistep route for obtaining the polynucleating open-chain systems **3**−**5** is reported. These advanced intermediates required elaborate processes that proceeded for the pentanuclear protophanes **3** in seven steps, whereas the trinuclear compounds **4** and **5** were obtained in six steps

Acyclic polydentate building blocks containing heteroaromatic subunits are of interest for the construction of a broad array of molecules from crown ethers[1,2] and macrocycles[1,3] to a variety of multitopic metal-binding molecules and supramolecular entities, e.g., metallosupramolecular systems.[1,4] Accordingly, the proton-ionizable molecules of generalized structure **1** and **2** could allow access to novel molecular architectures, e.g., within polyazamacrocycles, the [1$_n$]heterophanes with a bis-betaine nature.[5] On the other hand, the building blocks of either simple or complex chemical targets are difficult to synthesize.[6] Therefore, we set out to develop a multistep route for obtaining the chemical building blocks **1** and **2**. The advanced intermediates **3**−**5** required elaborate processes which proceeded for the pentanuclear protophanes **3** in seven steps, whereas the trinuclear compounds **4** and **5** were obtained in six steps.

Among the general routes to simple 1,2,4-triazoles,[1b,c] hydrazine-induced cyclization to specific 3,5-bis-(substituted)-1,2,4-triazoles appears to be the most appropriate[2b,c] and it has been conveniently applied for the synthesis of nonclassical [1$_4$]-*meta*-heterophanes containing betaine subunits[7a,b] as well as for protophane **3a**.[7c] According to the retrosynthetic analysis of Figure 1, the cyanomethyl compounds **6** and **7** could react with hydrazine to form the targeted symmetrical 3,5-disubstituted-1*H*-1,2,4-triazoles **3b**,**c**, **4**, and **5**.

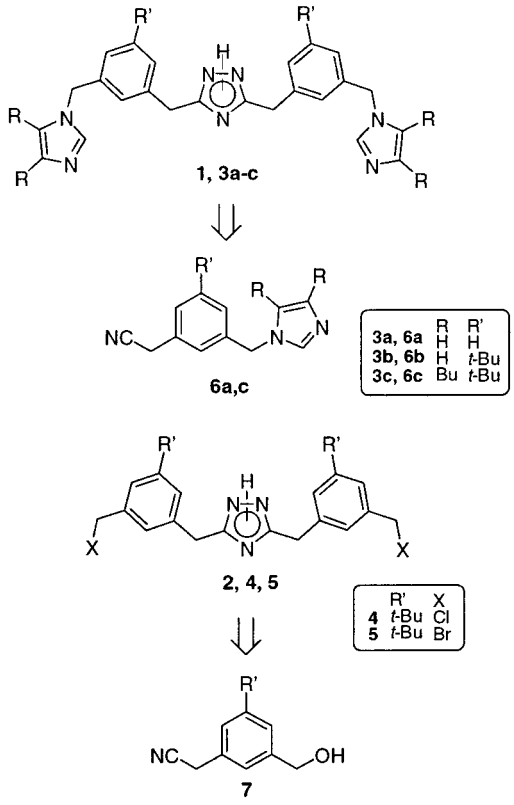

Figure 1.

By a two-step sequence shown in Scheme 1, the pentanuclear building blocks **3b** and **3c** were formed from the corresponding cyanomethyl derivatives **6b** and **6c**. Similarly, 3-cyanomethylbenzylic alcohol **7** was transformed to the trinuclear bis-hydroxymethyl derivative **10**, and subsequent halogenation gave the 3,5-bis[3-(halomethyl)benzyl]-1*H*-1,2,4-triazoles **4** and **5**. Due to their reactivity, the targeted bis-halomethyl trinuclear subunits **4** and **5** have a limited stability and they should be stored, but for no more than 24 h.

The structures of the new protophanes were characterized on the basis of spectroscopic data, and all gave satisfactory elemental analysis. Table 1 shows the most relevant ^{1}H and ^{13}C NMR chemical shifts, and individual assignments were made using NMR experiments.

