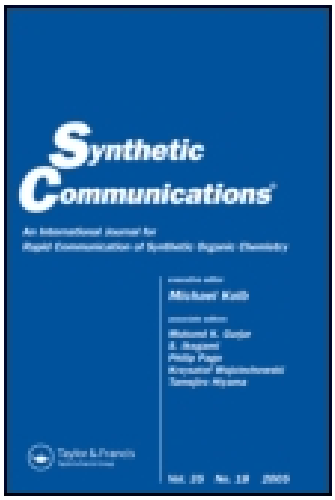

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FACILE PREPARATION OF O-SUBSTITUTED ACYCLIC PHENOL-FORMALDEHYDE OLIGOMERS

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FACILE PREPARATION OF *O*-SUBSTITUTED ACYCLIC PHENOL–FORMALDEHYDE OLIGOMERS

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ABSTRACT

Acyclic *p*-cresol-formaldehyde oligomers (dimer, trimer, and tetramer) having ester, carboxylic acid, amide groups on the phenolic OH groups were prepared in good yields.

Key Words: Acyclic phenol-formaldehyde oligomer; Calixarene; Molecular recognition

Calixarenes are cyclic phenol–formaldehyde condensation products, which are extensively investigated as host molecules and enzyme mimics.[1] The corresponding acyclic oligomers have also been found to form stable complexes with organic molecules, although only a few examples are available.[2] Recently, we have reported that acyclic phenol–formaldehyde oligomers with methylene bridges ortho to the phenolic OH group and their sulfur-bridged and carbonyl-bridged analogs.[3] The inclusion behavior

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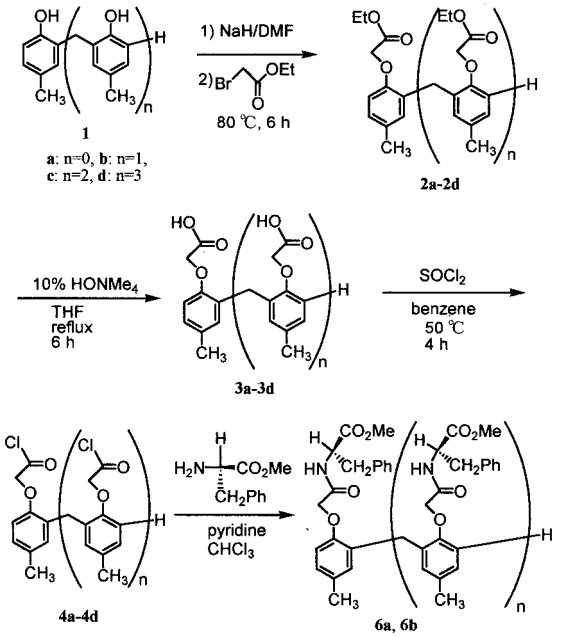
was remarkably influenced by the bridge moieties and the number of the phenol units. As an extension of our studies, we synthesized *O*-substituted acyclic phenol–formaldehyde oligomers by replacing the phenolic hydrogens with functional groups such as ester, carboxylic acid, and amide. It is known that calixarene derivatives having such functional groups serve as host molecules toward anions, cations, and neutral molecules.[4–6] Here the results will be reported.

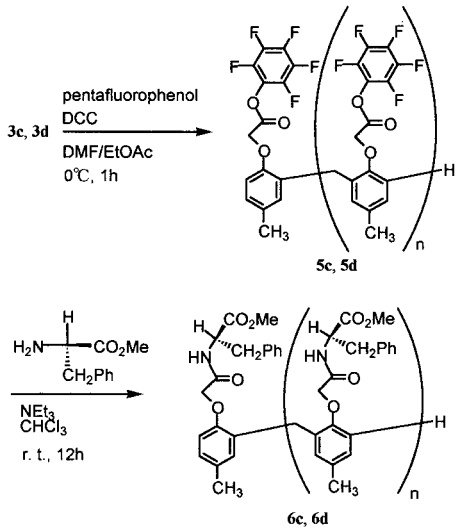
Acyclic *p*-cresol-formaldehyde oligomers (**1**) were synthesized by the stepwise method based on repeated hydroxymethylation–arylation reaction sequences.[3a] **1** were treated with 2-bromoethyl acetate and NaH in *N*,*N*-dimethylformamide at 80°C to generate the ethyl ester derivatives (**2**) in 36–83% yields. Hydrolysis of **2** was carried out by the use of 10% tetramethylammonium hydroxide aqueous solution to afford the corresponding carboxylic acids (**3**) in 70–83% yields.[5] We examined the synthesis of amide derivative (**6**) by the reaction of an amine with the acid chloride (**4**), which was prepared by the chlorination of **3** by using thionyl chloride.[6] Reactions of monomer (**4a**) or dimer (**4b**) with L-phenylalanine methyl ester as an amine gave the required amide derivatives (**6a** and **6b**) in 30 and 80% yields, respectively. However, the similar reactions using trimer (**4c**) and tetramer (**4d**) gave complex materials due to the instability of **4c** and **4d**. Therefore, we prepared the pentafluorophenyl ester (**5c** and **5d**) in 86 and 66% yields, respectively, employing a dicyclohexylcarbodiimide (DCC) mediated esterifications of **3c** and **3d** with pentafluorophenol.[7] The reactions of **5c** and **5d** with L-phenylalanine methyl ester gave the corresponding amides (**6c** and **6d**) in 52 and 67% yields, respectively.

