

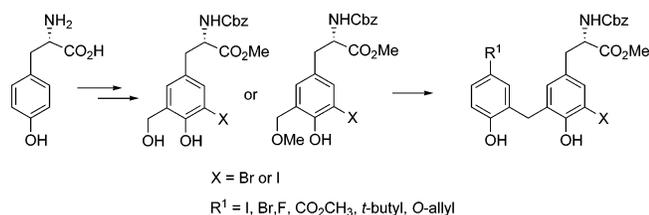
Acid-Catalyzed Synthesis of Methylene-Bridged (S)-Tyrosine–Phenol Dimers

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The efficient synthesis of 2,2'-arylmethylene dimers from 3-hydroxymethyl or 3-methoxymethyl-5-halo-(*S*)-tyrosines and para-substituted phenols under acid-catalyzed reaction conditions using either conventional or microwave-assisted protocols is described.

We required the previously unreported methylene-bridged (*S*)-tyrosine–phenol adducts **1–6** (Figure 1). To enable their synthesis we also required high-yielding protocols for **7** and/or **8** as well as **9** and **10**. There are only a handful of reports that detail the synthesis of tyrosine derivatives **7–10** (Figure 1). The widespread use of tyrosine and its derivatives means that protocols affording entities based on or similar to **1–10** are of importance. 2,2'-Methylenebisphenols (Figure 1) are synthesized via acid-catalyzed procedures employing *o*-hydroxymethylphenols and phenols. Their ease of synthesis has undoubtedly contributed to their widespread use as: Novolac resins,¹ metal-coordinating complexes,² Salbutamol dimers,³ asymmetric catalysts,⁴ calix[4]arene precursors,⁵ host–guest entities,⁶ and anti-cancer agents.⁷

Our strategy toward synthesizing **1–6** included two parts: (1) a base-catalyzed hydroxymethylation reaction between a (*S*)-tyrosine derivative and formaldehyde and (2) an acid-catalyzed reaction between the previously synthesized intermediate and

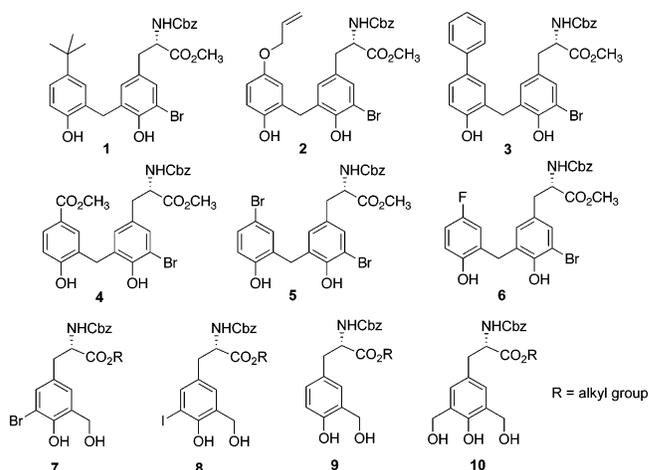


FIGURE 1. (*S*)-Tyrosine-derived dimers and their starting materials.

a phenol. Critical to the overall strategy, the synthesis of our target dimers had to be efficient, less than four synthetic steps from readily available starting materials, and amenable to the production of reasonable quantities of products.

As core starting materials towards **1–6** we required efficient synthetic routes to **7–10**. Space considerations here do not permit a lengthy discussion on our attempted application of literature protocols for their synthesis; needless to say, the application of seemingly straightforward procedures proved problematic. Negating this we did develop methods that afforded **7**, **9**, and **10** efficiently.⁸ The Supporting Information contains full synthetic procedures and the physicochemical data associated with compounds **7**, **9**, and **10**. With reliable protocols to core building blocks **7–10** established, their subsequent application to dimer formation, i.e., **1–6**, was initiated. Dissolving **11** (120 mg) and *p*-*tert*-butylphenol in dichloromethane containing a catalytic amount of PTSA we isolated, after microwave irradiation at 120 °C for 30 min, a 62% yield of **1**. Repeating the reaction but on a larger scale (incorporating 800 mg of **11**) afforded a 68% yield of the desired dimer **1**. Concerned that the reaction conditions employed may epimerize the stereogenic center on the α -amino acids of the dimers we undertook to ascertain the stereochemical integrity of **1** using chiral HPLC analysis (Chiralpak AD 250 \times 4.6 mm). Using optically active **1** as our substrate and chiral HPLC analysis we were able to demonstrate, when run against racemic **1**, that the stereochemical center of our product was indeed intact (see the Supporting Information for HPLC data).

