JOURNAL OF combinatorial CHEMISTRY

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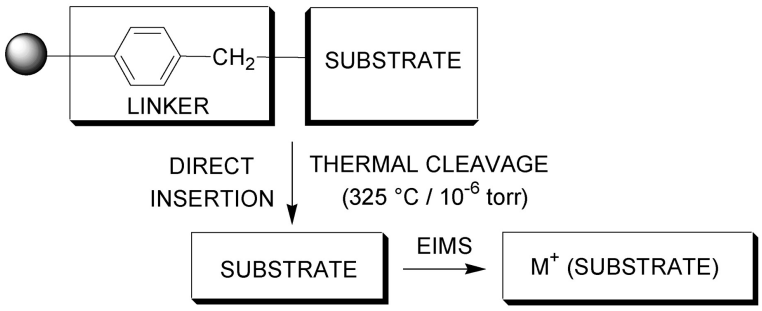
J. Comb. Chem., **2003**, 5 (2), 149-154• DOI: 10.1021/cc0200540 • Publication Date (Web): 13 December 2002



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Method for Analysis of Polymer-Supported Organic Compounds Using Mass Spectrometry Direct Insertion

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Received July 22, 2002

A new approach on the use of mass spectrometry direct-insertion and a quadrupole detector for analysis of organic compounds supported in solid phase has been developed. This is a simple and efficient method based on cleavage due to the thermal-instability of the benzylic group of most commercial resins. The cleavage of supported compounds takes place in the spectrometer as a consequence of the high temperature in the instrument's chamber. These compounds are detected using a similar fragmentation pattern and a molecular ion corresponding to the same compound obtained by traditional synthesis. Polymer degradation fragments do not interfere with the spectrum interpretation, because only a few peaks and low intensities are detected. We report here the identification of different types of compounds supported in Merrifield resin, such as bis-*o*-aminobenzamides and simple aromatic and aliphatic compounds, using this new approach.

Introduction

The rapid identification of solid-phase supported compounds is strategically important for scientists in combinatorial chemistry programs. Analyses of reaction species are needed at each synthetic step, preferably avoiding destructive cleavage methods. The key to success in these polymer-supported programs is the procedures by which the intermediates are fully characterized.[1]

Generation of libraries using combinatorial chemistry has focused primarily on the synthesis of several types of compounds, mainly those having biological activity. Solid-phase strategy provides a large number of compounds in a reasonable length of time. Moreover, automation of the synthetic process yields larger numbers of compounds in shorter times, leaving chemical characterization of chemical species as the slower step in the entire process.[2] Therefore, successful polymer-supported programs depend on the availability of analytical methods, especially those using nondestructive cleavage methods.

The most common procedures used to identify compounds using nondestructive characterization of supported organic compounds are reported, including IR spectroscopy,[3] NMR spectroscopy (gel-phase[4] and magic angle spinning[5]). Mass spectrometry (MS) has become an essential element in the repertoire of tools available for the characterization of combinatorial libraries; however, use of this analytical method which is considerably more sensitive than any other conventional techniques, such NMR and IR, is not common in the identification of polymer-supported organic compounds. Some mass spectral techniques have been successfully employed to determine the structure of supported compounds either delinked from a single polystyrene bead using matrix-assisted laser desorption ionization (MALDI) MS[6,7] or previous cleavage of the bond linking the organic compounds to the polymer by two different methods: (a) a 1% solution of trifluoroacetic acid (TFA) followed by electrospray MS[7] and (b) gaseous trifluoroacetic acid followed by MALDI-MS.[8] The popularity of this method stems in part from the chemical specificity, sensitivity, and speed of MS, with the inconvenience of expensive equipment available only to few a research groups. Thus, development of new strategies based on structural characterization is needed. In this regard, we focused on the quadrupole system, which is one of the most popular detectors in mass spectrometry equipment in the research world, but is uncommon for the analysis of polymer-supported species. In this paper, we show the results obtained on a mass spectrometer with a quadrupole detector for organic compounds supported on the solid phase.

