

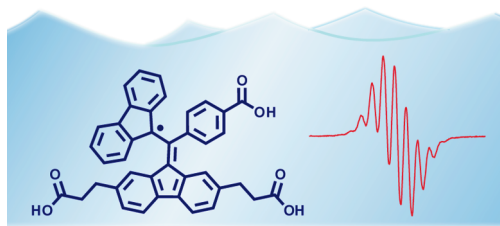
Synthesis of a Water-Soluble 1,3-Bis(diphenylene)-2-phenylallyl Radical

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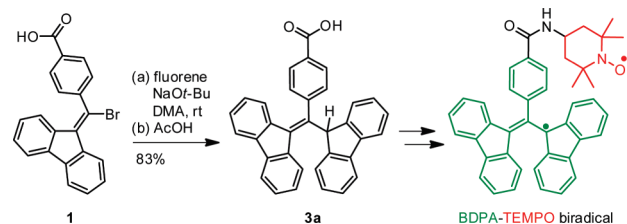


The design and synthesis of a water-soluble 1,3-bis(diphenylene)-2-phenylallyl (BDPA) radical via the conjugate addition of a derivatized fluorene nucleophile is described. The compound is designed for use in dynamic nuclear polarization NMR. Its 9 GHz EPR spectrum in glycerol/water is reported.

The 1,3-bis(diphenylene)-2-phenylallyl (BDPA) radical¹ (Scheme 1, green) is an air-stable, carbon-centered radical that is unique among organic radicals in the extent of delocalization of its unpaired electron. The unpaired electron is predominantly located at the 1- and 3-positions of the compound's allyl core, but is further stabilized by delocalization into the two biphenyl ring systems attached at those positions.² In addition, the propeller-like geometry of the compound has been suggested to sterically shield and further protect the radical from potential reaction partners.³

The BDPA radical's resonance has a narrow line width in high-field EPR, presumably because it is highly delocalized, which makes it attractive for use in certain NMR experiments utilizing dynamic nuclear polarization (DNP).⁴ DNP can be used to increase the signal-to-noise ratio in NMR

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spectra by transferring the polarization of electrons to nuclei.⁵ Electrons are inherently easier to polarize because of their larger magnetic moment. Unfortunately, BDPA cannot be used in experiments that require an aqueous cosolvent, such as studies with DNP to improve NMR protein structure determination, because of its hydrophobicity.^{5b}

We report the synthesis of a water-soluble BDPA (WS-BDPA) radical. Previous syntheses of BDPA derivatives have not focused on imparting water solubility.^{1b,3a,6} However, there are several reports of water-soluble derivatives of the triarylmethyl (trityl) radical.⁷ In addition to their use in DNP-NMR, some water-soluble trityl derivatives have been used as EPR probes for oxygen concentration and pH, which is a possible application of water-soluble BDPA derivatives.⁸

Building on our previously reported synthesis of a BDPA-TEMPO biradical⁹ (Scheme 1), the conjugate addition of a fluorene anion to compound **1** became the crucial transformation in our route to WS-BDPA. Compound **1** contains a carboxylic acid at the para-position of its phenyl ring that can aid in aqueous solubility. We reasoned that the addition of two additional carboxylic acids, masked as esters, at the 2- and 7-positions of the fluorene nucleophile would greatly improve the solubility of the resulting BDPA radical in polar solvents. However, we observed that adding electron-withdrawing groups to fluorene slows the conjugate addition. For example, when 2,7-dibromofluorene ($pK_a = 17.9$ in DMSO) is used as the nucleophile instead of fluorene ($pK_a = 22.6$ in DMSO)¹⁰ the required reaction time increases from 1 to 24 h. The stabilization of the fluorene carbanion results