Utilizing a general procedure based on that outlined in Scheme 1, the synthesis of **2–6** (Figure 1) was achieved in consistent and reasonable yields (50–69%). It is worthy of note that both electron-rich phenol-substituted dimers (**1–3**) and electron-poor phenol-substituted dimers (**4–6**) were readily synthesized. However, the yields of the dimers were slightly higher when electron-rich phenols were employed. Performing

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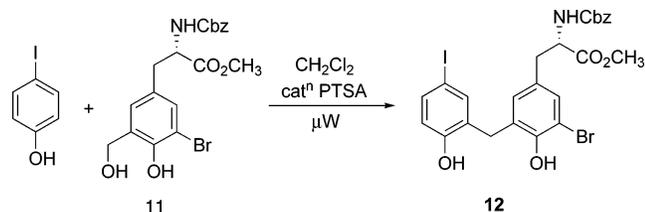
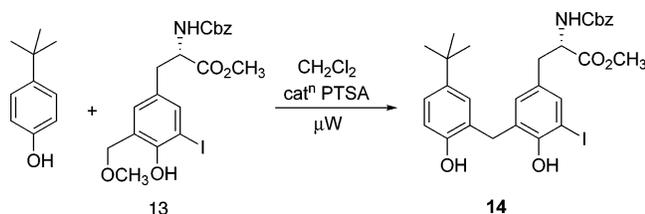
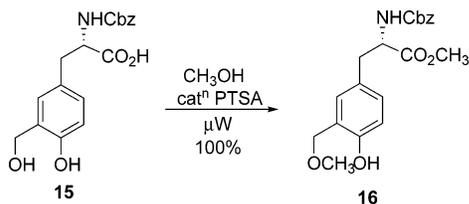
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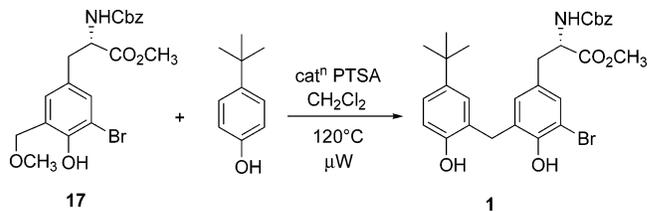
SCHEME 1. Synthesis of (*S*)-Tyrosine Dimer 12 from 11 and *p*-Iodophenol**SCHEME 2. Synthesis of (*S*)-Tyrosine Dimer 14 from 13 and *p*-*tert*-Butylphenol****SCHEME 3. Synthesis of 3-Methoxymethyl-*N*-Cbz-(*S*)-tyrosine Methyl Ester**

an acid-catalyzed microwave-irradiated condensation reaction between **11** and *p*-iodophenol we isolated **12** in a 56% yield with the majority of the mass balance (32%) being **11** (Scheme 1).

Similarly employing the corresponding 3-iodo derivative **13** and *p*-*tert*-butylphenol the efficient synthesis of the corresponding (*S*)-tyrosine dimer **14** was undertaken. In both examples (Schemes 1 and 2) we found no evidence of any byproducts resulting from the decomposition of the relatively heat labile weak carbon–iodine bond.