Results and Discussion

We are proposing a simple method based on mass spectrometry direct-insertion, electronic impact as a method of ionization and a quadrupole detector for the analysis of polymer-supported species. This technique consists of placing 2−8 mg of resin with the supported organic compound in the direct insertion device and setting up the instrument's isothermal rate at 325 °C and acquisition of the spectrum according to the instrument's software. High temperature and vacuum promotes thermal cleavage on the benzylic position of the resin, liberating the supported molecules from the polymer. It was reasoned that the thermolysis is due to the thermal instability of the benzylic position of most of the resins used in organic synthesis in solid phase. Once the molecules are liberated, the mass spectrum is obtained in full-scan mode with the normal technique of electron impact ionization and a quadrupole detector. The spectrum shows

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10.1021/cc0200540 CCC: $25.00
Published on Web 12/13/2002

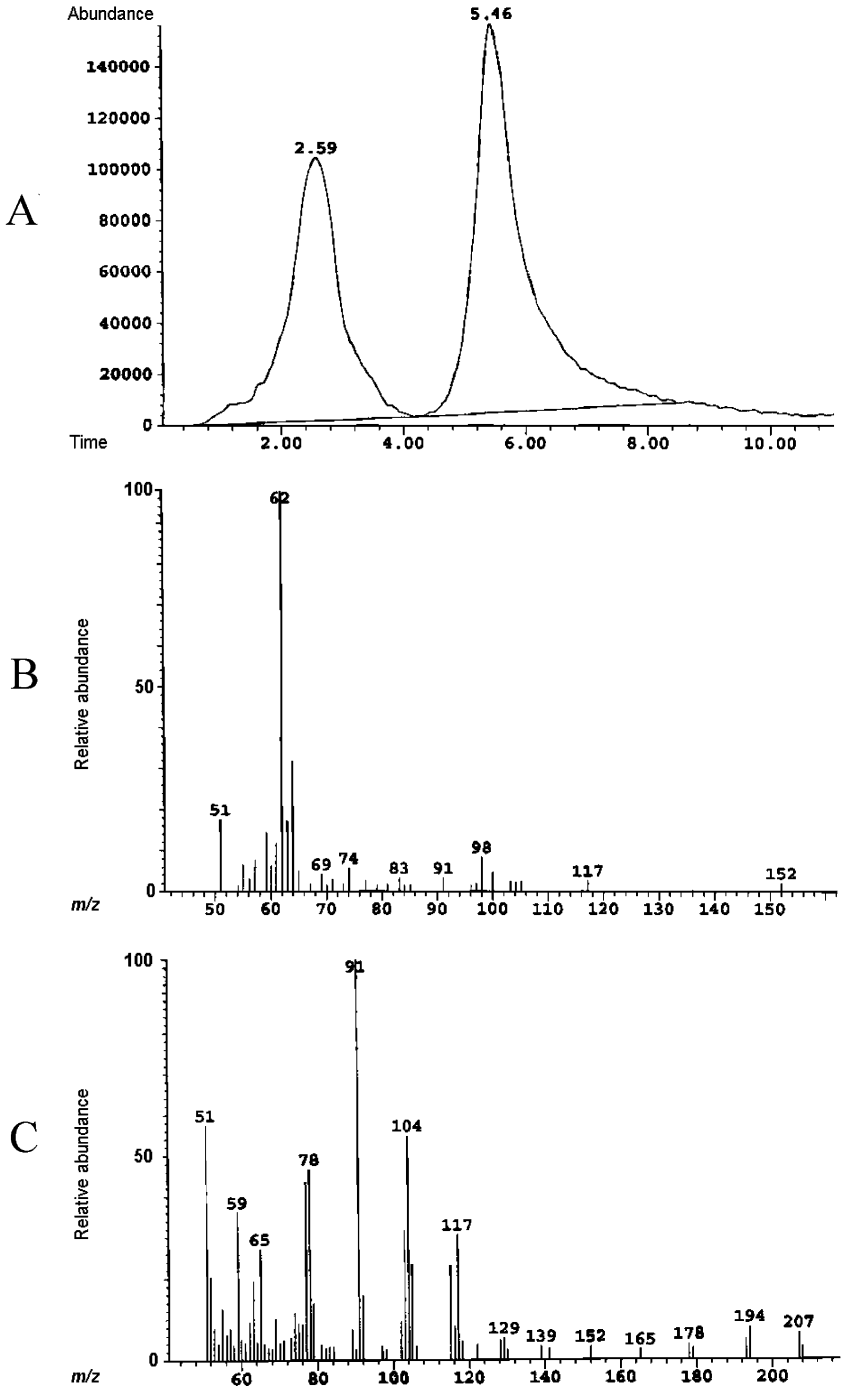


Figure 1. (A) Total ion chromatogram for the Merrifield resin. (B) Mass spectrum at 2.6 min. (C) Mass spectrum at 5.5 min.

the typical data of the liberated species. Thermal degradation of the polymer produces small fragments of polymer without interfering with interpretation of the spectra. Merrifield resin[9] degradation shows two stages (Figure 1), one at 2.6 min with typical fragmentation patterns of *m*/*z* 62, 98, 117, and 152, and the second stage at 5.5 min with fragment ions *m*/*z* 51, 78, 91, 104, 117, 194, and 207 (Figure 1). These observable fragment ions of Merrifield resin are less abundant than those of the thermally liberated organic compound, providing a good direction for characterization of the organic species supported on the solid phase using the proposed method.

To confirm the usefulness of this simple method, we examined the structures of different types of compounds supported on the solid phase. Their spectra were obtained and compared with those registered for the free compounds. The following worked examples serve to demonstrate how the approach was applied in practice. A series of bis-*o*-aminobenzamides with an