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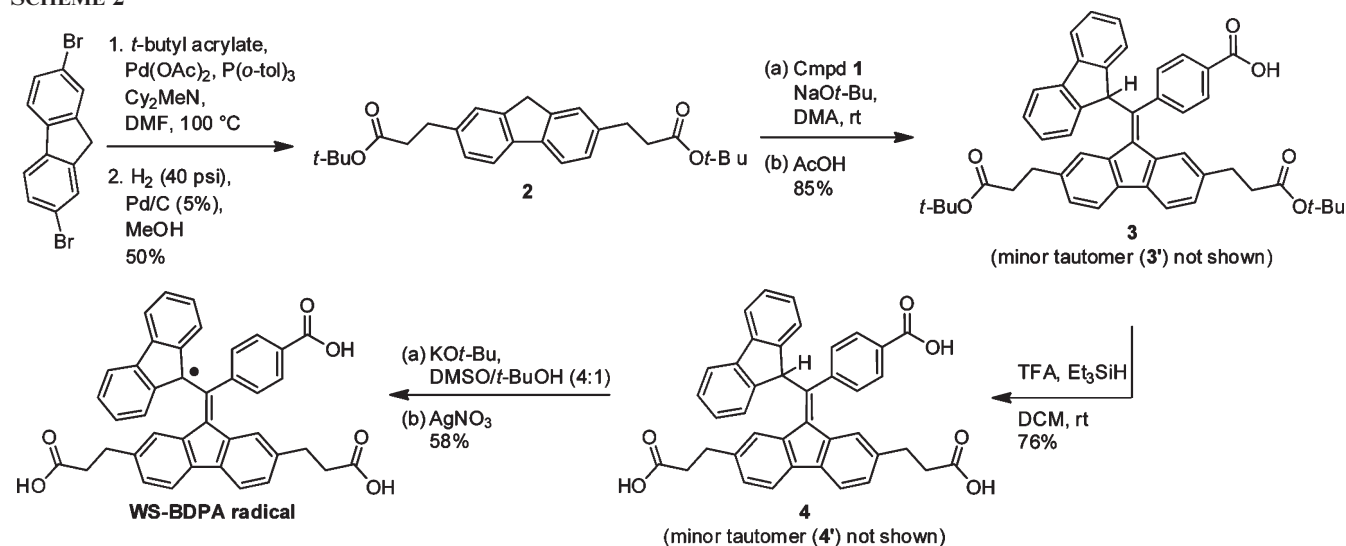
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SCHEME 2



in decreased nucleophilicity and less driving force to form the more stabilized BDPA carbanion ($pK_a = 14$).¹¹ As a result, a fluorene with esters directly attached would likely not be a good reaction partner with **1**. A fluorene derivative with a saturated carbon between the aromatic ring system and the ester would likely have the desired nucleophilicity at the 9-position, but its benzylic protons located α to an ester could be deprotonated under the reaction conditions. The simplest route to separate the esters from the conjugated system and still maintain selectivity for deprotonation at the 9-position of the fluorene ring system was to introduce an ethylene linker, as in **2** (protons α to the ester in **2** have a $pK_a \approx 30$ in DMSO¹²).

Diester **2** was synthesized in moderate yield from 2,7-dibromofluorene and *tert*-butyl acrylate via a Heck reaction¹³ followed by hydrogenation (Scheme 2). The reaction conditions for the addition of **2** to **1** required adjustment from those of the previous procedure.⁹ We found that the slow addition of **2** to a stirring solution of **1** and excess sodium *tert*-butoxide in dimethylacetamide (DMA) improved yields, as compared to the previous procedure in which **1** was added to a solution of the fluorene anion. Maintaining a low concentration of fluorene anion inhibits side reactions. In addition, we found that freshly prepared sodium *tert*-butoxide¹⁴ was superior to the commercially available material, likely because it contained less sodium hydroxide and therefore caused less unwanted ester cleavage. In this regard, the use of dry DMA was also important. After protonation and purification, the product was isolated as a 2:1 mixture of tautomers.

The tautomers have distinct ¹H NMR spectra, as shown in Figure 1. Previously, we reported NMR experiments and an X-ray crystal structure of **3a**, which revealed the origin of the signals outside the normal range of aromatic protons,

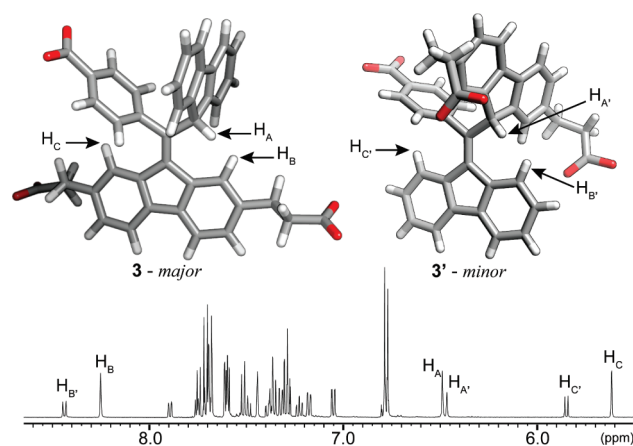


FIGURE 1. Molecular models of **3** and **3'** (*tert*-butyl groups have been omitted for clarity) and the aromatic region of the ¹H NMR spectrum.