During our attempts to synthesize **7** we undertook the esterification of **15** using a methanolic hydrogen chloride solution. To our surprise a complex mixture of products resulted from which we isolated a 48% yield of the desired methyl carboxylate ester. Interestingly, substituting the methanolic hydrogen chloride solution for methanol and PTSA did not return the desired ester but instead the corresponding *N*-Cbz-3-methoxymethyl-(*S*)-tyrosine methyl ester **16** in an excellent 90% yield. Furthermore, conducting the reaction under microwave irradiation (110 °C) afforded in 30 min a quantitative yield of **16** (Scheme 3).

Disappointed that the chemoselective esterification of **15** had failed, we pondered the possibility that a suitable derivative of **16** may, under favorable reaction conditions, behave in a chemically analogous manner to **11** viz à viz dimer formation. In that case, derivatives of **16** would be of significant interest because of their straightforward synthesis and the fact that they should be easier to purify than the corresponding hydroxymethyl derivatives, e.g., **11**. Therefore, utilizing derivatives of **16** as “core” starting materials would further enhance our overall strategy of utilizing acid-catalyzed reaction protocols for the synthesis of methylene bridged (*S*)-tyrosine-phenol adducts. To

SCHEME 4. Synthesis of (*S*)-Tyrosine Dimer 1 from 17 and *p*-*tert*-Butylphenol

test our theory, the synthesis of **1** via a PTSA-catalyzed reaction between *p*-*tert*-butylphenol and **17** was undertaken. After flash chromatography, a 42% and 25% yield of **1** and **17** was formed, respectively. When a similar reaction employing microwave irradiation was used the yield of **1** increased to 70% (Scheme 4).

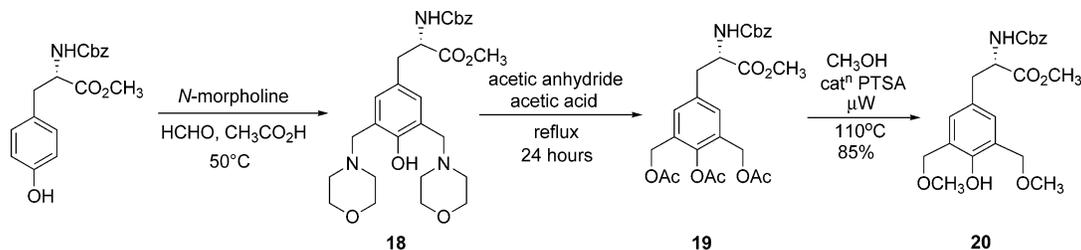
When electron-rich monoprotected *O*-allylhydroquinone and *p*-hydroxybiphenyl were employed we isolated **2** and **3** (Figure 1) in good yields (56% and 66% yields, respectively). However, the synthesis of methylene-bridged (*S*)-tyrosine-phenol dimers **4–6** and **12** using **17** and electron-poor phenols, i.e., methyl *p*-hydroxybenzoate, *p*-bromo-, *p*-fluoro-, and *p*-iodophenol all resulted in failure (**17** was returned).

As part of our wider strategy toward utilizing **1–6** (Figure 1), we also required a convenient synthesis of *N*-Cbz-3,5-bis-(hydroxymethyl)-(*S*)-tyrosine alkyl ester (**10**, R = CH₃, Figure 1). Based on our previous experience of the difficulties in purifying hydroxylated tyrosine derivatives, we sought an alternative procedure. Intrigued by a report by Crisp and Turner describing the Mannich reaction between para-substituted phenols, *N*-morpholine, and formaldehyde affording, in good yields, the corresponding 2,4,6-trisubstituted phenols,⁹ we adapted the protocol recruiting *N*-Cbz-(*S*)-tyrosine methyl ester as the starting material (Scheme 5). Undertaking the Mannich reaction, we observed the complete consumption of the (*S*)-tyrosine starting material. However, isolation of **18** was complicated by its highly water-soluble nature. To obviate this procedural problem, a one-pot protocol for the synthesis of **19** was adopted which afforded a respectable overall yield of 80% for **19**. Verification of the identity of **19** as the expected *N*-Cbz-*O*-acetyl-3,5-bis(acetoxymethyl)-(*S*)-tyrosine methyl ester was confirmed via X-ray analysis (see Figure 1 in the Supporting Information). Our attempts at hydrolyzing the acetyl groups on **19** using potassium carbonate in methanol (reflux, 12 h) returned **10** (R = H, Figure 1) and not the expected *N*-Cbz-3,5-bis-(hydroxymethyl)-(*S*)-tyrosine methyl ester. Furthermore, and perhaps not surprisingly, when **19** was subjected to microwave irradiation in the presence of catalytic amounts of PTSA in methanol at 120 °C it was transformed into the 3,5-bis-(methoxymethyl) derivative **20** in an excellent 85% yield.