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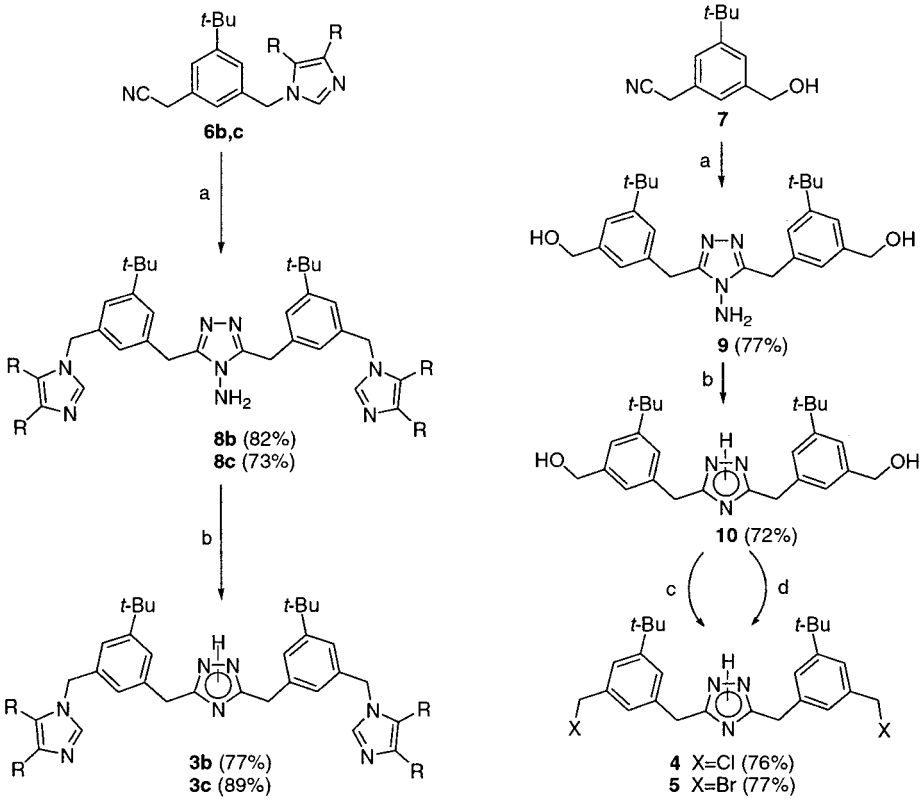
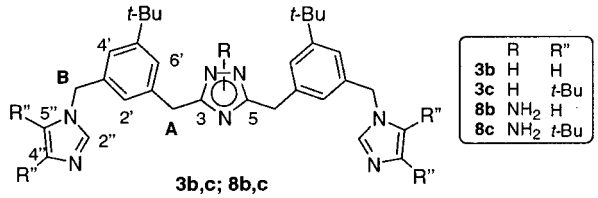
10.1021/jo0056794 CCC: $20.00
Published on Web 03/07/2001

Scheme 1[a]

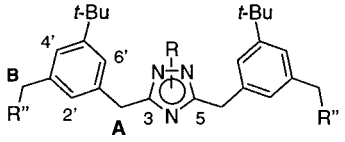


[a] Reagents: (a) $NH_2-NH_2 \cdot H_2O$; (b) $NaNO_2$/HCl; (c) $SOCl_2$; (d); $SOBr_2$.

Table 1. Selected ^{1}H NMR and ^{13}C NMR Data in $CDCl_3$ of Compounds 3b,c, 8b,c, 4, 5, 9, and 10