specifically those above 8.0 ppm and below 6.0 ppm.⁹ The upfield shift in signals H_C and H_{C'} is caused by an interaction with the magnetic field of the nearby phenyl ring. The downfield signals (H_B, H_{B'}) result from a steric interaction with H_A and H_{A'}.¹⁵ An NOE of 20% was measured between the analogous protons in **3a**.⁹

To prepare triacid **4**, removal of the *tert*-butyl groups is achieved with trifluoroacetic acid in dichloromethane with the addition of triethylsilane as a carbocation trap.¹⁶ The acidic conditions do not cause a change in the ratio of tautomers in **4** as compared to **3**.

To generate the radical by one-electron oxidation, compound **4** was deprotonated to form the tetra-anion (see Figure 2, blue solution). We found that a large excess (20 equiv) of potassium *tert*-butoxide in a 4:1 solution of DMSO/*tert*-butanol provided the best results. Because excess base can cause reduction of the radical back to the carbanion, the amount of oxidant had to be increased to ensure complete

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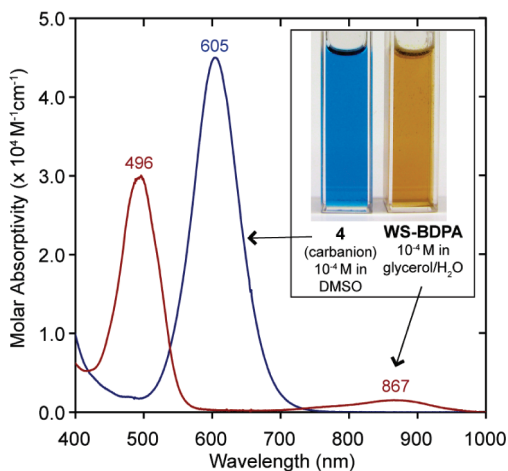


FIGURE 2. Absorption spectra of carbanion **4** in dimethyl sulfide and WS-BDPA in 3:2 glycerol and water.

oxidation. Addition of the oxidant was quickly followed by a dilution of the reaction mixture with acidic water (pH 2), and subsequent extraction of the triacid into diethyl ether. The isolated red-brown powder showed no ^1H NMR signals at a concentration of 20 mM in d_4 -methanol beyond those of the solvent and water, as would be expected for a paramagnetic compound. HRMS and FT-IR agreed with the proposed structure. As shown in Figure 2, in a glycerol and water solution (3:2) the radical has a strong absorption in the visible region ($\lambda_{\text{max}} = 496$ nm) and a weak absorption in the near-infrared region ($\lambda_{\text{max}} = 867$ nm). BDPA in dichloromethane has similar absorbance maxima, which are 485 and 859 nm, respectively.^{1b,3a}

The solubility of the radical in aqueous solution (PBS buffer, pH 8.0) was approximately 1.0 mM. Because the material was designed for use in DNP-NMR experiments dealing with biomolecules, we also tested the solubility of the radical in a 3:2 solution of glycerol and water, a solvent mixture favored for those experiments.^{5b} The radical was soluble at 1 mM at pH 7, but required the addition of sodium bicarbonate to be soluble at 10 mM (pH 8). Figure 3 shows the 9 GHz EPR spectrum of WS-BDPA in glycerol/water beneath the spectrum of BDPA in toluene. The radicals have the same g -value ($g = 2.003$) and a similar coupling pattern (see the Supporting Information for a simulated spectrum).^{1b,2,17} In addition, the radical was persistent at room temperature both in the solid state and in solution, but detailed studies of its stability as compared to BDPA have not yet been performed.

In conclusion, the design and synthesis of a water-soluble derivative of the BDPA radical is reported. We characterize the pair of tautomers that are a consequence of constructing the BDPA skeleton with nonidentical fluorene rings. Finally, the generation of the stable radical and its characterization by EPR spectroscopy in aqueous solution are reported.