The structures of the products (**2**, **3**, **4**, **5**, and **6**) were established on the basis of their spectral data and elemental analysis. Their ^{1}H and ^{13}C NMR spectral data are compatible with the deduced structures as shown in Schs. 1 and 2. In IR spectra, the characteristic absorptions of carbonyl stretching bands of the products (**2**: ca. 1758 cm^{-1} for ester group, **3**: ca.1730 cm^{-1} for carboxylic acid group, **4**: ca. 1800 cm^{-1} for acid chloride group, **5**: ca.1800 cm^{-1} for ester group, **6**: ca. 1750 cm^{-1} for ester group and ca. 1670 cm^{-1} for amide group) were observed. The Fab-mass spectra were shown at molecular ion peaks $(M+H)^{+}$ corresponding to the products. Interestingly, trimer (**2c** and **3c**) and tetramer (**2d** and **3d**) bearing ethyl ester or carboxylic acid groups on the phenolic OH moieties also gave $(M+Na)^{+}$ peaks clearly. This result suggests that these acyclic oligomers can serve as an ionophore for alkaline metal cations.

In order to elucidate the sodium cation affinity of **2**, we measured ^{13}C NMR spectra of **2** (50 mM) in the presence of sodium picrate (50 mM) in $CDCl_3 : CD_3OD$, 1 : 1 solution at 20°C. The large downfield shift was observed for the carbonyl carbon atom of **2c** ($\Delta\delta$ co = +0.31, +0.14 ppm)



Scheme 1.



Scheme 2.

and **2d** ($\Delta\delta$ co = +0.35, +0.12 ppm) in the presence of sodium picrate. It can be rationalized by the C=O···Na^+ interaction. In contrast, the chemical shifts of **2a** ($\Delta\delta$ co = +0.05 ppm) and **2b** ($\Delta\delta$ co = +0.08 ppm) scarcely changed. These results suggest that the phenol–formaldehyde trimer and tetramer skeleton play an important role to bind sodium cation.

In summary, we have achieved the preparation of acyclic phenol–formaldehyde oligomers bearing ester, carboxylic acid, and amide groups on the hydroxyl groups. The study of the molecular recognition using **2**, **3**, and **6** is now in progress.

EXPERIMENTAL

Melting points were measured by Yanagimoto micro melting point apparatus and were not corrected. ^{1}H and ^{13}C NMR spectra were measured by Varian INIOVA 500 spectrophotometers (500 MHz for ^{1}H, 125 MHz for ^{13}C). Fab-mass spectra were collected by JEOL JMS AX-505HA spectrometer using *m*-nitrobenzyl alcohol as a matrix. IR spectra were recorded on FORIBA FT-720 spectrophotometer. All chemicals were reagent grade and were used without further purification. Compounds (**1b–1d**) were prepared by methods already reported in the literature.[3a]

General Procedure for the Preparation of 2

To a solution of **1** (10 mmol) in 90 mL of DMF was added NaH (17 mmol for **1a**, 34 mmol for **1b**, 51 mmol for **1c**, 68 mmol for **1d**). Subsequently, 2-bromoethyl acetate (13 mmol for **1a**, 26 mmol for **1b**, 39 mmol for **1c**, 52 mmol for **1d**) was added and the mixture was heated at 80°C for 2 h. The reaction mixture was cooled and treated with a second portion of NaH. 2-Bromoethyl acetate was then added. The reaction mixture was heated again at 80°C for a further 2 h. This operation was repeated untile no starting materials, followed by ^{1}H NMR spectra. Removal of DMF under reduced pressure gave oily residue, which was dissolved with chloroform. The solution was washed with water and then the organic layer was dried over anhydrous sodium sulfate. Removal of chloroform gave oily residue, which was subjected to column chromatography on silica gel using hexane : ethyl acetate 1 : 4 as an eluent to give **2** as a pure form.