aliphatic chain was prepared in solution (**1**−**4**) and then bound to Merrifield resin (**1a**−**4a**). Mass spectra for the free compounds and supported compounds were very similar. Table 1 shows the principal fragment ions for free organic (**1**−**4**) and polymer-supported (**1a**−**4a**) compounds. The abundance of the molecular ions and main fragment ions on the supported species is retained, as in the free compounds, thus making possible the identification of the different compounds. In Figure 2, mass spectra for the free compound hexyl-bis-*o*-aminobenzamide (**3**) and supported (**3a**) are presented. The molecular ion and frag-

Table 1. Diagnostic EIMS Fragment Ions of **1**−**4** and **1A**−**4A**

compd	M^+ [a]	$M^+ - 120$ [b]	*m/z* 120 [b]	*m/z* 92 [b]
1	312 (14)	1	100	52
1a	312 (16)	nd[c]	100	34
2	326 (25)	3	100	47
2a	326 (25)	2	100	55
3	354 (41)	1	100	21
3a	354 (27)	nd[c]	100	50
4	382 (36)	3	100	34
4a	382 (43)	3	100	34

[a] Rel int. percent in parentheses. [b] Rel int. percent shown. [c] Not detected.

mentation patterns obtained for the supported compound (**3a**) were in excellent agreement with those given by the free species (**3**), and most important, fragment ions resulting from the resin residue do not interfere with the characterization of this supported compound when using mass spectrometry direct insertion.Simple organic compounds, such as 2,4,6-trihydroxybenzaldehyde (**5**), 1,3,5-trihydroxybenzene (**6**), and 10-methanol-9-anthracencarboxaldehyde (**7**) were polymer-supported to generate **5a**, **6a**, and **7a**, respectively. These supported compounds were also identified by mass spectrometry direct insertion, with MS spectra similar to those of the free compounds (see Experimental Section). These types of compounds are useful as starting materials for more complex species synthesized in the solid phase in which every synthetic step could be monitored without using the traditional methods of destructive cleavage.

Finally, 1,4-cyclohexanediol (**8**) was supported on the resin and then oxidized in order to obtain 4-hydroxycyclohexanone (**9a**) bonded to the polymer. MS data for **9a** enabled the unknown to be unequivocally identified as a 4-hydroxycyclohexanone (**9**) as an oxidation product.