Experimental Section

Di-*tert*-butyl 3,3'-(9H-Fluorene-2,7-diyl)dipropionate (2). To a 250 mL flask were added 5.00 g (15.4 mmol, 1.0 equiv) of

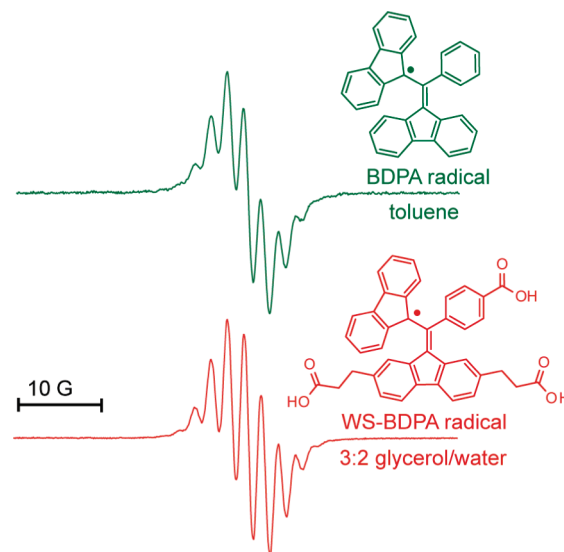


FIGURE 3. The 9 GHz EPR of BDPA (0.1 mM, 4 mm diameter tube) in toluene and WS-BDPA (10.0 mM, 150 μL flat cell) in glycerol/water. Experimental parameters: rt, 2 mW, modulation amplitude 10 mT.

2,7-dibromofluorene, 0.087 g (0.390 mmol, 2.5 mol %) of palladium acetate, 0.470 g (0.780 mmol, 5 mol %) of tri(*o*-tol)-phosphine, 5 mL of dicyclohexylmethylamine, and 100 mL of anhydrous dimethylformamide. The solution was degassed with bubbling argon and 7.00 mL (6.13 g, 47.8 mmol, 3.1 equiv) of *tert*-butyl acrylate was added. After heating to 80 $^{\circ}\text{C}$ for 4 h and cooling overnight, excess water was added and the resulting solid was filtered, washed with water, and dried on the filter pad. The material was suspended in 150 mL of methanol and 1.00 g of 5% Pd/C was added. Hydrogenation was performed overnight in a Parr Hydrogenator at 40 PSI with shaking. After removal of the methanol, the crude material was chromatographed with silica gel and eluted with increasingly polar mixtures of hexane and ethyl acetate to yield 3.25 g (50%) of a white powder. ^1H NMR (500 MHz, CD_2Cl_2 , δ) (all coupling constants (J) in Hz) 7.64 (d, $J = 7.5$, 2H), 7.36 (s, 2H), 7.18 (d, $J = 8.0$, 2H), 3.82 (s, 2H), 2.94 (t, $J = 7.5$, 4H), 2.54 (t, $J = 7.5$, 4H), 1.39 (s, 18 H); ^{13}C NMR (126 MHz, CD_2Cl_2 , δ) 172.6, 144.1, 140.2, 140.0, 127.4, 125.6, 119.9, 80.6, 37.8, 37.2, 31.8, 28.4; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{34}\text{O}_4\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 445.2349, found 445.2329. FT-IR (KBr, thin film) ν_{max} (cm^{-1}) 2978, 1729 (s), 1454, 1365, 1257, 1133, 1009, 956, 817, 741. Mp 99–101 $^{\circ}\text{C}$ (methanol).

4-((2,7-Bis(3-*tert*-butoxy)-3-oxopropyl)-9H-fluoren-9-ylidene)-(9H-fluoren-9-yl)methyl)benzoic Acid (3) and 4-((2,7-Bis(3-*tert*-butoxy)-3-oxopropyl)-9H-fluoren-9-yl)-(9H-fluoren-9-ylidene)-methyl)benzoic Acid (3'). To a 100 mL flask were added 0.100 g (0.265 mmol, 1.0 equiv) of bromide **2**, 0.255 g (2.65 mmol, 10 equiv) of sodium *tert*-butoxide, and 6.0 mL of degassed, anhydrous dimethylacetamide (DMA). The solution was cooled to 0 $^{\circ}\text{C}$. In a separate flask, 0.168 g (0.398 mmol, 1.5 equiv) of ester **1** was dissolved in 10 mL of DMA and this solution was slowly added to the first flask over a period of 20 min. The reaction became deep blue. After stirring at room temperature for 2 h, excess (3 mL) of acetic acid was added, turning the reaction from deep blue to light yellow. Additional water was added and the solution was extracted with diethyl ether (3×30 mL). The ether was washed twice with water and once with brine and dried over sodium sulfate. After removal of the solvent, the crude material was purified by silica gel column chromatography, using increasingly polar mixtures of ethyl acetate in dichloromethane, after which 0.163 g (85%) of a light yellow powder was isolated.