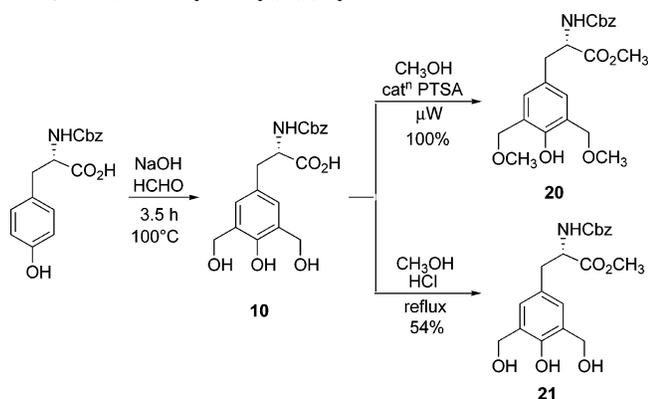
Although the protocol affording **20** in a 63% overall yield for the three steps worked well, the reaction times of 15 and 24 h for the transformations yielding **18** and **19** respectively (Scheme 5) were not conducive to a rapid synthesis. Switching to the original hydroxymethylation protocol reported by Müller et al.,⁸ we undertook the synthesis of **10** (R = H); however, because of its highly polar nature, we anticipated its purification to be a potential problem. Furthermore, the literature C-3 hydroxymethylation reaction times of 120 h were too long. Developing a slightly modified procedure to that reported by

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SCHEME 5. Synthesis of 3,5-Bis(methoxymethyl)-(S)-tyrosine Derivative 20



SCHEME 6. Efficient Synthesis of 3,5-Bis(hydroxymethyl)- or 3,5-Bis(methoxymethyl)-(S)-tyrosine Derivatives 20 and 21



Müller et al., we were able via a one-pot procedure, to synthesize, in substantially shorter reaction times (3.5 h), multigram quantities of **10** ($R = H$). Refluxing an acidic methanolic solution of **10** afforded a 54% yield of **21**. Although purification of **10** was, as predicted, problematic, its transformation into **20** using the previously outlined microwave irradiation protocol negated this. Purification of **20** was readily undertaken and returned the product in an overall 50% yield (Scheme 6).

Efficient protocols for the synthesis of halogenated *N*-Cbz-(*S*)-tyrosine alkyl esters and their C-3 hydroxymethylated analogues have been developed. The unexpected transformation of *N*-Cbz-3-hydroxymethyl-(*S*)-tyrosine into the corresponding *N*-Cbz-3-methoxymethyl-(*S*)-tyrosine methyl ester has been identified. Utilizing these as starting materials, via acid-catalyzed processes, a series of innovative methylene bridged *N*-Cbz-3-bromo-(*S*)-tyrosine methyl ester-5-(4-substituted phenol) entities have been assembled by conventional as well as microwave-assisted procedures. These unique chemical entities have numerous uses in synthetic, pharmaceutical, agrochemical, and material chemistry arenas.

