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Synthesis of (*S*,*S*)-Isodityrosine by Dötz Benzannulation

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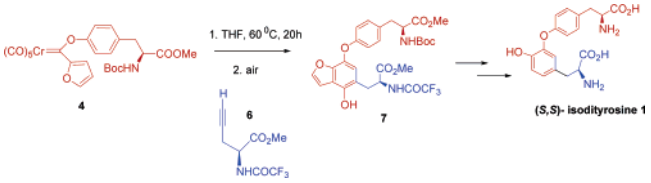

A synthesis of (*S*,*S*)-isodityrosine **1**, a naturally occurring, key structural subunit of numerous biologically active macromolecules, is described. A formal [3 + 2 + 1] cycloaddition (Dötz benzannulation) approach was utilized to simultaneously construct an aromatic ring and the diaryl ether linkage in one step. This key step was extended to the synthesis of (*S*,*S*)-isodityrosine in two separate convergent synthetic routes. This method demonstrates a novel and mild method for the synthesis of diaryl ethers.

The aryloxyphenol moiety of isodityrosine **1** (Figure 1) is a key structural unit found in a large class of biologically active natural products containing an endocyclic diaryl ether.[1a,b] These compounds range from the monocyclic macrocycles K-13 and OF4949 I−OF4949 IV to the bicyclic bouvardins and complex polycyclic glycopeptide antibiotics such as vancomycin.

K-13 is a noncompetitive inhibitor of angiotensin I converting enzyme (ACE),[2a] while the OF4949 derivatives I−IV are competitive inhibitors of aminopeptidase B.[2b] Bouvardin and deoxybouvardin are bicyclic hexapeptides that inhibit protein synthesis and belong to a family of related compounds with potent antitumor properties.[2c] Common to these compounds is the oxidatively cross-linked diaryl ether amino acid isodityrosine **1**. Boger has shown that the cycloisodityrosine core of the bouvardins is the acting pharmacophore.[2d]

Since its isolation from the plant cell wall glycoprotein extensin,[1a,b] several syntheses of isodityrosine have been reported.[3] Central to these syntheses is the development of improved ways of procuring the diaryl ether moiety.[4a] This includes Ullmann type coupling,[4b,c] S_NAr displacement of *o*-nitro-substituted aryl fluorides[4d] or benzoquinones,[4e] oxidative phenolic couplings,[4f] and Diels−Alder reactions.[4g] Several alternative approaches to diaryl ethers include displacement reactions on arene ruthenium complexes,[4h] substitution of aryl iodonium salts by sodium phenolates,[4i] ring opening of cyclohexenone oxides with phenols,[4j] and substitution of 2,6-dihalo-substituted triazenes with phenols.[4k] The palladium-catalyzed formation of diaryl ethers has also gained attention due to the efforts of Buchwald and Hartwig.[4l,m] Jung and Lazarova report an interesting synthesis of (*S*,*S*)-isodityrosine **1** by coupling two natural amino acid derivatives, one of which was arylboronic acid derived from 4-iodophenylalanine.[3b]

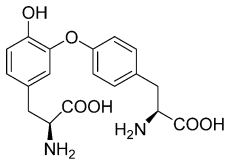

FIGURE 1. (*S*,*S*)-Isodityrosine **1**.

In this note, we report a synthesis of isodityrosine by a Dötz benzannulation strategy,[5] formally a [3 + 2 + 1] cycloaddition, which was reported by us for diaryl ether formation.[6] Boc-tyrosine methyl ester **2** was treated with *t*-BuLi at −78 °C, followed by quenching the in situ

