An Improved Synthesis of Selectively Protected L-Dopa Derivatives from L-Tyrosine

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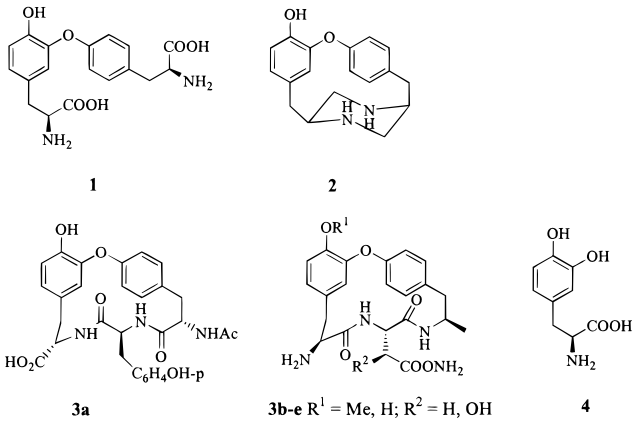
Many biologically active natural products such as the piperazinomycin (**2**),[1] K-13 (**3a**),[2] OF4949-I−IV (**3b**−**e**),[3] bouvardin and deoxybouvardin,[4] and RA-I−IV[5] contain a key structural unit isodityrosine (**1**) which is a naturally occurring dimeric form of L-Dopa [L-3-(3,4-dihydroxyphenyl)alanine, **4**]. L-Dopa derivatives with two differentiated



protecting groups on the catechol are useful building blocks for synthetic construction of these molecules. Several methods toward the synthesis of selectively protected L-Dopa derivatives have been reported in the literature.[6−8] The synthesis reported by Boger and Yohannes[6] provides the 4-*O*-benzyl-*N*-Cbz-L-Dopa methyl ester (**8**) from L-tyrosine (**5**) in six steps (34% overall yield). Boger's approach utilized an acid-promoted oxidative rearrangement of a benzylic hydroperoxide to obtain the target compound (Scheme 1).

Recently Jung and Lazarova reported a five-step synthesis of 4-*O*-benzyl-*N*-Boc-L-Dopa (**12**) from L-tyrosine (**5**) via sequential Reimer−Tiemann and Dakin reactions (Scheme 2).[8] However, the Reimer−Tiemann formylation of *N*-Boc-tyrosine (**9**) required rather vigorous reaction conditions (7.5 equiv of NaOH, $CHCl_3$, reflux, 4 h) for a chiral amino acid,[9] and gave a low yield of **10** (33% isolated yield, 64% yield based on 31% recovered stating material).

Although the Baeyer−Villiger oxidation of N-protected-3-acetyl-L-tyrosine esters is reported in poor yields (∼30%),[10] the similar oxidation of 3-acetyl-L-tyrosine hydrochloride (**13**) proceeds in 75% yield to give undifferentiated L-Dopa.[7f] We reasoned that it may be possible to achieve a higher yield of the desired phenol by optimizing reaction conditions for the Baeyer−Villiger oxidation of N-protected 3-acetyl-L-tyrosine or its ester derivative. Herein, we report an efficient method for the synthesis of selectively O-protected derivatives of L-Dopa, which can be utilized as suitable intermediates in the total synthesis of natural products such as compounds **2**−**3e**.[11] This method is based on a modified Baeyer−Villiger oxidation of N-protected 3-acetyl-L-tyrosine esters, resulting in a selective phenol introduction.[12]

3-Acetyl-L-tyrosine (**13**) was prepared according to Boger's protocol in 77% yield.[6] Amine protection with Boc anhydride (Boc_2O, $NaHCO_3$, dioxane−H_2O, 94%) provided **14**. Fully protected 3-acetyl-L-tyrosine **15** was obtained by converting the free phenol and the acid to the corresponding benzyl ether and benzyl ester respectively, utilizing the conditions described by Boger[6] to minimize possible racemization (2.5 equiv of $PhCH_2Br$, 2.5 equiv of K_2CO_3, 0.1 equiv of Et_4NI, DMF, 25 °C, 91%). The final transformation was a Baeyer−Villiger oxidation of the acetophenone to provide the required phenol. We investigated several different conditions and chose the m-CPBA oxidation at room temperature. Thus, the acetyl-L-tyrosine **15** was treated with 2 equiv of *m*-chloroperbenzoic acid in dichloromethane at room temperature for 7 days. Although the oxidation was sluggish it was very