	R	R"
3b	H	H
3c	H	*t*-Bu
8b	NH_2	H
8c	NH_2	*t*-Bu



	R	R"
4	H	Cl
5	H	Br
9	NH_2	OH
10	H	OH

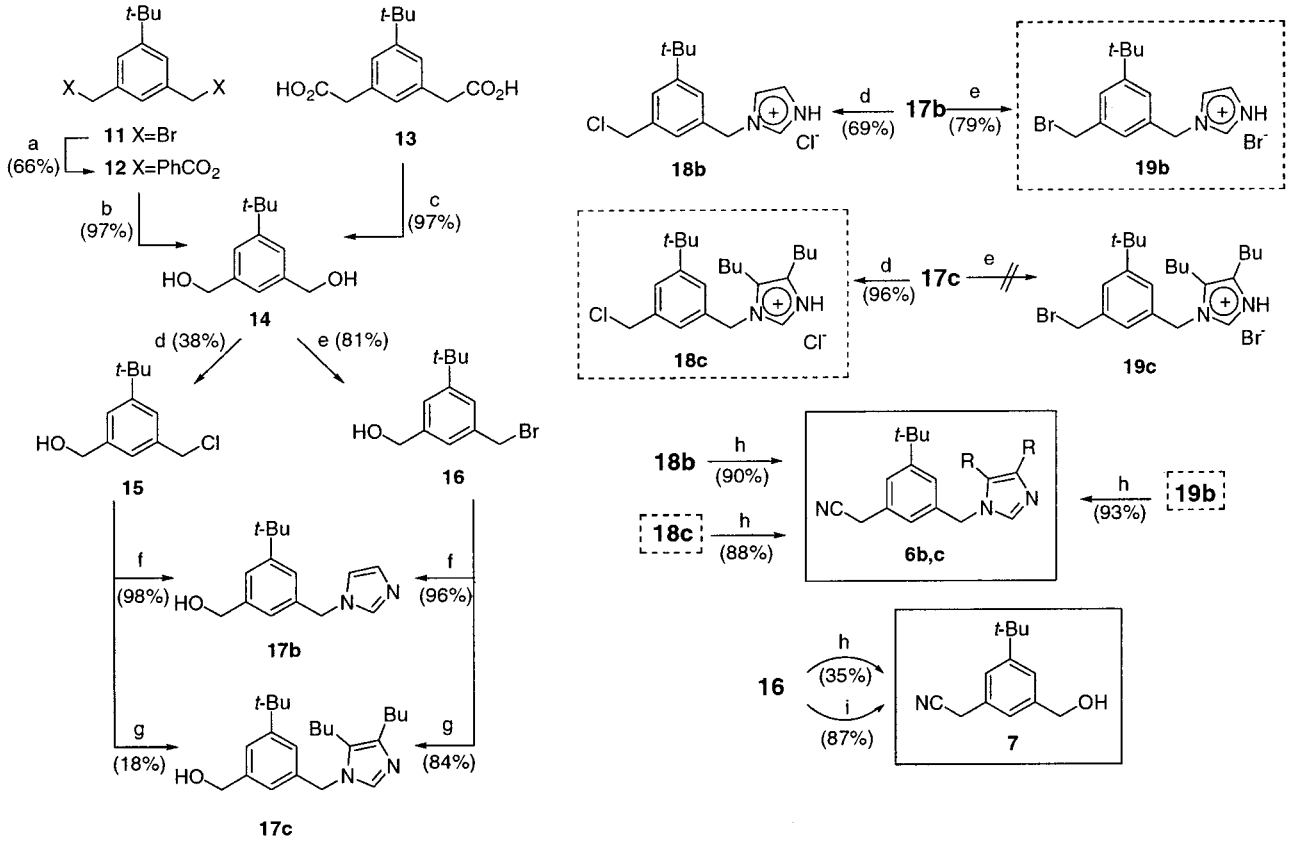
Compd	CH_2-A	CH_2-B	H-2'	H-2''	H-4''	H-5''	CH_2-A	CH_2-B	C-2'	C-2''	C-3,5
3b[a,b]	4.99	4.03	6.86	7.42	6.93	6.83	50.9	34.6	125.0	137.1	154.0
3c	4.92	4.05	6.85	7.28	---	---	48.7	32.1	124.4	137.7	*c*
8b	5.01	4.08	6.86	7.42	7.01	6.81	50.7	30.5	124.9	137.0	154.0
8c	4.96	4.11	6.75	7.33	---	---	48.4	32.1	123.9	135.6	153.9
4	4.49	3.96	7.06	---	---	---	46.3	34.7	126.2	---	158.6
5	4.44	3.99	7.06	---	---	---	33.7	33.2	126.2	---	158.6
9[a,d]	4.63	4.24	7.15	---	---	---	63.7	29.5	124.0	---	154.5
10[d]	4.63	4.10	7.12	---	---	---	65.3	34.2	125.5	---	160.7

[a] Unambiguous assignments were made by NOESY. [b] Unambiguous assignments were made by HMBC, HMQC. [c] Signal not observed. [d] CD_3OD.