Experimental Section

Compound 1. Representative Conventional Procedure. A mixture of **11** (120 mg, 0.26 mmol), *p*-*tert*-butylphenol (60 mg, 0.4 mmol), and PTSA (10 mg, 0.32 mmol) was dissolved in toluene (15 mL) and heated at reflux for 18 h under argon. After cooling, the solvent was removed in vacuo, the residue was redissolved in ethyl acetate, washed with aqueous sodium bicarbonate, water, and brine, dried over magnesium sulfate, filtered, and the solvent evaporated in vacuo. Column chromatography using dichloromethane–ethyl acetate (10%) afforded **1** as a clear oil (58 mg, 42%).

Representative Microwave Procedure. *p*-*tert*-Butylphenol (50 mg, 0.33 mmol), **11** (100 mg, 0.22 mmol), and PTSA (5 mg) in dichloromethane (4 mL) was heated in a sealed tube in the microwave at 120 °C for 30 min. Chromatography (hexanes–ethyl

acetate 5–30%) afforded **1** as a clear oil (78 mg, 62%): $[\alpha]_D^{21} +41.5$ ($c = 3$, $CHCl_3$); IR (neat) 3314, 2953, 2360, 1692, 1507, 1206, 695 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) $\delta = 7.34$ – 7.31 (m, 5 H), 7.19 (s, 1 H), 7.08 (dd, $J = 8.9$, 1.9 Hz, 1 H), 6.90 (d, $J = 1.9$ Hz, 1 H), 6.68 (s, 1 H), 6.59 (d, $J = 8.9$ Hz, 1 H), 5.25 (d, $J = 8.4$ Hz, 1 H), 5.10 (d, $J = 12.2$ Hz, 1 H), 5.07 (d, $J = 12.2$ Hz, 1 H), 4.58 (dd, $J = 8.4$, 5.8 Hz, 1 H), 3.88 (s, 2 H), 3.60 (s, 3 H), 2.97 (d, $J = 5.8$ Hz, 2 H), 1.26 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 172.1$, 155.9, 150.9, 149.3, 143.9, 136.1, 131.2, 130.8, 128.7, 128.6, 128.4, 128.2, 127.9, 125.1, 125.0, 115.5, 110.7, 67.2, 60.2, 54.8, 52.3, 37.0, 33.9, 31.8, 31.5 ppm; MS (EI) m/z 569.1 (M)⁺; HRMS (ES) 587.1749 ($M + NH_4$)⁺ (calcd for $C_{29}H_{36}N_2O_6$ 587.1751).

Larger Scale Synthesis of 1. *p*-*tert*-Butylphenol (664 mg, 4.42 mmol), **11** (800 mg, 1.36 mmol), and PTSA (50 mg) in dichloromethane (10 mL) were heated in a sealed tube in the microwave at 120 °C for 120 min. Chromatography (hexanes–ethyl acetate 5–30%) afforded **1** as a clear oil (680 mg, 68%).

Compound 2. *O*-Allylhydroquinone (75 mg, 0.5 mmol), **11** (100 mg, 0.22 mmol), and PTSA (5 mg) in anhydrous dichloromethane (4 mL) were heated in a sealed tube in the microwave at 120 °C for 60 min. Chromatography (hexanes–ethyl acetate 5–30%) afforded **2** as a clear oil (82 mg, 65%): $[\alpha]_D^{21} +23.8$ ($c = 1.3$, $CHCl_3$); IR (neat) 3312, 2951, 2360, 1698 cm^{-1} ; 1H NMR (400 MHz, CD_3OD) $\delta = 7.32$ – 7.21 (m, 5 H), 7.17 (d, $J = 1.7$ Hz, 1 H), 6.90 (d, $J = 1.7$ Hz, 1 H), 6.69 (d, $J = 8.6$ Hz, 1 H), 6.63 (d, $J = 3.0$ Hz, 1 H), 6.58 (dd, $J = 8.6$, 3.0 Hz, 1 H), 5.95 (complex m, 1 H), 5.28 (qd, $J = 17.1$, 1.6 Hz, 1 H), 5.15 (qd, $J = 10.5$, 1.6 Hz, 1 H), 5.00 (m, 2 H), 4.44 (m, 1 H), 4.35 (m, 2 H), 3.85 (s, 2 H), 3.59 (s, 3 H), 2.95 (dd, $J = 13.7$, 5.1 Hz, 1 H), 2.77 (dd, $J = 13.7$, 5.1 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, CD_3OD) $\delta = 172.6$, 157.2, 152.4, 150.4, 148.2, 136.9, 134.1, 131.3, 130.5, 129.8, 129.6, 128.2, 127.7, 127.5, 127.4, 116.9, 116.1, 115.3, 113.4, 110.4, 69.2, 66.4, 55.7, 51.5, 36.4, 30.7 ppm; MS (EI) m/z 571.1 (M)⁺; HRMS (ES) 592.0941 ($M + Na$)⁺ (calcd for $C_{28}H_{28}NO_7BrNa$ 592.0930).