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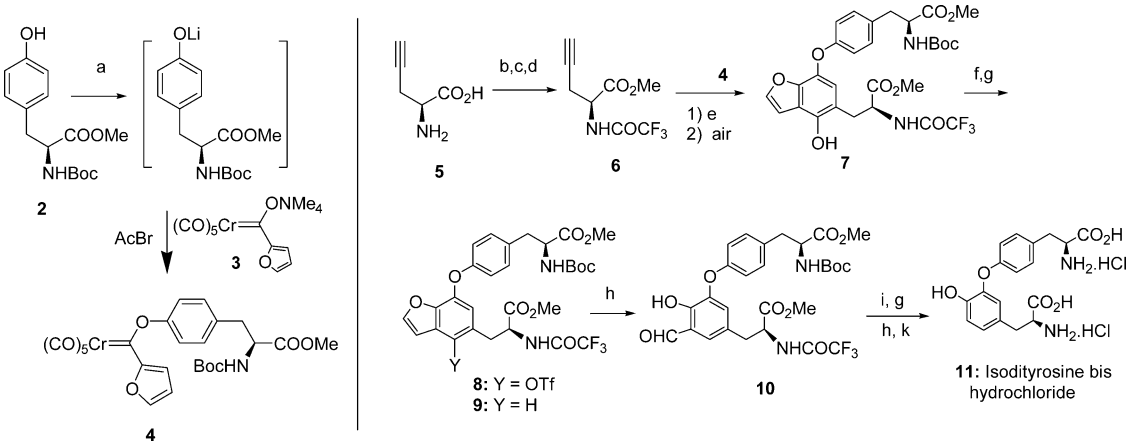
SCHEME 1[a]

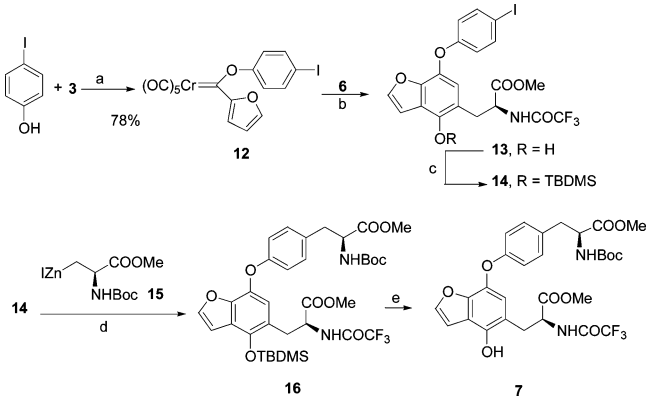


[a] (a) *t*-BuLi, Et_2O, −78 °C, 3, 45%; (b) MeI/K_2CO_3/DMF; (c) CF_3CO_2H; (d) $(CF_3CO)_2O$ (overall 78%); (e) 60 °C, THF 20 h (60%); (f) Tf_2O, pyridine, 0 °C to room temperature, 60%; (g) $Pd(OAc)_2$, dppf, TEA, HCOOH, DMF, 70 °C, 95%; (h) O_3 CH_2Cl_2, −78 °C, 65%; (i) $RhPPh_3Cl$, toluene −78 °C, 78%; (j) K_2CO_3, MeOH, H_2O; (k) 6 N HCl, reflux, (70%).

generated lithium phenolate with acylated carbene complex **3**[7] to furnish the desired tyrosine carbene complex **4** (Scheme 1).

Commercially available L-propargylglycine **5**[8] was derivatized to (*S*)-methyl *N*-trifluoroacetylpropargylglycinate **6** as shown in Scheme 1. Carbene complex **4** was then subjected to benzannulation by heating with alkyne **6** under argon at 60 °C for 20 h. Exposure of the reaction mixture to air oxidized the coordinated chromium, which was removed by filtration, and the diaryl ether **7** was obtained in 60% yield. Model reactions of carbene complex **4** with racemic propargylglycinate protected with an *N*-Boc group gave low yields of the desired diaryl ether, presumably due to participation of the nitrogen atom in unwanted side reactions.[9] Trifluoroacetyl group protection was necessary to reduce the reactivity of the nitrogen atom and increase the yield of the desired diaryl ether **7**. For palladium-catalyzed reductive deoxygenation,[10] the diaryl ether **7** was reacted with Tf_2O in pyridine, and the triflate **8**, obtained in 60% yield, was treated with $Pd(OAc)_2$-dppf in DMF at 70 °C in the presence of Et_3N and HCOOH giving **9** in 95% yield. Ozonolysis of **9** at −78 °C furnished the aldehyde **10** in 65% yield, which was subjected to deformylation[11] with Wilkinson's catalyst at −78 °C. The corresponding phenol, obtained in 78% yield, was treated with K_2CO_3/methanol/H_2O to remove the trifluoroacetyl group. This was followed by treatment with 6 N HCl to hydrolyze the ester moiety as well as to remove the Boc-protecting group providing isodityrosine bis-hydrochloride **11** in 70% yield. The spectral data[4j] were identical to those reported, and $[\alpha]_D = -28.3$ (*c* 0.5 in MeOH).