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(9) No optical rotation or chiral analysis data was reported for these compounds by Jung and Lazarova.[8] Boger and Yohannes observed that benzylation of tyrosine phenol under vigorous reaction conditions (2 equiv of K_2CO_3, acetone, 60 °C) results in substantial racemization (15−20%).[6] Selectively protected catechol derivatives of D,L-Dopa have been prepared from isovanillin, see: Wilcox, M. E.; Wyler, H.; Mabry, T. J.; Dreiding, A. S. *Helv. Chim. Acta* **1965**, *48*, 252.

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(12) Selectively protected L-Dopa derivatives have been reported. These methods have relied on the monoprotection of the unsymmetrical catechol of Dopa derivatives,[7a−c,e−f] diazotization of 3-amino-L-tyrosine derivatives and subsequent copper(I)-promoted phenol introduction,[7d] or Baeyer−Villiger oxidation of 3-acetyl-L-tyrosine derivatives.[10] All these methods provide the desired compounds in yield 30% or less.

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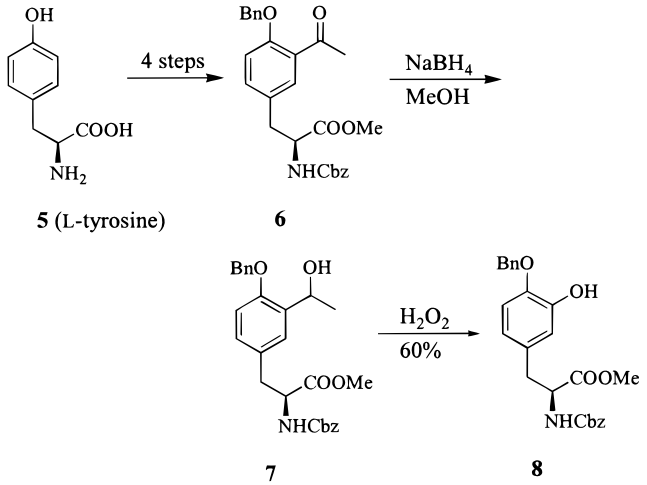
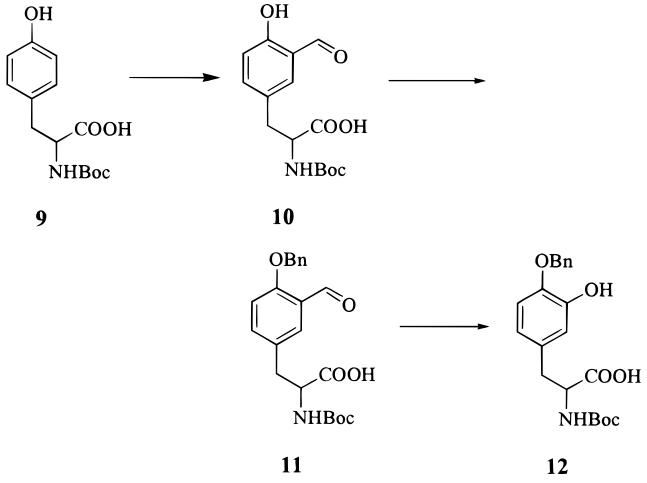
Scheme 1