2a: The yield is 83%. Oil. IR ($CDCl_3$) 1758 (ν_{CO}) cm^{-1}. Fab-mass *m*/*z* 195 (M+H)$^+$. ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.0 Hz, –OCH_2CH_3, 3H), 2.29 (s, Ar-CH_3, 3H), 4.27 (q, J = 7.0 Hz, –OCH_2CH_3, 2H), 4.59 (s, –OCH_2CO–, 2H), 6.81 (m, Ar-H × 2, 2H), 7.09 (m, Ar-H × 2, 2H). ^{13}C NMR ($CDCl_3$) δ

14.2, 20.5, 61.3, 65.6, 114.5, 130.0, 131.0, 155.7, 169.1. Elemental Analysis Calcd for $C_{11}H_{14}O_3 \cdot 0.25\,(H_2O)$: C, 66.48; H, 7.35. Found: C, 66.16; H, 7.60.

2b: The yield is 56%. M.p. 87–92°C. IR ($CDCl_3$) 1758 (ν_{CO}) cm^{-1}. Fab-mass m/z 401 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.29 (t, $J = 7.0$ Hz, $-OCH_2CH_3 \times 2$, 6H), 2.22 (s, Ar-$CH_3 \times 2$, 6H), 4.05 (s, $ArCH_2Ar$, 2H), 4.25 (q, $J = 7.0$ Hz, $-OCH_2CH_3 \times 2$, 4H), 4.58 (s, $-OCH_2CO- \times 2$, 4H), 6.65 (d, $J =$ 8.0 Hz, Ar-H × 2, 2H), 6.93 (dd, $J =$ 1.5, 8.0 Hz, Ar-H × 2, 2H), 7.02 (d, $J =$ 1.5 Hz, Ar-H × 2, 2H). ^{13}C NMR ($CDCl_3$) δ 14.2, 20.6, 29.7, 61.1, 66.2, 111.6, 127.3, 129.7, 130.8, 131.8, 153.9, 169.3. Elemental Analysis Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.17; H, 7.36.

2c: The yield is 36%. Oil. IR ($CDCl_3$) 1758 (ν_{CO}) cm^{-1}. Fab-mass m/z 607 $(M+H)^+$, 629 $(M+Na)^+$. ^1H NMR ($CDCl_3$) δ 1.28 (t, $J = 7.0$ Hz, $-OCH_2CH_3 \times 3$, 9H), 2.16 (s, Ar-CH_3, 3H), 2.23 (s, Ar-$CH_3 \times 2$, 6H), 4.06 (s, $ArCH_2Ar \times 2$, 4H), 4.25 (q, $J = 7.0$ Hz, $-OCH_2CH_3 \times 3$, 6H), 4.37 (s, $-OCH_2CO-$, 2H), 4.59 (s, $-OCH_2CO- \times 2$, 4H), 6.66 (d, $J = 8.0$ Hz, Ar-H × 2, 2H), 6.76 (s, Ar-H × 2, 2H), 6.91 (d, $J = 2.5$ Hz, Ar-H × 2, 2H), 6.95 (dd, $J = 2.5$, 8.0 Hz, Ar-H × 2, 2H). ^{13}C NMR ($CDCl_3$) δ 14.1, 20.5, 20.9, 29.5, 60.9, 61.0, 66.1, 70.2, 111.7, 127.5, 129.5, 129.7, 130.9, 131.6, 133.2, 133.7, 152.8, 153.9, 169.1, 169.6. Elemental Analysis Calcd for $C_{35}H_{42}O_9 \cdot 1.4(H_2O)$ C, 66.52; H, 7.15. Found: C, 66.74; H, 7.15.

2d: The yield is 50%. Oil. IR ($CDCl_3$) 1758 (ν_{CO}) cm^{-1}. Fab-mass m/z 813 $(M+Na)^+$, 835 $(M+Na)^+$. ^1H NMR ($CDCl_3$) δ 1.27 (t, $J = 7.0$ Hz, $-OCH_2CH_3 \times 2$, 6H), 1.28 (t, $J = 7.0$ Hz, $-OCH_2CH_3 \times 2$, 6H), 2.15 (s, Ar-$CH_3 \times 2$, 6H), 2.23 (s, Ar-$CH_3 \times 2$, 6H), 4.05 (s, $ArCH_2Ar \times 2$, 4H), 4.07 (s, $ArCH_2$, 2H), 4.21 (q, $J = 7.0$ Hz, $-OCH_2CH_3 \times 2$, 4H), 4.24 (q, $J = 7.0$ Hz, $-OCH_2CH_3 \times 2$, 4H), 4.35 (s, $-OCH_2CO- \times 2$, 4H), 4.59 (s, $-OCH_2CO- \times 2$, 4H), 6.65 (d, $J = 8.5$ Hz, Ar-H × 2, 2H), 6.68 (d, $J = 2.5$ Hz, Ar-H × 2, 2H), 6.77 (d, $J = 1.5$ Hz, Ar-H × 2, 2H), 6.90 (d, $J = 1.5$ Hz, Ar-H × 2, 2H), 6.95 (dd, $J = 2.5$, 8.5 Hz, Ar-H × 2, 2H). ^{13}C NMR ($CDCl_3$) δ 14.1, 14.2, 20.6, 20.9, 29.5, 61.0, 61.1, 66.0, 70.1, 111.5, 127.5, 129.4, 129.5, 129.7, 130.9, 131.6, 133.2, 133.3, 133.9, 152.8, 153.8, 169.1, 169.2. Elemental Analysis Calcd for $C_{47}H_{56}O_{12} \cdot 2.7(H_2O)$, C, 65.52; H, 7.18. Found: C, 65.43; H, 6.95.