Conclusions

It is important to realize that the benefit of using this approach extends beyond improving the efficiency of the structure elucidation on the follow up of organic reaction in solid phase. A minimal detection limit was determined using supported octyl-bis-*o*-aminobenzamide (**4a**). Results showed that only 0.1 mg of resin gives a MS spectrum clear enough to identify the compound. This quantity of resin corresponds to 40 μg of delinked octyl-bis-*o*-aminobenzamide (**4**). After liberation of the compound as a result of the thermal instability of the benzylic position of most resins, the noise produced by cleavages of the polymer is not critical for the structure elucidation of the supported compound. Moreover, thermal degradation of the resin does not increase the frequency of the ion source's cleaning procedures, because fragmentation products of the polymer are not vaporized. Consequently, neither ion source nor detector is contaminated.

This method saves time and effort because of short times of analysis. The average time of analysis for different samples is around 12 min plus the waiting time for cooling the DIP device; only small quantities are needed for this destructive technique, and delinking organic species is not necessary. Best of all, this strategy of structure elucidation is available to any research laboratory with a mass spectrometer and a quadruple detector.

Experimental Section

Merrifield resin was purchased from Sigma Chemical Co. M7875, Chloromethylated divinylbenzene cross-linked polystyrene, 200−400 mesh, 1.19 meq/g, 1% cross-linked. Melting points were determined on an Electrothermal 88629 apparatus and are uncorrected. Infrared (IR) spectra were taken on a Perkin-Elmer FT-IR 1600 spectrometer. ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a Varian Mercury 200 spectrometer in $CDCl_3$ with TMS as internal standard at 200 MHZ and 50.289 MHz, respectively. Mass spectra were obtained on a Hewlett-Packard 5989 MS spectrometer at 70 eV by direct insertion. Combinatorial chemistry was carried out in a Reactor Quest Argonaut model SLN-210. Polymer-supporting yields were calculated according to Volhard titration of residual chlorine content in the Merrifield resin.[10]

General Method for the Synthesis of Alkyl-bis-*ortho*-aminobenzamides. A solution of alkyldiamine (9.0 mmol) in DMF (20 mL) was stirred, and isatoic anhydride (18.0 mmol, in ice bath) was dropped. The temperature was increased to 60 °C and stirred for 1 h. Hot water was added to the reaction mixture, and the solid was collected by filtration and recrystalizated from ethanol.

Propyl-bis-*o*-aminobenzamide (1). White solid, mp 171−172 °C. Yield 2.52 g (88%). IR (KBr) 3471, 3362, 3300, 3062, 1627, 1582, 1300, 1264, 1150 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 8.19 (t, J = 5.3 Hz, 2H, −N*H*), 7.47 (dd, J = 7.9, 1.3 Hz, 2H, H-6), 7.13 (ddd, J = 8.3, 8.1, 0.9 Hz, 2H, H-4), 6.68 (dd, J = 8.3, 0.9 Hz, 2H, H-3), 6.51 (ddd, J = 8.3, 7.9, 0.9 Hz, 2H, H-5), 6.35 (bs, −NH_2), 3.26 (td, J = 6.7, 5.5 Hz, 4H, CH_2-α), 1.74 (q, J = 6.8 Hz, 2H, CH_2-β). ^{13}C NMR (DMSO-d_6) δ 168.5 (C═O), 149.3 (C-2), 131.3 (C-4), 127.5 (C-6), 115.6 (C-5), 114.1 (C-1), 113.4 (C-3), 36.7 (C-α), 29.1 (C-β). For EIMS, see Table 1.