Scheme 2

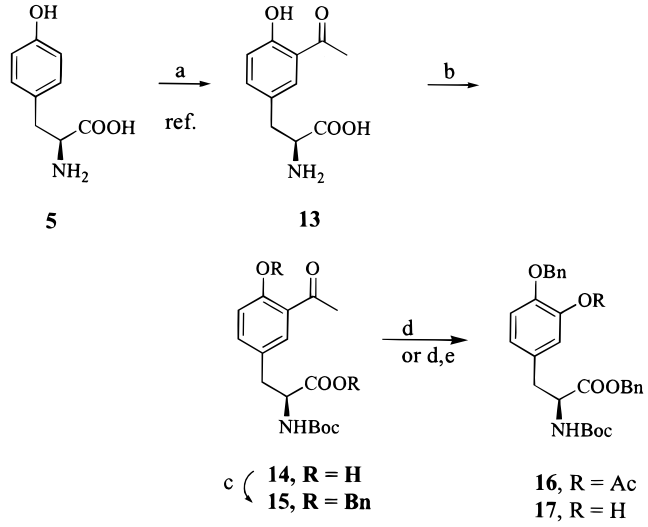


clean, and the corresponding acetoxy derivative **16** was isolated in 81% yield after a simple aqueous workup and crystallization. These conditions were tested on 0.1 to 10 g scales, and the yields were very consistent. Similar results were obtained when peracetic acid was used as oxidizing reagent (83% yield).[13] Heating the reaction in dichloromethane solvent did not help since more oxidant was required for complete conversion and the yield was lower, consistent with results reported by Boger.[6] The acetyl group was cleaved by treatment of the reaction mixture with methanolic ammonia for 1 h before workup to afford the desired L-Dopa **17** in an overall yield of 74% for the two steps (Scheme 3). Thus, in a four-step procedure, the selectively monoprotected L-Dopa derivative, *N*-Boc-L-3-(3-hydroxy-4-benzoxyphenyl)alanine (**17**), was synthesized from L-tyrosine (**5**) in 49% overall yield.

To determine the optical purity of the (L)-3-hydroxytyrosine derivatives, compound **16** was converted to L-3-(3-hydroxy-4-benzoxyphenyl)alanine (**18**) hydrochloride salt (4 N HCl in dioxane), which was then coupled with (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid and (*S*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid (EDC, DMAP, DMF, rt) (Scheme 4). The two Mosher's amide derivatives[14] (**19a** and **19b**) were characterized by both proton and fluorine NMR spectra, which showed a single isomer for both **19a** and **19b** (ee > 95%).

(13) On one millimole scale using peracetic acid (32 wt % in acetic acid, 2 equiv, room temperature, 10 days).

Scheme 3[a]



[a] Reagents: (a) $AcCl/AlCl_3/PhNO_2$/100 °C, 77%; (b) $Boc_2O/NaHCO_3$/dioxane−H_2O, 94%; (c) $BnBr/K_2CO_3/Et_4NI$(cat.)/DMF/rt, 91%; (d) mCPBA/CH_2Cl_2, rt, 81%; or CH_3CO_3H/CH_2Cl_2/rt, 83%; (e) NH_3MeOH, rt, 74% from **15**.

In conclusion, we have described here an efficient synthesis of the important selectively protected L-Dopa derivative **17** from L-tyrosine (**5**) via a modified Baeyer−Villiger oxidation. This compound can be used in the synthesis of natural products such as compounds **2**−**3e**.

Experimental Section

***N*-(*tert*-Butyloxycarbonyl)-3-(3-acetyl-4-hydroxyphenyl)-L-alanine (14).** l-3-(3-Acetyl-4-hydroxyphenyl)alanine hydrochloride[6] (**13**, 18 g, 50 mmol) was suspended in dioxane−water (1:1, 250 mL) and treated portionwise with sodium bicarbonate (12.6 g, 150 mmol). This solution was then treated with Boc_2O (1.2 equiv), and the mixture was vigorously stirred at room-temperature overnight before it was concentrated in vacuo to about 100 mL. This residue was acidified with 2 N HCl to pH 2, and the product was extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was dissolved in hot dichloromethane and treated with hexanes to precipitate a white solid (23 g, 94%): mp 110−112 °C; $[\alpha]^{22}_D$ +21.6° (*c* 2.2, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): 1.33 (s, 0.4 × 9H), 1.42 (s, 0.6 × 9H), 2.60 (s, 3H), 3.02 (m, 2H), 4.35 (m, 0.4H), 4.61 (m, 0.6H), 5.09 (d, J = 7.8 Hz, 0.6H), 6.74 (d, J = 6.9 Hz, 0.4H), 6.92 (d, J = 8.1 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.55 (s, 1H), 8.42 (brs, 2H); CI-MS, *m*/*e* 234 (M + H − Boc). Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.21; H, 6.93; N, 4.24.