General Procedure for the Preparation of 3

A solution of **2** (10 mmol) in THF (125 mL for **2a**, 250 mL of **2b**, 375 mL for **2c**, 500 mL for **2d)** was added to 10% aqueous tetramethylammonium hydroxide (125 mL for **2a**, 250 mL of **2b**, 375 mL for **2c**, 500 mL for **2d**). The mixture was refluxed for 24 h. After cooling to room temperature, the reaction mixture was acidified with 35% HCl aqueous solution and stirred for

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12 h. The resulting white precipitate was collected by filtration and washed with water. The precipitate was dried under reduced pressure.

3a: The yield is 70%. M.p. 137–140°C. IR ($CDCl_3$) 3430 (ν_{OH}), 1733 (ν_{CO}), 1702 (ν_{CO}) cm^{-1}. Fab-mass *m/z* 166 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ. 2.30 (s, Ar-CH_3, 3H), 4.66 (s, –OCH_2CO–, 2H), 6.83 (m, Ar-H × 2, 2H), 7.11 (m, Ar-H × 2, 2H), 7.80 (bs, OH, 1H). ^{13}C NMR (DMSO-d_6) δ 20.5, 65.0, 114.5, 130.1, 131.4, 155.2, 174.2. Elemental Analysis Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.20; H, 6.40.

3b: The yield is 85%. M.p. 248–253°C. IR ($CDCl_3$) 3403 (ν_{OH}), 1737 (ν_{CO}) cm^{-1}. Fab-mass *m/z* 345 $(M+H)^+$, 367 $(M+Na)^+$. ^1H NMR (DMSO-d_6) δ 2.14 (s, Ar-CH_3 × 2, 6H), 3.87 (s, $ArCH_2Ar$, 2H), 4.63 (s, –OCH_2CO– × 2, 4H), 6.73 (d, $J = 8.0$ Hz, Ar-H × 2, 2H), 6.91 (dd, $J =$ 1.5, 8.0 Hz, Ar-H × 2, 2H), 6.96 (d, $J = 1.5$ Hz, Ar-H × 2, 2H). ^{13}C NMR (DMSO-d_6) δ 20.4, 29.2, 65.2, 111.6, 127.5, 128.8, 129.6, 131.3, 153.8, 170.7. Elemental Analysis Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.18; H, 6.03.

3c: The yield is 73%. M.p. 243–245°C. IR ($CDCl_3$) 3437 (ν_{OH}), 1726 (ν_{CO}) cm^{-1}. Fab-mass *m/z* 523 $(M+H)^+$, 545 $(M+Na)^+$. ^1H NMR (DMSO-d_6) δ 2.06 (s, Ar-CH_3, 3H), 2.17 (s, Ar-CH_3 × 2, 6H), 3.91 (s, $ArCH_2Ar$ × 2, 4H), 4.33 (s, –OCH_2CO–, 2H), 4.64 (s, –OCH_2CO– × 2, 4H), 6.74 (s, Ar-H × 2, 2H), 6.76 (d, $J = 8.0$ Hz, Ar-H × 2, 2H), 6.88 (d, $J = 1.5$ Hz, Ar-H × 2, 2H), 6.96 (dd, $J = 1.5$, 8.0 Hz, Ar-H × 2, 2H). ^{13}C NMR (DMSO-d_6) δ 20.3, 20.6, 29.1, 65.0, 69.8, 111.7, 127.6, 128.7, 129.1, 129.5, 131.2, 132.9, 133.2, 152.5, 153.7, 170.3, 170.5. Elemental Analysis Calcd for $C_{29}H_{30}O_9$: C, 66.66; H, 5.79. Found: C, 66.67; H, 6.03.