Butyl-bis-*o*-aminobenzamide (2). White solid, mp 199−200 °C. Yield 2.71 g (90%). IR (KBr) 3480, 3374, 3296, 3056, 2938, 1625, 1584, 1320, 1266, 1156 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 8.19 (t, J = 5.5 Hz, 2H, −N*H*), 7.46 (dd, J = 7.9, 1.3 Hz, 2H, H-6), 7.11 (ddd, J = 7.6, 7.1, 1.5 Hz, 2H, H-4), 6.67 (d, J = 7.5 Hz, 2H, H-3), 6.49 (dd, J = 7.9, 7.5 Hz, 2H, H-5), 6.37 (brs, −NH_2), 3.23 (brd, J = 5.5 Hz, 4H, CH_2-α), 1.54 (brs, 4H, CH_2-β). ^{13}C NMR (DMSO-d_6) δ 168.6 (C═O), 149.3 (C-2), 131.3 (C-4), 127.9 (C-6), 116.1 (C-5), 114.9 (C-1), 114.4 (C-3), 38.5 (C-α), 26.8 (C-β). For EIMS, see Table 1.

Hexyl-bis-*o*-aminobenzamide (3). White solid, mp 165 °C. Yield 2.77 g (85%). IR (KBr) 3474, 3376, 3334, 3066, 2918, 1631, 1580, 1542, 1317, 1260, 1156 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 8.16 (brt, 2H, −N*H*), 7.45 (d, J = 7.9 Hz, 2H, H-6), 7.11 (ddd, J = 8.3, 7.0, 1.2 Hz, 2H, H-4), 6.67 (d, J = 8.3 Hz, 2H, H-3), 6.49 (dd, J = 7.9, 7.1 Hz, 2H, H-5), 6.37 (brs, −NH_2), 3.20 (td, J = 6.5, 6.1 Hz, 4H, CH_2-α), 1.51 (brt, 4H, CH_2-β), 1.33 (brs, 4H, CH_2-γ). ^{13}C NMR (DMSO-d_6) δ 168.5 (C═O), 149.3 (C-2), 131.3 (C-4), 127.8 (C-6), 116.1 (C-5), 115.0 (C-1), 114.4 (C-3), 38.7 (C-α), 29.2 (C-β), 26.3 (C-γ). For EIMS, see Table 1.