***N*-(*tert*-Butyloxycarbonyl)-3-(3-acetyl-4-benzyloxyphenyl)-L-alanine Benzyl Ester (15).** A solution of *N*-(*tert*-butyloxycarbonyl)-3-(3-acetyl-4-hydroxyphenyl)-L-alanine (**14**, 13 g, 40 mmol) in dry DMF (150 mL) at room temperature was treated with potassium carbonate (14 g, 100 mmol), benzyl bromide (17.1 g, 100 mmol), and tetraethylammonium iodide (1.2 g, 5 mmol). The resulting reaction mixture was stirred at room-temperature overnight and partitioned into ether and water. The aqueous phase was extracted with ether, and the combined ether extract was washed with 1 N HCl and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was chromatographed on silica gel to give the product as a colorless oil (18.3 g, 91% yield), $[\alpha]^{22}_D$ −2.9° (*c* 1.4, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): 1.42 (s, 9H), 2.57 (s, 3H), 3.00 (dd, J = 6.3, 13.8 Hz, 1H), 3.07 (dd, J = 5.1, 13.8 Hz, 1H), 4.58 (m, 1H), 5.02 (d, J = 8.1 Hz, 1H), 5.12 (s, 2H), 5.13 (d, J = 5.7 Hz, 1H), 5.15 (d, J = 5.7

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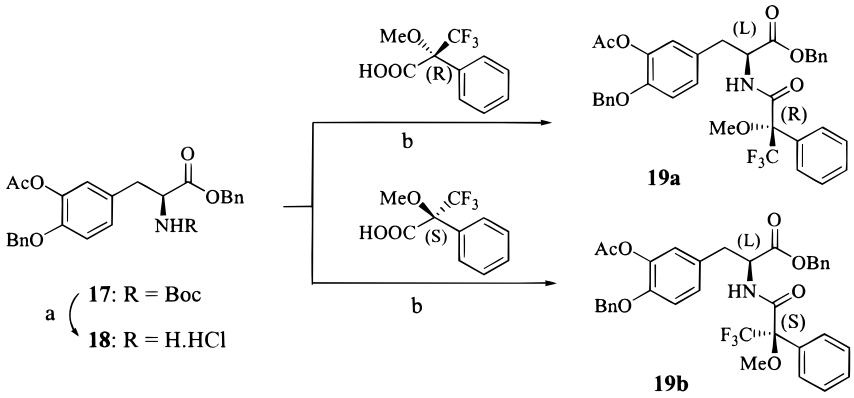
Scheme 4[a]



[a] Reagents: (a) 4 N HCl in dioxane, rt; (b) EDC/DMAP/DMF/Et_3N/rt.

Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 7.12 (dd, J = 2.4, 8.4 Hz, 1H), 7.38 (m, 10H), 7.51 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.0, 31.1, 36.9, 54.3, 66.8, 70.4, 79.5, 112.7, 127.2, 127.8, 128.0, 128.1, 128.2, 128.3, 128.4, 128.6, 130.9, 134.0, 134.8, 135.7, 154.7, 162.0, 171.1, 198.7; CI-MS *m/e* 404 (M + H − Boc). Anal. Calcd for $C_{30}H_{33}NO_6$: C, 71.55; H, 6.61; N, 2.78. Found: C, 71.17; H, 6.70; N, 2.76.