The "3 + 5" convergent stepwise synthesis of [1_8]-*meta*-heterophanes was improved using the bis-bromomethyl trinuclear protophane **5** instead of the bis-chloromethyl counterpart **4** due to its greater reactivity.[5] The simple mononuclear building block is 3,5-bis(bromomethyl)-1*H*-1,2,4-triazole, and its preparation was then explored. Bromination of bis(hydroxymethyl)-1*H*-1,2,4-triazole[2c] with thionyl bromide produced only alteration and decomposition products.[8]

The synthesis of the cyanomethyl key compounds **6b**,**c** and **7** started with 3-bromomethyl-5-*tert*-butylbenzylic alcohol **16**, which was obtained in 79% by a two-step sequence from commercially available 5-*tert*-butylisophthalic acid **13**[9] (Scheme 2). 3-Chloromethyl-5-*tert*-

Scheme 2[a]



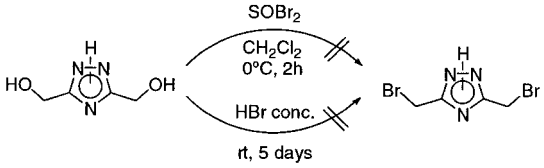
[a] Reagents: (a) $PhCO_2H$/NaOH/TBABr; (b) NaOH; (c) BH_3•THF (ref 11b); (d) $SOCl_2$; (e) HBr concentrated; (f) imidazole/KOH; (g) 4,5-dibutylimidazole•HCl/KOH; (h) NaCN/DMF; (i) NaCN/TBABr, H_2O/CH_2Cl_2

butylbenzylic alcohol **15** was also prepared. Comparison of the reaction between the compound pair **15** or **16**[10a] and the appropriate imidazole revealed that the bromomethyl counterpart **16** is the best key intermediate, which provided significantly higher yield (84%) of **17c** and purity of compounds **17b** and **17c**.

The conversion of the benzylic alcohols **17b** and **17c** to the benzylic halides **18b**,**c** and **19b**[10b] was the critical step toward the synthesis of the multitopic molecules **3**. The use of thionyl chloride gave good yet variable yields of **18b** due to its troublesome isolation and purification, whereas the chloromethyl derivative **18c** was obtained in high yield and purity (Scheme 2). Reaction with HBr concd was similarly capricious within "b" and "c" series, and it was possible to obtain the desired intermediate of "b" series (**19b**). Further, standard transformation of **19b** and **18c** provided the key arylacetonitriles **6b**,**c** (Scheme 2). Similarly, 3-bromomethyl-5-*tert*-butylbenzylic alcohol **16** was transformed to 3-cyanomethylbenzylic alcohol **7**.

In summary, we report the synthesis of polynuclear acyclic systems which constitute a reservoir of structural building blocks based on π-excessive heteroaromatic and aromatic structural motifs for the construction of new molecular architectures and materials, such as macrocyclic systems and multitopic scaffolds with metal-ion binding capabilities.

(8) The 3, 5-bis(chloromethyl)-1*H*-1,2,4-triazole was prepared according to Bradshaw *et al.*[2c] from 3, 5-bis(hydroxymethyl)-1*H*-1,2,4-triazole and it is the mononuclear building block for producing both the dicationic [1$_4$]-*meta*-heterophanes[7a, b] and [1$_6$]-*meta*-heterophanes,[5a] through the convergent "3 + 1" and "5 + 1" approaches. As shown in eq 1, attempts were made to prepare the bis-bromomethyl counterpart. Using thionyl bromide, bis-hydroxymethyl compound gave products of alteration and decomposition, whereas using HBr concd the starting material was recovered unaltered (see the Experimental Section).



(eq 1)

(9) An alternative and less efficient three-step procedure was, however, studied starting from the bis-bromomethyl compound **11** (Scheme 2).

(10) (a) The benzylic halide pair **15** and **16** are unstable and they should not be left to stand for more than 24h. (b) The benzylic halides **18b**,**c** and **19b** were fairly stable.

Experimental Section

General Methods. Melting point: CTP-MP 300 hot-plate apparatus with ASTM 2C thermometer (see Table 2, Supporting Information). IR (NaCl or KBr disks): Nicolet 205 FT spectrophotometer. ^{1}H NMR: Varian Gemini 200 and Varian Gemini 300 spectrometers (200 and 300 MHz) at 298 K. Chemical shifts were referenced and expressed in ppm (δ) relative to the central peak of methanol-d_4 (3.40 ppm) and TMS for chloroform-*d*. ^{13}C NMR: Varian Gemini 200 and Varian Gemini 300 spectrometers (50.3 and 75.4 MHz) at 298 K. Chemical shifts were referenced and expressed in ppm (δ) relative to the central peak of methanol-d_4 (49.0 ppm) and chloroform-*d* (77.0 ppm). HMQC, HMBC and NOESY experiments: Varian VXR-500 spectrometer (500 MHz). TLC: Merck precoated silica gel 60 F_{254} plates or Panreac aluminum oxide 60-200 UV_{254} Polyester CCM plates using UV light (254 nm) as visualizing agent and/or H_2PtCl_2 3% aq/KI 10% aq (1:1) or

$KMnO_4$ ethanolic solution. Column chromatography was performed on neutral aluminum oxide 90 activity II−III (Merck).