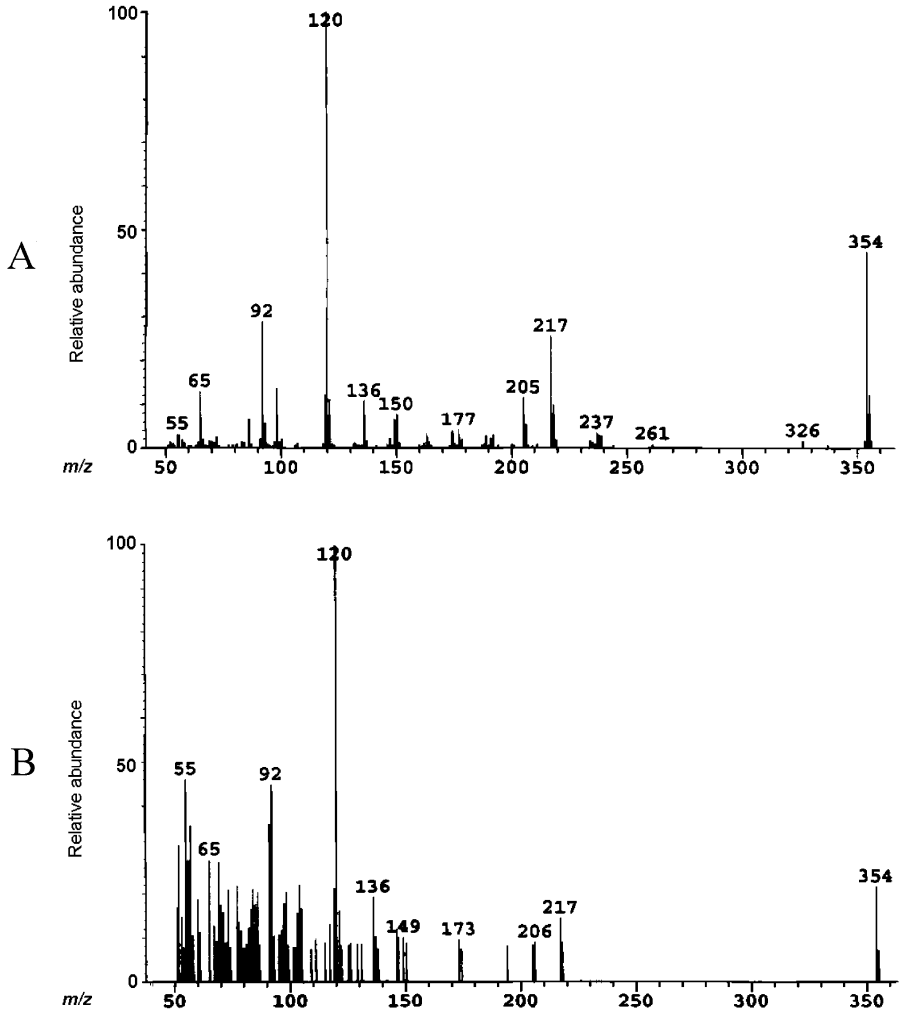
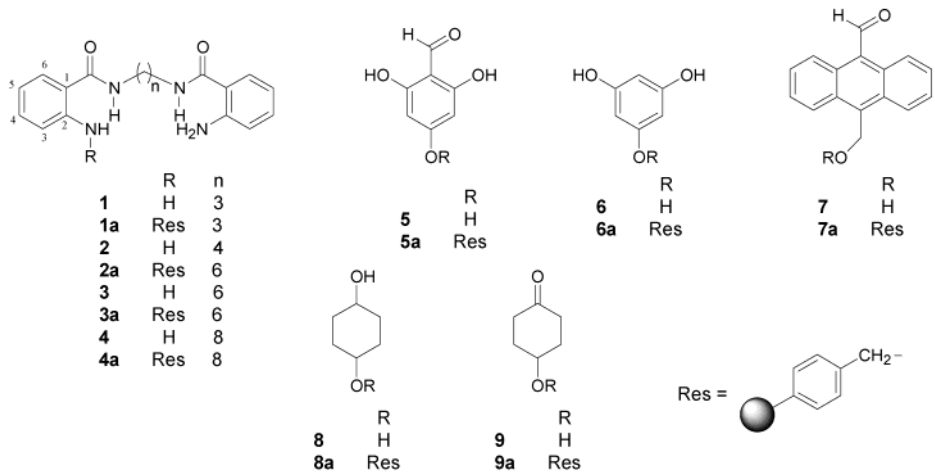


Figure 2. Mass spectra comparison for (A) free hexyl-bis-*o*-aminobenzamide (**3**) and (B) Polymer-supported hexyl-bis-*o*-aminobenzamide (**3a**).

Chart 1



Octyl-bis-*o*-aminobenzamide (4). White solid, mp 175−177 °C. Yield 2.99 g (85%). IR (KBr) 3475, 3364, 3296, 3067, 2927, 1625, 1580, 1544, 1318, 1262, 1155 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.18 (t, J = 5.5 Hz, 2H, −N*H*), 7.45 (dd, J = 7.9, 1.5 Hz, 2H, H-6), 7.12 (ddd, J = 8.2, 7.7, 1.5 Hz, 2H, H-4), 6.67 (dd, J = 8.2, 1.1 Hz, 2H, H-3), 6.50 (ddd, J = 7.9, 7.7, 1.1 Hz, 2H, H-5), 6.39 (brs, −NH_2), 3.19 (td, J = 6.5, 5.5 Hz, 4H, CH_2-α), 1.50 (m, 4H, CH_2-β), 1.30 (brs, 8H, H-CH_2-γ,δ). ^{13}C NMR (DMSO-d_6) δ 168.5 (C═O), 149.3 (C-2), 131.3 (C-4), 127.9 (C-6), 116.2 (C-1), 116.1 (C-5), 114.4 (C-3), 38.7 (C-α), 29.2 (C-β), 28.8 (C-δ), 26.5 (C-γ). For EIMS, see Table 1.