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^1H NMR (500 MHz, CD_2Cl_2 , δ) (all coupling constants (J) in Hz) for **3**: 8.25 (s, 1H), 7.75 (d, $J=8.0$, 1H), 7.71 (d, $J=8.0$, 2H), 7.69 (d, $J=8.0$, 2H), 7.60 (ddd, $J=8.0$, 1.0, 0.5, 2H), 7.59 (d, $J=8.0$, 1H), 7.36 (td, $J=8.0$, 1.0, 2H), 7.32 (dd, $J=8.0$, 1.0, 1H), 7.29 (td, $J=8.0$, 1.0, 2H), 7.05 (dd, $J=8.0$, 1.0, 1H), 6.78 (d, $J=8.0$, 2H), 6.49 (s, 1H), 5.62 (s, 1H), 2.95 (t, $J=7.5$, 2H), 2.54 (t, $J=7.5$, 2H), 2.45 (t, $J=7.5$, 2H), 2.07 (t, $J=7.5$, 2H), 1.35 (s, 9H). ^1H NMR (500 MHz, CD_2Cl_2 , δ) (all coupling constants (J) in Hz) for **3'**: 8.44 (ddd, $J=8.0$, 1.0, 0.5, 1H), 7.89 (ddd, $J=8.0$, 1.0, 0.5, 1H), 7.75 (ddd, $J=8.0$, 1.0, 0.5, 1H), 7.69 (d, $J=8.0$, 2H), 7.52 (d, $J=8.0$, 2H), 7.49 (td, $J=8.0$, 1.0, 1H), 7.44 (s, 2H), 7.38 (td, $J=8.0$, 1.0, 1H), 7.23 (td, $J=8.0$, 1.0, 1H), 7.18 (d, $J=8.0$, 2H), 6.79 (td, $J=8.0$, 1.0, 1H), 6.78 (d, $J=8.0$, 2H), 6.47 (s, 1H), 5.85 (d, $J=8.0$, 1H), 2.90 (t, $J=7.5$, 4H), 2.49 (t, $J=7.5$, 4H), 1.35 (s, 18H). ^{13}C NMR (126 MHz, CD_2Cl_2 , δ) 172.5, 172.4, 172.3, 171.6, 171.5, 145.2, 144.9, 144.6, 144.4, 144.0, 143.5, 142.5, 141.8, 140.7, 140.6, 140.5, 140.4, 139.4 (2), 139.3, 139.0, 138.5, 136.7, 136.6, 130.0, 129.5, 129.2, 129.0, 128.6, 128.5 (3), 128.3, 128.2, 128.0, 127.7, 127.1, 126.5, 126.3, 125.9, 125.8 (2), 125.7, 120.6, 120.5, 120.2, 119.7, 119.3, 80.7 (2), 80.4, 52.8, 52.7, 37.8 (2), 36.7, 32.1, 31.7, 31.6, 28.3, 28.2. HRMS (ESI) calcd for $\text{C}_{48}\text{H}_{45}\text{O}_6$ $[\text{M} - \text{H}]^-$ 717.3222, found 717.3206. FT-IR (KBr, thin film) ν_{max} (cm^{-1}) 2977, 2930, 1727 (s), 1694 (s), 1607, 1447, 1419, 1367, 1260, 1148, 1018, 846, 822, 736.