Materials. Solvents were distilled prior to use and dried. Imidazole and compound **13** are commercially available. Compounds **11**[11a] and **14**[11b] together with 4,5-dibutylimidazole hydrochloride[11c] were prepared as described in the literature. ***Caution*: bis-halomethyl trinuclear compounds (4**) and (**5**) are severe skin irritants and should be handled with care.

3,5-Bis[[3-*tert*-butyl-5-(imidazolylmethyl)phenyl]-methyl]-1,2,4-triazole 3b and 3,5-Bis[[[3-*tert*-butyl-5-(4,5-dibutylimidazolyl)methyl]phenyl]methyl]-1,2,4-triazole 3c. To a cold solution (0−10 °C) of 1.18 mmol of compound **8b** or **8c** (0.63 or 0.90 g) in 40 mL of aqueous 3 M HCl (for **8c**, additional 15 mL ethanol was added) was added dropwise a solution of $NaNO_2$ (0.20 g, 2.90 mmol) in 15 mL of water. The mixture was then warmed to room temperature for 4 or 5 h, respectively. The mixture was adjusted to pH 8 with Na_2CO_3 (for **8c**, an additional 100 mL of water was added). The suspension was extracted with CH_2Cl_2 (3 × 100 mL), the combined organic layers were dried (anhydrous Na_2SO_4), and the solvent was eliminated in a rotary evaporator to afford compound **3b** or **3c** (0.47 or 0.78 g) as a foamy solid.

3,5-Bis[[3-*tert*-butyl-5-(chloromethyl)phenyl]methyl]-1,2,4-triazole 4. To a suspension of diol **10** (0.21 g, 0.51 mmol) in 10 mL of dry CH_2Cl_2 at 0 °C was added dropwise a solution of $SOCl_2$ (0.4 mL, d = 1.635, 5.50 mmol) in dry CH_2Cl_2 (3 mL). The reaction mixture was stirred at room temperature for 5 h, and the solvent was then removed to dryness under reduced pressure to give compound **4** as a white foamy hygroscopic solid.

3,5-Bis[[3-(bromomethyl)-5-*tert*-butylphenyl]methyl]-1,2,4-triazole 5. To a suspension of 0.15 g (0.36 mmol) of diol **10** in 10 mL of dry CH_2Cl_2 at 0 °C was added dropwise a solution of $SOBr_2$ (0.27 mL, d = 2.683, 3.60 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 1.5 h, and then the solvent was removed to dryness under reduced pressure. The crude residue was dissolved in 25 mL of CH_2Cl_2, washed in a saturated aqueous solution of Na_2CO_3 (2 × 25 mL) and water (2 × 25 mL), the organic layer was dried (anhydrous Na_2SO_4), and the solvent was removed under reduced pressure to afford 0.15 g of compound **5** as a pale yellow foamy hygroscopic solid.

[3-*tert*-Butyl-5-(imidazolylmethyl)phenyl]acetonitrile 6b and [3-*tert*-Butyl-5-[(4,5-dibutylimidazolyl)-methyl]phenyl]acetonitrile 6c. To a suspension of NaCN (0.30 g, 6.12 mmol) in DMF (15 mL) was added 1.29 mmol of **19b** or **18c** (0.50 or 0.53 g, respectively) in DMF (40 mL). The reaction mixture was heated to 80 °C (5 or 24 h, respectively), a saturated aqueous solution of Na_2CO_3 (100 mL) was added, and the solvent was removed in a rotary evaporator. The residue was dissolved in water (200 mL) and extracted with 3 × 100 mL portions of CH_2Cl_2. The combined extracts were dried (anhydrous Na_2SO_4), and the solvent was removed in vacuo to afford compound **6b** or **6c** as an oil.

[3-*tert*-Butyl-5-(hydroxymethyl)phenyl]acetonitrile 7. To a solution of NaCN (3.4 g, 70 mmol) and tetrabutylammonium bromide (0.2 g, 0.68 mmol) in water (20 mL) was added 3.6 g (14.08 mmol) of **16** in CH_2Cl_2 (200 mL). The reaction mixture was stirred at room temperature for 48 h, and the layers were then separated. The aqueous layer was washed in CH_2Cl_2 (2 × 50 mL), the combined organic layers were dried (anhydrous Na_2SO_4), and the solvent was eliminated in rotary evaporator to give 2.47 g of pale yellow oil **7**.