General Method for the Synthesis of Polymer-Supported (PS) Alkil-bis-*orto*-aminobenzamides. To the Mer-

rifield resin (1.19 meq/g) swelled in DMF (30 mL) was added K_2CO_3 (6.0 mmol) and the appropriate propyl-bis-*o*-aminobenzamide (6.0 mmol) in 15 mL of DMF at room temperature. The temperature was increased to 70 °C, and the reaction was mixed for 6 h. The reaction was cooled to room temperature and filtered, and the resin was washed with H_2O, MeOH, THF, Et_2O, and DCM (3 × 25 mL each).

PS Propyl-bis-*o*-aminobenzamide (1a). Yield 96%. IR (KBr) 3453, 3353, 3021, 2918, 1654, 1600, 1492, 1451 cm^{-1}. For EIMS, see Table 1.

PS Butyl-bis-*o*-aminobenzamide (2a). Yield 95%. IR (KBr) 3450, 3355, 3019, 2918, 1647, 11597, 1490, 1450 cm^{-1}. For EIMS, see Table 1.

PS Hexyl-bis-*o*-aminobenzamide (3a). Yield 96%. IR (KBr) 3455, 3353, 3020, 2915, 1652, 1603, 1492, 1451 cm^{-1}. For EIMS, see Table 1.

PS Octyl-bis-*o*-aminobenzamide (4a). Yield 94%. IR (KBr) 3449, 3348, 3025, 2915, 1652, 1605, 1490, 1455 cm^{-1}. For EIMS, see Table 1.

2,4,6-Trihydroxybenzaldehyde (5). Aldrich Chemical Co. T6,540-4. EIMS *m*/*z* [M^+] 154 (100), [$M^+ - 1$] (97), 136 [$M^+ - H_2O$] (4), 125 [$M^+ - 29$] (2), 108 (12), 69 (60).

PS 2,4,6-Trihydroxybenzaldehyde (5a). To a solution of 1.8 g (11.9 mmol) of 2,4,6-trihydroxybenzaldehyde in DMF (30 mL) in an ice bath was slowly added NaH (0.342 g, 14.25 mmol), and the reaction was mixed at room temperature for 15 min. Merrifield resin 5 g (1.19 meq/g) was added, and the reaction was heated at 90 °C for 24 h. The reaction was cooled to room temperature and filtered, and the resin was washed with DMF, MeOH, H_2O, MeOH, and DCM (3 × 20 mL each). The resin was dried in vacuo to provide **5a** (90%). IR (KBr) 3448, 3025, 2912, 1653, 1600 cm^{-1}. EIMS *m*/*z* [M^+] 154 (100), [$M^+ - 1$] (94), 125 [$M^+ - 29$] (nd), 108 (11), 69 (54).

1,3,5-Trihydroxybenzene (Phloroglucinol) (6). Spectrum Quality Products, Inc. PH165. EIMS *m*/*z* [M^+] 126 (100), 111 (6), 97 (14), 85 (22), 80 (19), 69 (34), 55 (13).

PS 1,3,5-Trihydroxybenzene (6a). To a solution of 1.78 g (11.9 meq) of 1,3,5-trihydroxybenzene in DMF (30 mL) in an ice bath were added Merrifield resin (5 g, 1.19 meq/g) and Na_2CO_3 (0.7 g, 6.6 mmol), and the reaction was heated at 90 °C for 24 h. The reaction was cooled to room temperature and filtered, and the resin was washed with DMF, MeOH, H_2O, MeOH, and DCM (3 × 20 mL each) and dried in vacuo (yield 88%). IR (KBr) 3416, 3018, 2929, 1675, 1450 cm^{-1}. EIMS *m*/*z* [M^+] 126 (54), 111 (6), 97 (13), 85 (14), 80 (4), 69 (38), 55 (75).