3d: The yield is 70 %. M.p. 237–240°C. IR ($CDCl_3$) 3448 (ν_{OH}), 1728 (ν_{CO}) cm^{-1}. Fab-mass *m/z* 701 $(M+H)^+$, 723 $(M+Na)^+$. ^1H NMR (DMSO-d_6) δ 2.07 (s, Ar-CH_3 × 2, 6H), 2.16 (s, Ar-CH_3 × 2, 6H), 3.91 (s, $ArCH_2Ar$ × 2, 4H), 3.96 (s, $ArCH_2Ar$, 2H), 4.28 (s, –OCH_2CO– × 2, 4H), 4.61 (s, –OCH_2CO– × 2, 4H), 6.63 (d, $J = 1.5$ Hz, Ar-H × 2, 2H), 6.75 (d, $J = 8.0$ Hz, Ar-H × 2, 2H), 6.77 (d, $J = 1.5$ Hz, Ar-H × 2, 2H), 6.86 (d, $J = 1.5$ Hz, Ar-H × 2, 2H), 6.95 (dd, $J = 1.5$, 8.0 Hz, Ar-H × 2, 2H). ^{13}C NMR (DMSO-d_6) δ 20.5, 20.8, 29.3, 29.4, 65.2, 70.0, 111.9, 127.9, 128.9, 129.3, 129.6, 129.8, 131.4, 133.3, 133.4, 133.5, 152.9, 153.8, 170.5, 170.7. Elemental Analysis Calcd for $C_{39}H_{40}O_{12}$: C, 66.85; H, 5.75. Found: C, 66.59; H, 6.06.

General Procedure for the Preparation of 4

To a suspention of **3** (4 mmol) in dry benzene (40–200 mL) was added thionyl chloride (40 mmol for **3a**, 80 mmol for **3b**, 120 mmol for **3c**,

150 mmol for **3d**) at room temperature over 1 h. After the addition was completed, the mixture was stirred at 50°C for 3 h. Removal of benzene and excess thionyl chloride by rotary evaporator gave **4** as pale yellow crystals. The product is instability on the purification process. Therefore, **4** were used at next step without further purification.

4a: The yield 98%. M.p. 68–71°C. IR (KBr) 1809 (ν_{CO}) cm^{-1}. Fab-mass m/z 185 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.30 (s, Ar-CH_3, 3H), 4.92 (s, –OCH_2CO, 2H), 6.80 (m, Ar-H × 2, 2H), 7.11 (m, Ar-H × 2, 2H). ^{13}C NMR ($CDCl_3$) δ 20.5, 72.9, 114.7, 130.2, 132.2, 154.8, 170.4.

4b: The yield 98%. M.p. 110–113°C. IR (KBr) 1822 (ν_{CO}) 1801 (ν_{CO}) cm^{-1}. Fab-mass m/z 381 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.17 (s, Ar-CH_3 × 2, 6H), 3.92 (s, $ArCH_2Ar$, 2H), 4.83 (s, –OCH_2CO × 2, 4H), 6.55 (d, $J = 8.0$ Hz, Ar-H × 2, 2H), 6.88 (d, $J = 2.0$ Hz, Ar-H × 2, 2H), 6.89 (dd, $J = 2.0$, 8.0 Hz, Ar-H × 2, 2H). ^{13}C NMR ($CDCl_3$) δ 20.5, 29.8, 73.0, 111.5, 127.6, 131.9, 152.7, 170.3.

4c: The yield is 95%. M.p. 99–104°C. IR (KBr) 1801 (ν_{CO}) cm^{-1}. Fab-mass m/z 577 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.19 (s, Ar-CH_3, 3H), 2.24 (s, Ar-CH_3 × 2, 6H), 3.97 (s, $ArCH_2Ar$ × 2, 4H), 4.52 (s, –OCH_2CO–, 2H), 4.81 (s, –OCH_2CO– × 2, 4H), 6.63 (d, $J =$ 8.0Hz, Ar-H × 2, 2H), 6.71 (s, Ar-H × 2, 2H), 6.88 (d, $J =$ 2.0 Hz, Ar-H × 2, 2H), 6.98 (dd, $J =$ 2.0, 8.0 Hz, Ar-H × 2, 2H). ^{13}C NMR ($CDCl_3$) δ 20.5, 20.8, 30.1, 73.0, 76.7, 111.8, 128.0, 129.3, 130.0, 131.8, 132.1, 132.8, 134.6, 151.8, 152.7, 169.7, 170.2.

4d: The yield is 93%. M.p. 101–103°C. IR (KBr) 1805 (ν_{CO}) cm^{-1}. Fab-mass m/z 774 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.20 (s, Ar-CH_3 × 2, 6H), 2.24 (s, Ar-CH_3 × 2, 6H), 3.97 (s, $ArCH_2Ar$ × 2, 4H), 3.98 (s, $ArCH_2Ar$, 2H), 4.53 (s, –OCH_2CO– × 2, 4H), 4.92 (s, –OCH_2CO– × 2, 4H), 6.64 (d, $J = 8.0$Hz, Ar-H × 2, 2H), 6.73 (d, $J =$ 2.0 Hz, Ar-H × 2, 2H), 6.78 (d, $J = 2.0$ Hz, Ar-H × 2, 2H), 6.88 (d, $J =$ 2.0 Hz, Ar-H × 2, 2H), 7.00 (dd, $J = 2.0$, 8.0 Hz, Ar-H × 2, 2H). ^{13}C NMR ($CDCl_3$) δ 20.6, 20.9, 30.1, 30.6, 72.8, 76.6, 111.6, 128.0, 129.0, 129.7, 130.3, 131.7, 132.1, 132.8, 132.9, 134.8, 151.9, 152.6, 169.8, 170.3.