4-Amino-3,5-bis[[3-*tert*-butyl-5-(imidazolylmethyl)-phenyl]methyl]-1,2,4-triazole 8b. A stirred solution of 2.19 g (8.69 mmol) of compound **6b** in hydrazine hydrate (4.0 mL, d = 1.032, 82.46 mmol) was maintained in a bath at 100 °C for 72 h, and then the bath temperature was raised to 170 °C for 3 h to distill off the excess of hydrazine and water. The residue was triturated in ethyl acetate (100 mL), and the yellow solid obtained was filtered and dried to afford 1.90 g of **8b**.

4-Amino-3,5-bis[[[3-*tert*-butyl-5-(4,5-dibutylimidazolyl)-methyl]phenyl]methyl]-1,2,4-triazole 8c. A stirred solution of 1.30 g of **6c** (3.56 mmol) and hydrazine hydrate (2.0 mL, d = 1.032, 41.23 mmol) was maintained in a bath at 100 °C for 1 h, and then the bath temperature was raised to 140 °C for 16 h. The excess of hydrazine and water was distilled off for 1h at 170 °C. The residue was dissolved in ethyl acetate (100 mL), and washed in aqueous saturated solution of NaCl (50 mL) and water (2 × 50 mL). The organic layer was dried (anhydrous Na_2SO_4) and the solvent was eliminated in rotary evaporator to give 0.99 g of **8c** as a yellow foamy solid.

4-Amino-3,5-bis[[3-*tert*-butyl-5-(hydroxymethyl)phenyl]-methyl]-1,2,4-triazole 9. A stirred solution of 1.60 g (7.88 mmol) of compound **7** in hydrazine hydrate (2.0 mL, d= 1.032, 41.23 mmol) was maintained in a bath at 100 °C for 48 h, and then the bath temperature was raised to 170 °C for 2 h to distill off the excess of hydrazine and water. The residue was triturated in ethyl acetate (50 mL), and the white solid obtained was filtered and dried to afford 1.32 g of pure aminotriazole **9**.

3,5-*bis*[[3-*tert*-butyl-5-(hydroxymethyl)phenyl]methyl]-1,2,4-triazole 10. To a cold solution (0−10 °C) of compound **9** (0.91 g, 2.09 mmol) in 50 mL of HCl (3 M in methanol) was added dropwise a solution of $NaNO_2$ (0.19 g, 2.75 mmol) in 10 mL of water. The mixture was warmed to room temperature for 24 h and treated with Na_2CO_3 to pH 8, and the solvent was removed in rotary evaporator. The residue was crushed with absolute ethanol (20 mL, 1 h) and filtered, and the ethanolic solution was evaporated to dryness to give a yellow solid that was purified by triturating in ethyl acetate (10 mL) to afford 0.67 g of triazole **10** as a white solid.

[3-(Benzoyloxymethyl)-5-*tert*-butylphenyl]methyl benzoate 12. A 15 g (46 mmol)portion of **11** in chloroform (100 mL) was added to a solution of benzoic acid (14.3 g, 117 mmol) in NaOH 4 M (150 mL) and tetrabutylammonium bromide (4.5 g, 14.11 mmol). The reaction mixture was refluxed for 12 h, and the layers were then separated. The aqueous layer was washed in chloroform (2 × 100 mL), the combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was eliminated in rotary evaporator. The crude residue was purified by column chromatography (silica gel; hexane/ethyl acetate, 95:5) to yield 12.5 g of diester **12** as a white solid.