SCHEME 2[a]



[a] (a) AcBr/NaH (95%); (b) 1. 60 °C, 2. air (68%); (c) TBDMSCl/Et_3N, DMF (75%); (d) Zn, TMSCl, DMA, $(dba)_3Pd{\cdot}CHCl_3$, 1,2-dibtromoethane (66%); (f) TBAF/THF (86%).

In an alternate route to **7**, carbene complex **3** was reacted with *p*-iodophenol in the presence of NaH and CH_3COBr to obtain **12** (Scheme 2) in 95% yield. Reacting carbene complex **12** with (*S*)-methyl *N*-trifluoroacetylpropargylglycinate **6** under the standard conditions at 60 °C gave the furan derivative **13** in 68% yield. Protection of the phenolic group of **13** with TBDMS followed by coupling with zinc iodoalanine **15**[12] under Pd(0) catalysis gave the desired bis-amino acid derivative **16** in 66% yield. Deprotection of the TBDMS ether group with TBAF in THF gave the phenolic diaryl ether **7** in 86% yield.

The optical purity of the tyrosine carbene complex **4** was assessed using Trost's procedure (Scheme 3).[13] Thus, compound **4** was benzannulated with 1-pentyne to give the desired diaryl ether **17** in 75% yield, which was acylated to generate **18**. Deprotection of the Boc group

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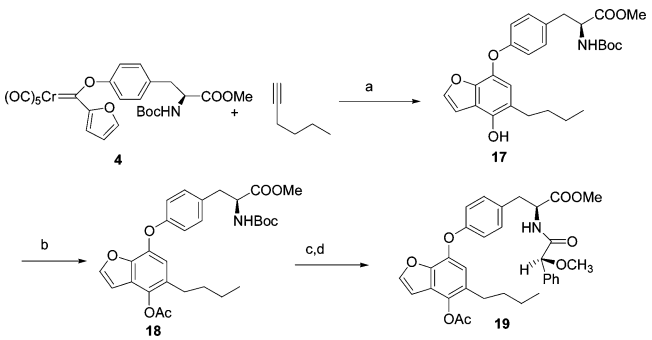
SCHEME 3[a]



[a] Optical purity of the tyrosine carbene **9**. (a) THF, 60 °C, 20 h; (b) Ac_2O, pyridine; (c) TFA, CH_2Cl_2; (d) (*S*)+methoxyphenylacetic acid, DCC, CH_2Cl_2.

from the amide **18** followed by derivatization with *S*-(+)-phenylacetic acid resulted in the desired amide **19** in 70% yield. Comparing the ^{1}H NMR spectral data and HPLC results of **19** with those of the racemic amide derivative proved that **19** is a single diastereomer, and in turn, carbene complex **4** is also a single enantiomer, and there is no loss of optical purity even after the benzannulation.

In conclusion, we have successfully completed a stereoselective sythesis of (*S*,*S*)-isodityrosine. The present synthesis features a novel benzannulation strategy to construct the C−O ether linkage. The amicable reaction conditions make it a versatile approach to the synthesis of this class of molecules.

Experimental Section

Tyrosine Carbene Complex 4. To a solution of *N*-Boc tyrosine **2** (400 mg, 1.30 mmol) in dry ether (5 mL) at −78 °C under argon we added *t*-BuLi (1.5 mL, 1.3 mmol) and slowly warmed it to room temperature. Freshly distilled acetyl bromide (0.2 mL, 1.3 mmol) was added to a solution of **3** (50 mg, 0.13 mmol) in dry dichloromethane (2 mL) to give a dark purple solution that was immediately cannulated into the solution of tyrosine phenolate. The reaction was stirred at room temperature for 2 h around as the solution turned red. The reaction mixture was evaporated to dryness and purified by flash column chromatography (hexane/ethyl acetate, 80:20) to give a red semisolid (344 mg, 45% yield); $[\alpha]_D$ +11.1 (*c* 1.2, $CHCl_3$), ^{1}H NMR (250 MHz) δ 7.94 (br s, 1H), 7.25 (m, 2H), 7.13 (d, m, 3H), 6.66 (m, 1H), 4.96 (br s, 1H), 4.61 (m, 1H), 3.73 (s, 3H), 3.18 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (62.9 MHz) δ 312.8, 224.4, 216.1, 171.9, 165.1, 157.6, 155.0, 146.7, 135.1, 130.6, 130.4, 122.6, 119.5, 113.3, 112.3, 79.9, 54.3, 52.2, 37.6, 28.2; IR (CH_2Cl_2) 3072, 2986.5, 2328.3, 2017.7, 1952.2, 1736, 1722.9.