***N*-(*tert*-Butyloxycarbonyl)-3-(3-acetoxy-4-benzyloxyphenyl)-L-alanine Benzyl Ester (16).** A solution of *N*-(*tert*-butyloxycarbonyl)-3-(3-acetyl-4-benzyloxyphenyl)-L-alanine benzyl ester (**15**, 1.01 g, 2 mmol) and mCPBA (57−84%, 1.25 g, ∼2 equiv) in dichloromethane (20 mL) was stirred at room temperature for 7 days. The solution was diluted with ether (200 mL) and washed with saturated sodium thiosulfate, saturated sodium bicarbonate, and brine, dried over sodium bicarbonate, filtered, and concentrated in vacuo. The residue was crystallized from ether−hexanes to give the product as a white solid (841 mg, 81% yield), mp 88−90 °C, $[\alpha]^{22}_D$ −5.6° (*c* 2.2, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): 1.56 (s, 9H), 2.26 (s, 3H), 3.02 (m, 2H), 4.58 (m, 1H), 4.99 (d, J = 8.1 Hz, 1H), 5.04 (s, 2H), 5.09 (d, J = 12.6 Hz, 1H), 5.17 (d, J = 12.6 Hz, 1H), 6.78 (s, 1H), 6.84 (s, 2H), 7.31 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.6, 28.2, 37.2, 54.3, 66.9, 70.5, 79.8, 113.7, 123.5, 126.9, 127.3, 127.7, 128.2 (brs), 128.3, 128.7, 135.0, 136.5, 139.8, 149.0, 154.8, 168.6, 171.3; CI-MS *m/e* 420 (M + H − Boc). Anal. Calcd for $C_{30}H_{33}NO_7$: C, 69.35; H, 6.40; N, 2.70. Found: C, 69.18; H, 6.45; N, 2.68.

***N*-(*tert*-Butyloxycarbonyl)-3-(3-hydroxy-4-benzyloxyphenyl)-L-alanine Benzyl Ester (17).** A solution of *N*-(*tert*-butyloxycarbonyl)-3-(3-acetyl-4-benzoxyphenyl)-L-alanine benzyl ester (**15**, 1.01 g, 2 mmol) was dissolved in dichloromethane (20 mL) and treated with *m*-chloroperbenzoic acid (57%−84%, 1.25 g). This solution was stirred at room temperature for 7 days. A 2 M solution of ammonia in methanol (4 mL) was added, and the mixture was stirred for another 1 h. The resultant mixture was concentrated in vacuo, and the residue was diluted with ether (200 mL) and washed with saturated sodium thiosulfate, saturated sodium bicarbonate and brine, dried over sodium bicarbonate, filtered, and concentrated in vacuo. The crude product was purified on silica gel with 1:2 ethyl acetate−hexanes to give the title compound as a colorless syrup (706 mg, 74% yield), $[\alpha]^{22}_D$ −4.0° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): 1.41 (s, 9H), 2.96 (d, J = 5.7 Hz, 2H), 4.56 (m, 1H), 5.02 (s, 2H), 5.04 (brs, 1H), 5.09 (d, J = 12.0 Hz, 1H). 5.14 (d, J = 12.0 Hz, 1H), 5.84 (brs, 1H), 6.48 (d, J = 8.4 Hz, 1H), 6.68 (d, J = 1.5 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 7.32 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.2, 37.5, 54.5, 66.9, 71.0, 79.8, 112.0, 115.7, 120.6, 126.7, 127.6, 128.1, 128.2, 128.3, 128.5, 129.2, 135.0, 136.1, 144.7, 145.0, 154.9, 171.5; CI-MS *m/e* 288 (M + H − Boc). Anal. Calcd for $C_{28}H_{31}NO_6$: C, 70.42; H, 6.54; N, 2.93. Found: C, 70.18; H, 6.73; N, 2.76.