General Procedure for the Preparation of 6a and 6b

To a mixture of L-phenyl alanine methyl ester (1.0 mmol for **4a**, 2.0 mmol for **4b**) and pridine (1.5 mmol for **4a**, 3.0 mmol for **4b**) in dry chloroform (10 mL) was added a solution of **4** (0.5 mmol) in dry chloroform (10 mL) at 0°C over 1 h. After the addition was complete, the mixture was stirred at room temperature for 24 h. The reaction mixture was washed with 10% HCl aqueous solution and water. The organic layer was dried over anhydrous sodium sulfate. Removal of solvent gave oily residue, which was

subjected to column chromatography on silica gel using hexane: ethyl acetate 1 : 2 as an eluent to give **6** as colorless crystals.

6a: The yield is 30%. M.p. 68–71°C. IR (KBr) 3415 (ν_{NH}), 1751 (ν_{CO}), 1664 (ν_{CO}) cm^{-1}. Fab-mass *m/z* 327 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.30 (s, Ar-CH_3, 3H), 3.14 (d, $J=$ 6.0 Hz, CH_2Ph, 2H), 3.72 (s, CO_2Me, 3H), 4.94 (td, $J=6.0$, 8.4 Hz, NCHR, 1H), 6.30–6.80 (m, Ar-H × 2, 2H), 6.98–7.12 (m, Ar-H × 2, Ph-H × 2 and NH, 5H), 7.21-7.26 (m, Ph-H × 3, 3H). ^{13}C NMR ($CDCl_3$) δ 20.5, 37.9, 52.4, 52.5, 67.4, 114.5, 127.2, 128.6, 129.2, 130.1, 131.4, 135.5, 155.1, 168.1, 171.4. Elemental Analysis Calcd for $C_{19}H_{21}NO_4 \cdot H_2O$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.36; H, 6.83; N, 3.55.

6b: The yield is 80%. M.p. 48–50°C. IR (KBr) 3411 (ν_{NH}), 1747 (ν_{CO}), 1687 (ν_{CO}) cm^{-1}. Fab-mass *m/z* 666 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.16 (s, Ar-CH_3 × 2, 6H), 2.80 (dd, $J=$ 7.5, 14.0 Hz, C*H*HPh × 2, 2H), 2.99 (dd, $J=5.0$, 14.0 Hz, CH*H*Ph × 2, 2H), 3.61 (s, CO_2Me × 2, 6H), 3.75 (s, $ArCH_2Ar$, 2H), 4.31 (d, $J=14.5$ Hz, –OC*H*HCO– × 2, 2H), 4.39 (d, $J=$ 14.5 Hz, –OCH*H*CO– × 2, 2H), 4.78 (ddd, $J=$ 5.0, 7.5, 8.0 Hz, NCHR × 2, 2H), 6.60 (d, $J=$ 8.0 Hz, Ar-H × 2, 2H), 6.73 (d, $J=$ 2.0 Hz, Ar-H × 2, 2H), 6.76 (d, $J=8.0$ Hz, NH × 2, 2H), 6.88–6.93 (m, Ar-H × 2, and Ph-H × 4, 6H) 7.04-7.07 (m, Ph-H × 6, 6H). ^{13}C NMR ($CDCl_3$) δ 20.6, 30.2, 37.8, 52.3, 52.7, 67.5, 111.7, 127.0, 128.0, 128.3, 128.5, 129.0, 131.1, 131.4, 135.6, 153.0, 168.2, 171.4. Elemental Analysis Calcd for $C_{39}H_{42}N_2O_8 \cdot 0.2(H_2O)$: C, 69.88; H, 6.38; N, 4.18. Found: C, 69.61; H, 6.48; N, 4.10.

General Procedure for the Preparation of 5c and 5d

To a solution of **3** (1.0 mmol) in DMF (20 mL) was added pentafluorophenol (3.3 mmol for **3c**, 4.4 mmol for **3d**) and ethyl acetate (3 mL). After cooloing the mixture to 0°C in an ice-bath, a solution of *N*,*N*-dicyclohexylcarbodiimide (3.3 mmol for **3c**, 4.4 mmol for **3d**) in DMF (5 mL) was added over 15 min at 0°C. After the addition was completed, the mixture was allowed to stir at 0°C for 1 h. The resulting precipitate was removed by filtration. The filtrate was condensed by rotary evaporator gave colorless oily residue, which was subjected to column chromatography on silica gel using hexane : ethyl acetate 3 : 1 as an eluent to give **5** as colorless crystals.