(*S*)-2-(2,2,2-Trifluoro-acetylamino)-pent-4-ynoic Acid Methyl Ester 6. To a solution of commercially available L-propargylglycine **5**[8c] (213 mg, 1 mmol) in 5 mL of dry DMF at 0 °C was added K_2CO_3 (276 mg, 2 mmol) followed by dropwise addition of methyl iodide (0.3 mL, 5 mmol). Aqueous workup and extraction with diethyl ether gave the methyl ester derivative that was used without further purification. The ester was dissolved in CH_2Cl_2 (2 mL) at 0 °C under argon, and trifluoroacetic acid (1 mL) was added. After 12 h, the reaction mixture was evaporated at reduced pressure and acylated without further purification. To this ester (253 mg, 1 mmol) in dry CH_2Cl_2 at 0 °C under argon was added dry pyridine (395 mg, 5 mmol) and trifluoroacetic anhydride (1.05 g, 5 mmol). After being stirred at room temperature for 8 h, the usual workup gave a crude product that was purified by flash column chromatography (hexane/ethyl acetate, 80:20) to give a semisolid (173 mg, 78% overall yield); $[\alpha]_D$ +134.67 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.26 (br s, 1H), 4.74 (m, 1H), 3.84 (s, 3H), 2.86 (m, 2H), 2.09 (m, 1H); ^{13}C NMR (125 MHz) δ 169.2, 157.4, 124.1, 77.63, 74.4, 53.1, 51.2, 21.7; IR (CH_2Cl_2) 3072, 2986.5, 1736, 1722.9; HRMS mass calcd. for $C_8H_8F_3NO_3$: 223.045; found: 223.044.

(*S*)-3-{7-[4-((*S*)-2-*tert*-Butoxycarbonylamino-2-methoxycarbonyl-ethyl)-phenoxy]-4-hydroxy-benzofuran-5-yl}-2-(2,2,2-trifluoro-acetylamino)-propionic Acid Methyl Ester 7. A solution of **4** (900 mg, 1.59 mmol) and **6** (1.065 g, 4.77 mmol) in dry THF (30.5 mL, 0.05 M) in a Schlenk flask was freeze−thawed and degassed 3−4 times. After complete degassing, the reaction mixture was exposed to argon, and the vessel was sealed and heated at 55 °C for 20 h during which time the red color turned greenish black. The reaction mixture was cooled to room temperature, exposed to air, evaporated to dryness, and purified by flash column chromatography (hexane/ethyl acetate, 60:40) to yield compound **7** (596 mg, 60% yield); $[\alpha]_D$ +48.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.74 (brs, 1H), 7.46 (brs, 1H), 7.33 (s, 1H), 7.04 (m, 2H), 6.85 (m, 3H), 6.59 (br s, 1H), 5.00 (brs, 1H), 4.76 (m, 1H), 4.53 (s, 1H), 3.63 (s, 6H), 3.26 (m, 2H), 3.21 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz,) δ 172.2, 171.5, 170.7, 157.3, 155.2, 146.6, 144.7, 144.0, 134.5, 130.4, 130.2, 119.5, 118.6, 116.8, 115.0, 113.7, 103.9, 80.2, 60.5, 54.2, 53.0, 52.2, 37.5, 31.8, 28.3; IR (CH_2Cl_2) 3439.6, 3344.6, 3002.6, 2252.2, 1729.8, 1625.3, 1549.3, 1511.3; HRMS mass calcd. for $C_{29}H_{31}F_3N_2O_{10}$: 624.1931; found: 631.2112 (M + Li).