Compound 3. A mixture of **11** (100 mg, 0.22 mmol), *p*-hydroxybiphenyl (85 mg, 0.5 mmol), and PTSA (5 mg) in dichloromethane (4 mL) was reacted as detailed for **1** at 120 °C for 45 min. The product was purified using flash chromatography (hexanes–ethyl acetate, 5 to 30%) affording **3** as a clear oil (90 mg, 69%): $[\alpha]_D^{21} +59.4$ ($c = 2.1$, $CHCl_3$); IR (neat) 3291, 2951, 2494, 2359, 1691, 1607 cm^{-1} ; 1H NMR (400 MHz, CD_3OD) $\delta = 7.46$ (s, 1 H), 7.44 (s, 1 H), 7.31–7.15 (m, 11 H), 6.93 (d, $J = 1.8$ Hz, 1 H), 6.84 (d, $J = 8.2$ Hz, 1 H), 4.92 (m, 2 H), 4.33 (m, 1 H), 3.95 (s, 2 H), 3.50 (s, 3 H), 2.92 (dd, $J = 13.8$, 5.5 Hz, 1 H), 2.76 (dd, $J = 13.8$, 5.5 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, CD_3OD) $\delta = 172.5$, 157.0, 154.1, 150.5, 141.2, 136.9, 133.1, 131.2, 130.4, 129.8, 129.7, 129.1, 128.5, 128.2, 127.7, 127.4, 127.1, 126.3, 126.2, 125.8, 115.1, 110.5, 66.3, 55.7, 51.5, 36.4, 30.7 ppm; MS (EI) m/z 591.2 (M)⁺; HRMS (ES) 612.0992 ($M + Na$)⁺ (calcd for $C_{31}H_{28}NO_6BrNa$ 612.0999).

Compound 4. Methyl *p*-hydroxybenzoate (60 mg, 0.4 mmol), **11** (100 mg, 0.22 mmol), and PTSA (5 mg) in dichloromethane (4 mL) were reacted as detailed for **1** (120 °C for 45 min). Chromatography with hexanes–ethyl acetate 5–30% afforded **4** as a clear oil (76 mg, 50%): $[\alpha]_D^{21.5} +31.4$ ($c = 2$, CH_3OH); IR (neat) 3347, 2951, 1692 cm^{-1} ; 1H NMR (400 MHz, CD_3OD) $\delta = 7.69$ (s, 1 H), 7.27–7.22 (m, 6 H), 7.16 (s, 1 H), 6.85 (s, 1 H),

6.80 (d, $J = 8.2$ Hz, 1 H), 4.99 (m, 2 H), 4.33 (m, 1 H), 3.91 (s, 2 H), 3.75 (s, 3 H), 3.58 (s, 3 H), 2.93 (dd, $J = 13.8, 5.4$ Hz, 1 H), 2.78 (dd, $J = 13.8, 5.4$ Hz, 1 H) ppm; ^{13}C NMR (75 MHz, CD_3OD) $\delta = 173.4, 168.5, 160.6, 157.9, 151.4, 137.7, 132.9, 132.0, 131.4, 130.5, 130.3, 130.0, 129.0, 128.5, 128.2, 127.9, 121.9, 115.2, 111.3, 67.1, 56.3, 52.1, 51.7, 36.9, 30.8$ ppm; MS (CI) m/z 574.1 (M^+); HRMS (ES) 594.0734 ($\text{M} + \text{Na}$) $^+$ (calcd for $\text{C}_{27}\text{H}_{26}\text{NO}_8\text{BrNa}$ 594.0734).