5c: The yield is 86%. M.p. 161–162°C. IR (KBr) 1803 (ν_{CO}) cm^{-1}. Fab-mass *m/z* 1020 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.14 (s, Ar-CH_3, 3H), 2.25 (s, Ar-CH_3 × 2, 6H), 4.07 (s, $ArCH_2Ar$ × 2, 4H), 4.70 (s, –OCH_2CO–, 2H), 4.96 (s, –OCH_2CO– × 2, 4H), 6.73 (d, $J=8.2$ Hz, Ar-H × 2, 2H), 6.78 (s, Ar-H × 2, 2H), 6.94 (d, $J=2.0$ Hz, Ar-H × 2, 2H), 7.02 (dd, $J=$ 2.0, 8.2 Hz, Ar-H × 2, 2H). ^{13}C NMR ($CDCl_3$) δ 20.6, 20.8, 29.7, 64.9, 68.9,

111.4, 124.4, 127.9, 129.7, 131.7, 131.8, 133.0, 134.4, 136.9, 138.7, 140.0, 140.6, 142.0, 152.4, 153.1, 165.3, 165.3. Elemental Analysis Calcd for $C_{47}H_{27}O_9F_{15}$: C, 55.31; H, 2.67. Found: C, 55.18; H, 2.55.

5d: The yield is 66%. M.p. 176–178°C. IR (KBr) 1799 (ν_{CO}) cm^{-1}. Fab-mass m/z 1365 $(M+H)^+$, 1387 $(M+Na)^+$. ^1H NMR ($CDCl_3$) δ 2.16 (s, Ar-CH_3 × 2, 6H), 2.24 (s, Ar-CH_3 × 2, 6H), 4.08 (s, $ArCH_2Ar$ × 2, 4H), 4.12 (s, $ArCH_2Ar$, 2H), 4.70 (s, –OCH_2CO– × 2, 4H), 4.97 (s, –OCH_2CO– × 2, 4H), 6.74 (d, $J = 8.5$ Hz, Ar-H × 2, 2H), 6.75 (s, $J = 2.0$ Hz, Ar-H × 2, 2H), 6.80 (d, $J = 2.0$ Hz, Ar-H × 2, 2H), 6.93 (d, $J = 2.0$ Hz, Ar-H × 2, 2H), 7.02 (dd, $J = 2.0$, 8.5 Hz, Ar-H × 2, 2H). ^{13}C NMR ($CDCl_3$) δ 20.5, 20.9, 29.8, 29.9, 64.9, 68.9, 111.3, 124.4, 127.9, 129.2, 129.7, 130.0, 131.7, 131.8, 133.0, 133.1, 134.6, 136.8, 138.7, 140.0, 140.6, 142.0, 152.4, 153.1, 165.3. Elemental Analysis Calcd for $C_{39}H_{36}O_8Cl_4$: C, 55.44; H, 2.66. Found: C, 55.45; H, 2.75.

General Procedure for the Preparation of 6c and 6d

To a solution of L-phenylalanine methyl ester (0.6 mmol for **5c**, 0.8 mmol for **5d**) and triethyl amine (0.3 mmol) in dry chloroform (5 mL) was added a solution of **5** (0.1 mmol) in dry chloroform (5 mL) at 0°C over 1 h. After the addition was complete, the mixture was allowed to stir at room temperature for 12 h. Removal of solvent gave oily residue, which was subjected to column chromatography on silica gel using hexane : ethyl acetate 1 : 2 as an eluent to give **6** as colorless crystals.