(*S*)-3-{7-[4-((*S*)-2-*tert*-Butoxycarbonylamino-2-methoxycarbonyl-ethyl)-phenoxy]-4-trifluoromethanesulfonyloxy-benzofuran-5-yl}-2-(2,2,2-trifluoro-acetylamino)-propionic Acid Methyl Ester 8. Compound **7** (372 mg, 0.58 mmol) was dissolved in dry CH_2Cl_2 (5 mL) under argon at 0 °C. To this was added pyridine (91.75 mg, 1.16 mmol) followed by distilled triflic anhydride (328.7 mg, 1.16 mmol). The reaction was stirred at room temperature until the TLC did not show the presence of starting material. The usual workup gave a crude product that was purified by flash column chromatography (hexane/ethyl acetate; 70:30), giving compound **8** (269 mg, 60% yield); $[\alpha]_D$ +67.2 (*c* 0.7, $CHCl_3$); ^{1}H NMR (250 MHz) δ 7.68 (m, 1H), 7.15 (m, 2H), 6.98 (m, 2H), 6.90 (m, 2H), 6.65 (br s, 1H), 5.05 (br s, 1H), 4.88 (br m, 1H), 4.58 (br s, 1H), 3.72 (s, 6H), 3.40 (m, 2H), 3.40 (m, 4H), 1.44 (s, 9H); ^{13}C NMR (62.9 MHz) δ 172.1, 169.9, 157.0, 156.2, 154.8, 147.0, 145.5, 133.3, 131.1, 130.8, 124.5, 121.7, 119.5, 118.8, 115.3, 115.0, 114.9, 104.7, 80.0, 54.4, 53.1, 52.7, 52.2, 37.4, 32.1, 28.2; IR (CH_2Cl_2) 3411.1, 3050.1, 2993.1, 2318.7, 1729.8, 1520.8; HRMS mass calcd. for $C_{30}H_{30}F_6N_2O_{12}S$: 756.1423; found: 763.1564 (M + Li).

(*S*)-3-{7-[4-((*S*)-2-*tert*-Butoxycarbonylamino-2-methoxycarbonyl-ethyl)-phenoxy]-benzofuran-5-yl}-2-(2,2,2-trifluoro-acetylamino)-propionic Acid Methyl Ester 9. To a solution of compound **8** (200 mg, 0.258 mmol) in DMF (4 mL) was added $Pd(OAc)_2$ (4 mg, 10 mol %), dppf (15 mg, 10 mol %), triethylamine (78.1 mg, 0.774 mmol), and formic acid (23.7 mg, 0.774 mmol). After being heated at 70 °C for 6 h, the mixture was filtered, washed with ethyl acetate (2 × 25 mL), and evaporated to give a crude product that was purified by flash column chromatography (hexane/ethyl acetate; 1:1), giving compound **9** (152 mg, 95% yield); $[\alpha]_D$ +28.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR (200 MHz) δ 7.60 (m, 1H), 7.15 (m, 3H), 6.89 (m, 3H), 6.77 (m, 1H), 6.57 (br s, 1H), 5.01 (br s, 1H), 4.85 (m, 1H), 4.55 (m, 1H), 3.71 (s, 6H), 3.16 (m, 4H), 1.42 (s, 9H); ^{13}C NMR (50.3 MHz) δ 172.2, 170.3, 162.2, 156.8, 155.0, 145.9, 145.0, 141.7, 131.3, 130.6, 130.5, 130.2, 118.5, 116.9, 114.9, 112.6, 106.7, 79.7, 60.3, 54.4, 53.9, 52.7, 52.4, 37.6, 34.3, 28.2; IR (CH_2Cl_2) 3420.6, 3002.6, 2252.2, 1729.8, 1606.3; HRMS mass calcd. for $C_{29}H_{31}F_3N_2O_9$: 608.1981; found: 615.2138 (M + Li).