Compound 5. *p*-Bromophenol (75 mg, 0.44 mmol), **11** (100 mg, 0.22 mmol), and PTSA (5 mg) in dichloromethane (3 mL) were reacted as detailed for **1** (120 °C for 45 min). Compound **5** was purified using chromatography (hexanes–ethyl acetate 5–30%) affording a clear oil (82 mg, 53%): $[\alpha]^{24.5}_{\text{D}} +45.3$ ($c = 2, \text{CHCl}_3$); IR (neat) 3327, 2951, 1692 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) $\delta = 7.30\text{--}7.16$ (m, 6 H), 7.10 (d, $J = 2.6$ Hz, 1 H), 7.08 (s, 1 H), 6.88 (s, 1 H), 6.67 (dd, $J = 9.0, 2.6$ Hz, 1 H), 5.01 (m, 2 H), 4.34 (m, 1 H), 3.85 (s, 2 H), 3.60 (s, 3 H), 2.95 (dd, $J = 13.7, 5.2$ Hz, 1 H), 2.78 (dd, $J = 13.7, 5.2$ Hz, 1 H) ppm; ^{13}C NMR (75 MHz, CD_3OD) $\delta = 173.4, 157.9, 154.9, 151.3, 137.7, 133.4, 132.1, 131.4, 130.6, 130.3, 129.9, 129.0, 128.5, 128.2, 117.2, 111.9, 111.3, 70.9, 67.1, 56.3, 52.2, 36.9, 30.8$ ppm; MS (EI) m/z 593.2 (M^+); HRMS (EI) 590.9881 (M^+) (calcd for $\text{C}_{25}\text{H}_{23}\text{NO}_6\text{Br}_2$ 590.9887).

Compound 6. *p*-Fluorophenol (61 mg, 0.5 mmol), **11** (100 mg, 0.22 mmol), and PTSA (5 mg) in dichloromethane (3 mL) were reacted as detailed for **1** (120 °C for 45 min). Compound **6** was purified using chromatography (hexanes–ethyl acetate 5–30%) affording a clear oil (68 mg, 51%): $[\alpha]^{24}_{\text{D}} +41.1$ ($c = 3, \text{CHCl}_3$); IR (neat) 3324, 2952, 2495, 1691 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) $\delta = 7.29\text{--}7.22$ (m, 6 H), 7.18 (d, $J = 1.6$ Hz, 1 H), 6.90 (d, $J = 1.6$ Hz, 1 H), 6.72 (s, 1 H), 6.69 (m, 1 H), 5.00 (m, 2 H), 4.35 (m, 1 H), 3.87 (s, 2 H), 3.59 (s, 3 H), 2.96 (dd, $J = 13.5, 5.5$ Hz, 1 H), 2.78 (dd, $J = 13.5, 5.5$ Hz, 1 H) ppm; ^{13}C NMR (75 MHz, CD_3OD) $\delta = 173.4, 157.9, 151.4, 151.3, 137.7, 132.1, 131.4, 130.6, 129.9, 129.0, 128.5, 128.2, 117.1, 116.8, 116.1, 116.0, 113.9, 113.6, 111.2, 67.1, 56.3, 52.1, 36.9, 31.0$ ppm; MS (CI) m/z 551.1 ($\text{M} + \text{NH}_4$) $^+$; HRMS (EI) 531.0687 (M^+) (calcd for $\text{C}_{25}\text{H}_{23}\text{NO}_6\text{BrF}$ 531.0689).