3,3'-(9-((4-Carboxyphenyl)(9H-fluoren-9-yl)methylene)-9H-fluorene-2,7-diyl)dipropionic Acid (4) and 3,3'-(9-((4-carboxyphenyl)(9H-fluoren-9-ylidene)methyl)-9H-fluorene-2,7-diyl)dipropionic Acid (4'). To a 50 mL flask were added 0.150 g (0.209 mmol, 1.0 equiv) of **3**, 9.0 mL of anhyd CH_2Cl_2 , 1 drop of triethylsilane, and 4.5 mL of TFA. The reaction mixture was stirred under an argon atmosphere for 30 min, after which excess sodium bicarbonate solution was added. The aqueous layer was washed with diethyl ether (2×10 mL) and acidified with 2 M HCl to a pH of 1. The aqueous layer was extracted with diethyl ether (3×10 mL). The combined ether layers were washed with brine and dried over sodium sulfate. Removal of the solvent followed by drying under high vacuum yielded 0.0960 g (0.158 mmol, 76%) of an off-white powder. ^1H NMR (500 MHz, d_4 -methanol, δ) (all coupling constants (J) in Hz) of **4**: 8.25 (s, 2H), 7.73 (d, $J=8.0$, 1H), 7.64 (d, $J=8.0$, 2H), 7.63 (d, $J=8.0$ Hz, 2H), 7.58 (d, $J=8.0$, 4H), 7.32 (m, 3H), 7.25 (t, $J=8.0$, 2H), 7.04 (d, $J=16.0$, 1H), 6.71 (d, $J=8.5$, 2H), 6.45 (s, 1H), 5.64 (s, 1H), 2.98 (t, $J=8.0$, 2H), 2.62 (t, $J=8.0$, 2H), 2.48 (t, $J=8.0$, 2H),

2.17 (t, $J=8.0$, 2H). ^1H NMR (500 MHz, d_4 -methanol, δ) (all coupling constants (J) in Hz) of **4'**: 8.41 (d, $J=8.0$ Hz, 1H), 7.87 (d, $J=7.5$, 1H), 7.72 (d, $J=7.5$, 1H), 7.64 (d, $J=8.0$, 2H), 7.48 (d, $J=8.0$, 2H), 7.46 (t, $J=8.0$, 1H), 7.43 (s, 2H), 7.36 (t, $J=8.0$, 1H), 7.19 (t, $J=8.0$, 1H), 7.16 (d, $J=8.0$, 2H), 6.74 (t, $J=8.0$, 1H), 6.71 (d, $J=8.0$, 2H), 6.42 (s, 1H), 5.85 (d, $J=8.0$, 1H), 2.92 (t, $J=8.0$, 4H), 2.57 (t, $J=8.0$, 4H). ^{13}C NMR (126 MHz, d_4 -methanol and CDCl_3 , δ) 176.3, 176.1, 175.8, 169.7, 144.9, 144.6, 144.3, 144.2, 144.0, 142.8, 142.1, 140.9, 140.4 (2), 139.7, 139.4, 139.2, 138.9, 136.8, 136.7, 129.8 (2), 129.6, 129.5, 129.3, 129.2, 128.4, 127.8, 127.2, 126.5, 126.0, 125.9, 125.7, 120.7 (2), 120.5, 119.9, 119.6, 53.1, 53.0, 36.9, 36.8, 35.8, 32.2, 31.8, 31.6. HRMS (ESI) calcd for $\text{C}_{40}\text{H}_{29}\text{O}_6$ $[\text{M} - \text{H}]^-$ 605.1970, found 605.1968. FT-IR (KBr, thin film) ν_{max} (cm^{-1}) 3600–2800 (br), 1700 (s), 1606, 1446, 1417, 1274, 1178, 1017, 824, 734.

WS-BDPA Radical. To a 200 mL flask were added 0.040 g (0.066 mmol, 1.0 equiv) of compound **4**, 0.150 g (1.34 mmol, 20 equiv) of sublimed potassium *tert*-butoxide, and 50 mL of a 4:1 mixture of DMSO/*t*-BuOH. After 30 min, 0.180 g (1.06 mmol, 16.0 equiv) of silver nitrate was added. The solution immediately became brown and was diluted after 1 min with 400 mL of 0.01 M HCl and extracted with diethyl ether (3×10 mL). The combined organic layers were washed with water (3×25 mL) and brine. After drying with sodium sulfate, the solvent was removed. The resulting solid was washed with hexane, and 0.023 g (58%) of a dark red-brown powder was isolated. HRMS (ESI) calcd for $\text{C}_{40}\text{H}_{29}\text{O}_6$ M^- 605.1970, found 605.1968. FT-IR (KBr, thin film) ν_{max} (cm^{-1}) 3600–2800 (br), 1708 (s), 1604, 1446, 1417, 1282, 1177, 1018, 824, 730. EPR (9 GHz) [WS-BDPA] 10 mM in 3:2 glycerol/ H_2O , quartz flat cell, g -value = 2.003.

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Supporting Information Available: Additional experimental details, and copies of ^1H , gCOSY, and ^{13}C NMR spectra for **2**, **3**, and **4**. This material is available free of charge via the Internet at <http://pubs.acs.org>.