(*S*)-3-{3-[4-((*S*)-2-*tert*-Butoxycarbonylamino-2-methoxycarbonyl-ethyl)-phenoxy]-5-formyl-4-hydroxy-phenyl}-2-(2,2,2-trifluoro-acetylamino)-propionic Acid Methyl Ester 10. Compound **9** (140 mg, 0.224 mmol) in dry CH_2Cl_2 (2 mL) was cooled to −78 °C, and ozone was bubbled through it for 10 min. The reaction mixture was stirred with Ph_3P for 2 h and then diluted with water (5 mL), worked up with CH_2Cl_2 (3 × 25 mL), and evaporated at reduced pressure. Quick chromatography gave 91 mg (65%) of compound **10**; $[\alpha]_D$ +32.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR (250 MHz) δ 10.96 (s, 1H), 9.89 (s, 1H), 7.10 (m, 3H), 6.90 (m, 4H), 5.05 (m, 1H), 4.83 (m, 1H), 4.68 (br s, 1H), 3.72 (s, 6H),

3.11 (m, 4H), 1.42 (s, 9H); ^{13}C NMR (75 MHz) δ 195.9, 172.2, 170.1, 156.0, 155.1, 152.7, 144.8, 131.9, 130.7, 128.8, 127.7, 126.5, 121.9, 117.2, 115.4, 77.4, 54.5, 53.5, 53.1, 52.2, 37.6, 36.3, 29.7; IR (CH_2Cl_2) 3430.1, 2993.1, 2261.7, 1703.3, 1682.3, 1520.8; HRMS mass calcd. for $C_{28}H_{31}F_3N_2O_{10}$: 612.1931; found: 619.2082 (M + Li).

Isodityrosine Bis-hydrochloride 11. Compound **10** (71 mg, 0.11 mmol) was dissolved in dry toluene and degassed thoroughly. To this was added Ph_3RhCl (71 mg, 0.11 mmol). After being refluxed for 3 h, the reaction mixture was evaporated and dry-loaded to a column (hexane/ethyl acetate; 1:1) to give 52 mg (78%) of the deformylated compound; $[\alpha]_D$ +40.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (200 MHz) δ 7.61 (m, 1H), 7.28 (m, 1H), 7.11 (m, 2H), 6.92 (m, 3H), 5.69 (br s, 1H), 4.83 (br s, 1H), 4.68 (br s, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 3.05 (m, 4H), 1.42 (s, 9H); ^{13}C NMR (50.3 MHz) δ 172.2, 170.2, 156.7, 155.5, 146.1, 142.7, 134.5, 131.6, 128.2, 126.8, 125.4, 119.2, 118.2, 116.5, 54.4, 53.5, 52.8, 37.6, 36.5, 28.3; IR (CH_2Cl_2) 3430.1, 2993.1, 2261.7, 1703.3, 1682.3, 1520.8; HRMS mass calcd. for $C_{27}H_{31}F_3N_2O_9$: 584.1981; found: 591.2118 (M + Li).

This deformylated compound (28 mg, 0.046 mmol) was dissolved in 5 mL of solution of 10% of K_2CO_3 in methanol/water (5:2) at 25 °C. The reaction mixture was stirred for 6 h and extracted with ether (1 × 3 mL), and the aqueous layer was adjusted to pH 7 by careful addition of 10% HCl. The aqueous layer was extracted with CH_2Cl_2 (6 × 5 mL), and the combined extracts were dried and concentrated in a vacuum. The crude amine (20 mg) was directly used for the next step. Aqueous 6 N HCl (1 mL) was added after refluxing for 6 h, the mixture was extracted with ethyl acetate (2 × 2 mL), and the aqueous phase was concentrated in a vacuum to give 13 mg (70%) of a pale white solid; $[\alpha]_D$ −28.16 (*c* 0.5, MeOH), $[\alpha]_D$ −28.2 (*c* 0.5, MeOH);[4i] ^{1}H NMR (500 MHz, methanol-d_4) δ 7.15 (m, 2H), 6.85 (m, 5H), 4.10 (m, 2H), 3.09 (m, 4H).

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Supporting Information Available: Procedures for the preparation of compounds **12**−**14** and **16**, spectroscopic data of compound **19**, ^{1}H and ^{13}C NMR spectra of compounds **4**, **6**−**10**, **12**−**14**, **16**, and ^{1}H NMR of **11** and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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