[3-*tert*-Butyl-5-(chloromethyl)phenyl]methanol 15. To a suspension of diol **14** (2 g, 10.3 mmol) in 1.2 mL (d = 0.983, 14.91 mmol) of pyridine and 60 mL of dry distilled toluene at −40 °C was added dropwise a solution of $SOCl_2$ (1.2 mL, d = 1.635, 16.49 mmol) in dry distilled toluene (10 mL). The reaction mixture remained at room temperature for 18 h and was then poured over water (50 mL) and extracted with diethyl ether (3 × 100 mL). The organic layer was washed in an aqueous solution of Na_2CO_3 5% (3 × 200 mL) and dried (anhydrous Na_2SO_4), and the solvent was eliminated in a rotary evaporator. The residue was purified by chromatography (silica gel, CH_2Cl_2) giving 0.83 g of colorless oil **15.**

[3-(Bromomethyl)-5-*tert*-butylphenyl]methanol 16. To 0.50 g (2.57 mmol) of diol **14** stirred at 0 °C, 3.5 mL (30.9 mmol) of HBr concentrated (48% v/v, aq) was added dropwise, and the reaction mixture remained at room temperature for 5 h. 50 mL of water was added and extracted with CH_2Cl_2 (2 × 50 mL). The organic layer was dried (anhydrous Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude residue was purified by chromatography (silica gel; diethyl ether/hexane, 9:1) to give 0.54 g of colorless oil **16**.

[3-*tert*-Butyl-5-(imidazolylmethyl)phenyl]methanol 17b. A stirred suspension of 1*H*-imidazole (0.2 g, 2.74 mmol) and finely powered KOH 85% (0.24 g, 3.56 mmol) in dry acetonitrile (60 mL) was maintained at room temperature for 2 h. To the yellow suspension, a solution of compound **15** or **16** (2.74 mmol) in dry acetonitrile (25 mL) was added dropwise, and the reaction mixture was refluxed for 24 h. The solvent was evaporated to dryness, and the solid residue was dissolved in water (200 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The

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organic layer was dried (anhydrous Na_2SO_4) and the solvent was eliminated in rotary evaporator to yield compound **17b** as a dark yellow oil.

[3-*tert*-Butyl-5-[(4,5-dibutylimidazolyl)methyl]phenyl]-methanol 17c. A suspension of 4,5-dibutyl-1*H*-imidazole (0.45 g, 2.08 mmol) and finely powered KOH 85% (0.40 g, 5.41 mmol) in a mixture of dry dioxane (50 mL) and dry acetonitrile (10 mL) was vigorously stirred at room temperature for 4 h. To the brown suspension, a solution of compound **15** or **16** (2.08 mmol) in dry acetonitrile (12 mL) was added dropwise and the reaction mixture was refluxed for 17 h. The solvent was evaporated to dryness, and the solid residue was dissolved in water (150 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was dried (anhydrous Na_2SO_4), and the solvent was eliminated in rotary evaporator to yield compound **17c** as a dark yellow oil.

[[3-*tert*-Butyl-5-(chloromethyl)phenyl]methyl]imidazolium chloride 18b and 4,5-Dibutyl-1-[[3-*tert*-butyl-5-(chloromethyl)phenyl]methyl]imidazolium chloride 18c. To a solution of 1.75 mmol alcohol **17b** or **17c** (0.68 or 0.62 g respectively) in 25 mL of dry CH_2Cl_2 at 0 °C, a solution of $SOCl_2$ (0.9 mL, $d = 1.635$, 12.25 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was stirred at room temperature for 5 h and the solvent was then removed to dryness under reduced pressure. The brown residue was triturated with dry hexane (25 mL) and filtered to give compound **18b** or **18c** as a beige solid.

[[3-(Bromomethyl)-5-*tert*-butylphenyl]methyl]imidazolium Bromide 19b. To 1.82 g (7.46 mmol) of alcohol **17b** stirred at 0 °C, 10 mL (89.5 mmol) of HBr concentrated (48% v/v, aq) was added dropwise, and the reaction mixture remained at room temperature for 18 h. The suspension was filtered, and the solid was washed in water (5 × 20 mL) and dried in a vacuum oven (80 °C, 3 h) to give 2.28 g of **19b** as a white solid.

The physical data of compounds **3**−**10**, **12**, and **15**−**19** are listed in Table 2 (see the Supporting Information).

Acknowledgment. We thank DGESICYT (MEC, Spain) for financial supports through grant PB 98-1164. Thanks are also due to the Comissionat per a Universitats i Recerca de la Generalitat de Catalunya for grants 1999SGR-77. C.A. thanks the Departament d'Ensenyament de la Generalitat de Catalunya for a F.P.I. fellowship.

Supporting Information Available: Physical data of compounds **3**−**10**, **12**, and **15**−**19** (Table 2). ^1H and ^{13}C NMR data for all compounds discussed therein (Tables 3 and 4) and ^1H NMR spectra for all compounds lacking CHN analyses. This material is available free of charge via the Internet at htpp://pubs.acs.org.

JO0056794