3-(3-Acetoxy-4-benzyloxyphenyl)-L-alanine Benzyl Ester Hydrochloride (18). A solution of *N*-(*tert*-butyloxycarbonyl)-3-(3-acetoxy-4-benzyloxyphenyl)-L-alanine benzyl ester (**16**, 2.5 g, 4.8 mmol) in 20 mL of CH_2Cl_2 was treated with 4 M HCl in dioxane (10 mL) and stirred overnight at room temperature under nitrogen. After overnight, some solid had formed, and the solution was triturated with 100 mL of ether. The suspension was stirred for 1 h and filtered to give a white solid, which was dried to yield compound **18** as a white solid, 1.86 g (85%); mp 194−6 °C; ^{1}H NMR (TMS/CD_3OD): 2.25 (s, 3H), 3.10 (dd, J = 6.9, 13.8 Hz, 1H), 3.18 (dd, J = 6.3, 13.8 Hz, 1H), 4.31 (dd, J = 6.3, 6.9 Hz, 1H), 5.09 (s, 2H), 5.23 (d, J = 10.8 Hz, 1H), 5.24 (d, J = 10.8 Hz, 1H), 6.92 (d, J = 2.1 Hz, 1H), 6.98 (d, J = 2.1, 8.4 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 7.35 (m, 10H); CIMS *m/e* 420 (M + 1). Anal. Calcd for $C_{25}H_{26}ClNO_5$: C, 65.86; H, 5.75; N, 3.07. Found: C, 65.82; H, 5.70; N, 3.00.

***N*-[(*R*)-(+)-α-Methoxy-α-trifluoromethylphenylacetyl]-3-(3-acetoxy-4-benzyloxyphenyl)-L-alanine Benzyl Ester (19a).** A solution of 3-(3-acetoxy-4-benzyloxyphenyl)-L-alanine benzyl ester hydrochloride (**18**, 200 mg, 0.44 mmol), (*R*)-(+)-α-methoxy-α-trifluorophenylacetic acid (105 mg, 0.45 mmol), EDC (115 mg, 0.6 mmol), triethylamine (0.14 mL, 1.0 mmol), and a catalytic amount of DMAP in DMF (5 mL) was stirred under nitrogen for 3 days. The reaction mixture was partitioned between ether (100 mL) and 1 N HCl (30 mL). The organic layer was separated and washed with brine (2 × 50 mL), dried over magnesium sulfate, and concentrated in vacuo. The product was purified on silica gel (R_f = 0.6, 30% EtOAc in hexane) to give the title compound as a colorless oil. ^{1}H NMR (TMS/$CDCl_3$): 2.26 (s, 3H), 3.08 (dd, J = 8.4, 14.0 Hz, 1H), 3.13 (dd, J = 5.4, 14.0 Hz, 1H), 3.20 (d, $J_{H,F}$ = 1.2 Hz, 3H), 4.70 (brs, 1H), 4.90 (m, 1H), 5.05 (s, 2H), 5.10 (d, J = 12.0 Hz, 1H), 5.19 (d, J = 12.0 Hz, 1H), 6.80 (s, 1H), 6.84 (s, 2H), 7.36 (m, 14H), 7.48 (m, 1H); ^{19}F NMR ($CFCl_3$/$CDCl_3$): −69.8; CIMS *m/e* 636 (M + 1); HRMS (FAB) calcd for $C_{35}H_{32}F_3NO_7$ *m/e* 636.2209, found 636.2230.

***N*-[(*S*)-(−)-α-Methoxy-α-trifluoromethylphenylacetyl]-3-(3-acetoxy-4-benzyloxyphenyl)-L-alanine Benzyl Ester (19b).** The product was obtained by coupling of **18** with (S)-(−)-α-methoxy-α-trifluorophenylacetic acid as described above. Colorless oil; ^{1}H NMR (TMS/$CDCl_3$): 2.25 (s, 3H), 3.01 (m, 2H), 3.40 (d, J = 1.8 Hz, 3H), 4.99 (m, 1H), 5.01 (s, 2H), 5.11 (d, J = 12.0 Hz, 1H), 5.20 (d, J = 12.0 Hz, 1H), 6.53 (m, 2H), 6.66 (d, J = 9.0 Hz, 1H), 7.02 (m, 1H), 7.37 (m, 15H). ^{19}F NMR ($CFCl_3$/$CDCl_3$): −69.1; CIMS *m/e* 636 (M + 1); HRMS (FAB) calcd for $C_{35}H_{32}F_3NO_7$ *m/e* 636.2209, found 636.2229.

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