10-Methanol-9-anthracencarboxaldehyde (7). To a solution of trimethylsulfonium iodide 12.78 g (62.43 mmol) in DMSO (20 mL) were added NaH (72.09 mmol) and anthraquinone (5.0 g, 24.03 mmol) in DMSO (20 mL), and the reaction was heated at 60 °C for 3 h. The final mixture was diluted with water (100 mL) and extracted with DCM (3 × 70 mL). The combined organic phases were washed with water (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed under vacuum, and crystallization from Et_2O gave 4.1 g of 9,10-anthracendiepoxide (yield 82%). IR (KBr) 3040, 1951, 1652, 1320 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 7.37(s, 8H), 3.24 (s, 4H, C*H*$_2$O). EIMS *m*/*z* [M^+] 236. To a solution of 9,10-anthracendiepoxide (2.0 g, 8.47 mmol) in acetonitrile (100 mL) was added LiCl (0.716 g, 16.94 mmol), and the mixture was stirred and refluxed for 20 h. The reaction was cooled, CH_2Cl_2 (50 mL) was added, and the solid collected by filtration gave **7**, 1.49 g (yield 75%). IR (KBr) 3396, 1667, 1259, 980 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 11.45 (C*H*═O), 8.91 (dd, J = 8.6, 1.8 Hz, 2H, H-1, 8), 8.58 (dd, J = 7.2, 4.5 Hz, 2H, H-4, -5), 7.67 (m, 4H, H-2, -3, -6, -7), 5.50 (s, 1H, O*H*), 3.42 (s, 2H, C*H*$_2$-O). EIMS *m*/*z* [M^+] 236 (88), 208 (10), 207 (62), 189 (27), 179 (100), 152 (12).

PS 10-Methanol-9-anthracencarboxaldehyde (7a). To the Merrifield resin (1.0 g, 1.19 meq/g) swelled in DMF (10 mL) were added 10-methanol-9-anthracencarboxaldehyde (0.281 g, 1.19 mmol) and NaH (0.071 g, 1.75 mmol). The temperature was increased to 96 °C, and the reaction was mixed for 6 h. The reaction was cooled to room temperature and filtered, and the resin was washed with DMF, MeOH, H_2O, MeOH, and DCM (3 × 5 mL each) to yield 0.94 g (yield 73%). IR (KBr) 3052, 1676, 1152, 685 cm^{-1}. EIMS *m*/*z* [M^+] 236 (23), 208 (100), 207 (28), 189 (nd), 179 (31), 152 (52).

PS 4-Hydroxy-cyclohexanone (9a). To a solution of 1,4-cyclohexanediol (**8**) 3.45 g (29.7 mmol) in THF (20 mL) was added NaH (1.64 g, 68.3 mmol), and the mixture was stirred at room temperature for 2 h. After this time, the Merrifield resin (5.0 g, 1.19 meq/g) swelled in THF (50 mL) was added, and the reaction was refluxed for 72 h. The reaction was cooled to room temperature and filtered, and the resin was washed with THF, MeOH, and DCM (3 × 25 mL each) to obtain polymer-supported 1,4-cyclohexanediol (**8a**), yield 89%. IR (KBr) 3283, 2941, 1075 cm^{-1}. To **8a** (1.106 g 1.19 mmol/g) swelled in DMF (15 mL) were added 4-methylmorpholine *N*-oxide (NMO) (0.5 g, 3.5 mmol) in 10 mL of DMF and tetrapropylammonium perruthenate (VII) (TPAP) (0.025 g, 0.071 mmol) under N_2 atmosphere. The reaction was stirred for 90 h at room temperature. The reaction was filtered, and the resin was washed with DMF, THF, and CH_2Cl_2 (3 × 30 mL each) to yield **9a** (1.02 g, 93%). IR (KBr) 1708, 1603, 1242, 1158, 1054, 1017 cm^{-1}. EIMS *m*/*z* [M^+] 114 (12), 112 (4), 86 (9), 71 (100), 57 (56).

Acknowledgment. We gratefully acknowledge support for this project by Consejo Nacional de Ciencia y Tecnología, México (CONACyT, Grant no. 28488-E) and Consejo Nacional de Educación Tecnológica, México (COSNET, Grants nos. 623.97-P and 630.01-P). The authors are indebted to Dr. Miguel Parra-Hake for encouragement. Adrián Ochoa, Marisela Castillo, Karla Espinoza, and Tania González thank CONACyT for graduate fellowships.

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