Compound 12. *p*-Iodophenol (88 mg, 0.4 mmol), **11** (100 mg, 0.22 mmol), and PTSA (5 mg) in dichloromethane (3 mL) were

reacted as detailed for **1** (120 °C for 60 min). Chromatography (hexanes–ethyl acetate 5–30%) afforded **12** as a clear oil (90 mg, 56%): $[\alpha]^{21}_{\text{D}} +57.1$ ($c = 2, \text{CHCl}_3$); IR (neat) 3328, 2950, 2504, 2358, 2325, 1693 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) $\delta = 7.30\text{--}7.21$ (m, 7 H), 7.16 (dd, $J = 9.1, 1.7$ Hz, 1 H), 6.86 (d, $J = 1.7$ Hz, 1 H), 6.56 (d, $J = 9.1$ Hz, 1 H), 5.01 (m, 2 H), 4.34 (m, 1H), 3.83 (s, 2 H), 3.59 (s, 3 H), 2.94 (dd, $J = 13.8, 5.6$ Hz, 1 H), 2.78 (dd, $J = 13.8, 5.6$ Hz, 1 H) ppm; ^{13}C NMR (75 MHz, CD_3OD) $\delta = 173.4, 157.9, 155.6, 151.3, 139.5, 137.7, 136.8, 132.1, 131.3, 130.8, 130.5, 129.9, 129.0, 128.5, 128.2, 117.8, 111.2, 81.5, 67.1, 56.4, 52.2, 37.0, 30.7$ ppm; MS (EI) m/z 639.1 ($\text{M} + \text{H}$) $^+$; HRMS (ES) 661.9639 ($\text{M} + \text{Na}$) $^+$ (calcd for $\text{C}_{25}\text{H}_{23}\text{NO}_6\text{BrI}$ 661.9646).

Compound 14. *p*-*tert*-Butylphenol (75 mg, 0.5 mmol), **13** (140 mg, 0.28 mmol), and PTSA (5 mg) in dichloromethane (4 mL) were reacted as detailed for **1** (100 °C for 60 min). Chromatography (hexanes–ethyl acetate 5–30%) affording **14** as a clear oil (102 mg, 57%): $[\alpha]^{22}_{\text{D}} +42.0$ ($c = 2, \text{CHCl}_3$); IR (neat) 3279, 2954, 2360, 1691 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) $\delta = 7.38$ (d, $J = 1.9$ Hz, 1 H), 7.29–7.20 (m, 5 H), 7.14 (d, $J = 2.4$ Hz, 1 H), 7.04 (dd, $J = 8.4, 2.4$ Hz, 1 H), 6.95 (d, $J = 1.9$ Hz, 1 H), 6.71 (d, $J = 8.4$ Hz, 1 H), 5.00 (m, 2 H), 4.33 (m, 1 H), 3.85 (s, 2 H), 3.54 (s, 3 H), 2.92 (dd, $J = 13.9, 5.5$ Hz, 1 H), 2.76 (dd, $J = 13.9, 5.5$ Hz, 1 H), 1.20 (s, 9H) ppm; ^{13}C NMR (75 MHz, CD_3OD) $\delta = 172.6, 157.1, 152.9, 151.2, 143.0, 137.6, 136.9, 131.3, 130.4, 128.7, 128.3, 127.7, 127.4, 125.7, 124.3, 114.3, 85.2, 66.4, 55.8, 51.5, 36.2, 33.6, 31.4, 30.9$ ppm; MS (CI) m/z 635.2 ($\text{M} + \text{NH}_4$) $^+$; HRMS (ES) 640.1172 ($\text{M} + \text{Na}$) $^+$ (calcd for $\text{C}_{29}\text{H}_{32}\text{NO}_6\text{NaI}$ 640.1167).

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Supporting Information Available: The synthesis of **7–11**, **13**, and **15–21** as well as the ^{13}C NMR and HPLC data for compounds **1–7**, **12–14**, **16**, **17**, **19**, and **20**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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