6c: The yield is 52%. M.p. 42–44°C. IR (KBr) 3411 (ν_{NH}), 1743 (ν_{CO}), 1685 (ν_{CO}) cm^{-1}. Fab-mass m/z 1006 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.13 (s, Ar-CH_3, 3H), 2.22 (s, Ar-CH_3 × 2, 6H), 2.90 (dd, $J =$ 7.0, 14.0 Hz, C*H*HPh × 2, 2H), 2.94 (dd, $J = 6.5$, 13.5 Hz, C*H*HPh, 1H), 3.09 (dd, $J = 5.5$, 14.0 Hz, CH*H*Ph × 2, 2H), 3.12 (dd, $J = 5.5$, 13.5 Hz, CH*H*Ph, 1H), 3.67 (s, CO_2Me × 3, 9H), 3.79 (d, $J = 16.0$ Hz, ArC*H*HAr × 2, 2H), 3.87 (d, $J = 16.0$ Hz, ArCH*H*Ar × 2, 2H), 4.18 (s, –OCH_2CO–, 2H), 4.37 (d, $J = 15.0$ Hz, –OC*H*HCO– × 2, 2H), 4.42 (d, $J = 15.0$ Hz, –OCH*H*CO– × 2, 2H), 4.88 (m, –NHC*H*(CO_2Me)– × 3, 3H), 6.65 (d, $J = 8.0$ Hz, Ar-H × 2, 2H), 6.66 (s, Ar-H × 2, 2H), 6.79 (d, $J = 2.0$ Hz, Ar-H × 2, 2H), 6.85 (d, $J = 8.0$ Hz, NH × 2, 2H), 6.90–6.97 (m, Ph-H × 6, 6H), 6.98 (dd, $J = 2.0$, 8.0 Hz, Ar-H × 2, 2H), 7.00–7.08 (m, Ph-H × 3, 3H), 7.10–7.17 (m, Ph-H × 6, 6H), 7.38 (d, $J = 8.0$ Hz, NH, 1H). ^{13}C NMR ($CDCl_3$) δ 20.6, 20.9, 29.9, 37.6, 37.9, 52.3, 52.4, 52.7, 52.8, 67.6, 71.2, 111.9, 126.9, 127.0, 128.2, 128.3, 128.4, 128.5, 129.0, 129.1, 129.5, 131.4, 131.5, 132.8, 134.6, 135.6, 135.9, 151.7, 153.0, 168.3, 168.5, 171.5, 171.6. Elemental Analysis Calcd for $C_{59}H_{63}N_3O_{12}\cdot 0.5(H_2O)$: C, 69.81; H, 6.26; N, 4.14. Found: C, 69.69; H, 6.39; N, 4.01.

6d: The yield is 67%. M.p. 58–61°C. IR (KBr) 3411 (ν_{NH}), 1743 (ν_{CO}), 1680 (amid I) cm^{-1}. Fab-mass m/z 1345 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.13 (s, Ar-$CH_3 \times 2$, 6H), 2.23 (s, Ar-$CH_3 \times 2$, 6H), 2.93 (dd, $J = 6.0$, 13.5 Hz, CH$H \times 2$, 2H), 2.95 (dd, $J = 6.0$, 13.5 Hz, CH$H \times 2$, 2H), 3.10 (dd, $J = 6.0$, 13.5 Hz, CHH $\times 2$, 2H), 3.12 (dd, $J = 6.0$, 13.5 Hz, CHH $\times 2$, 2H), 3.65 (s, $CO_2Me \times 2$, 6H), 3.67 (s, $CO_2Me \times 2$, 6H), 3.79 (d, $J = 16.0$ Hz, $ArCH_2Ar \times 2$, 2H), 3.83 (d, $J = 16.0$ Hz, $ArCH_2Ar \times 2$, 2H), 3.85 (s, $ArCH_2Ar$, 2H), 4.10 (d, $J = 15.0$ Hz, –OCHHCO– $\times 2$, 2H), 4.17 (d, $J = 15.0$ Hz, –OCHHCO– $\times 2$, 2H), 4.38 (d, $J = 15.0$ Hz, –OCHHCO– $\times 2$, 2H), 4.43 (d, $J = 15.0$ Hz, –OCHHCO– $\times 2$, 2H), 4.84–4.90 (m, –NCH– $\times 4$, 4H), 6.66–6.80 (m, Ar-H $\times 6$, 6H), 6.80 (d, $J = 2.0$ Hz, Ar-H $\times 2$, 2H), 6.89 (d, $J = 8.0$ Hz, NH $\times 2$, 2H), 6.97–7.00 (m, Ar-H $\times 6$, 6H), 7.04–7.10 (m, Ar-H $\times 10$, 10H), 7.12–7.15 (m, Ar-H $\times 6$, 6H), 7.36 (d, $J = 8.0$ Hz, NH $\times 2$, 2H). ^{13}C NMR ($CDCl_3$) δ 20.5, 20.6, 20.8, 20.9, 29.8, 29.9, 37.6, 37.8, 52.3, 52.4, 52.4, 52.6, 52.7, 52.8, 52.9, 67.7, 71.4, 111.8, 126.9, 127.0, 128.1, 128.3, 128.4, 128.5, 129.0, 129.1, 129.2, 129.7, 131.3, 131.4, 132.7, 132.8, 134.7, 135.6, 135.9, 151.8, 153.0, 168.2, 171.5, 171.7. Elemental Analysis Calcd for $C_{79}H_{84}N_4O_{16}\cdot(H_2O)$: C, 69.59; H, 6.36, N, 4.11. Found: C, 69.65; H, 6.42; N, 4.07.

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