136587-17-2; (±)-4'a, 136587-32-1; (±)-4b, 136616-25-6; (±)-4c, 136587-18-3; (±)-4d, 136587-19-4; (±)-4'b, 136587-33-2; (±)-5a, 126754-17-4; (±)-5'a, 136587-34-3; (±)-5b, 126754-18-5; (±)-5'b, 136587-35-4; (±)-5c, 136587-20-7; (±)-5d, 136587-21-8; (±)-6, 136587-22-9; (±)-7a, 136587-23-0; (±)-7b, 136587-24-1; (±)-7c, 136587-25-2; (±)-8a, 136587-26-3; (±)-8b, 136587-27-4; (±)-9a, 136587-28-5; (±)-9b, 136587-29-6; 3-furaldehyde, 498-60-2; (±)-pyroangolensolide, 52730-12-8.

Studies on the Synthesis of Aryl Ethers Using Arene–Manganese Chemistry

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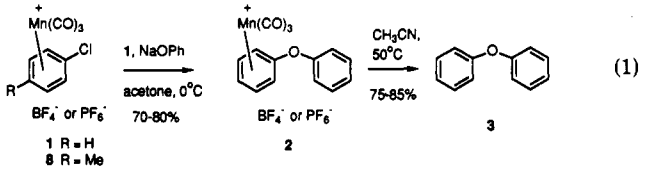
Selective arylation of polyfunctional phenols, using chlorobenzene- and *p*-chlorotoluene–manganese tricarbonyl cations, is described. The intermediate arene–manganese complexes are found to undergo stereo- and regioselective reactions with Schöllkopf's chiral glycine enolate equivalent to give dienyl–$Mn(CO)_3$ complexes. Treatment of these complexes with *N*-bromosuccinimide at room temperature, followed by hydrolysis of the dihydropyrazine, gives diaryl ethers in which one of the aromatic rings is an arylglycine methyl ester.

We are currently studying methods for the construction of diaryl ethers that have amino acid side chains attached to both aromatic rings,[1] which are expected to be useful for the preparation of synthetic building blocks for molecules related to the glycopeptide antibiotic vancomycin.[2] This paper reports observations on the chemistry of arene–manganese complexes that are showing promise in this general area of synthesis. It is known[3] that chloroarene–$Mn(CO)_3$ cations react with phenoxide nucleophiles to give, after decomplexation, diaryl ethers (eq 1). In this report



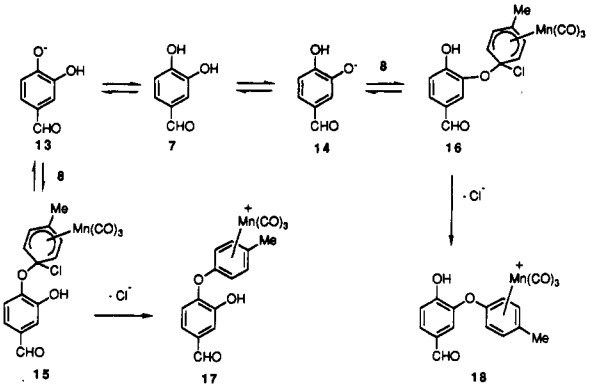
(1)

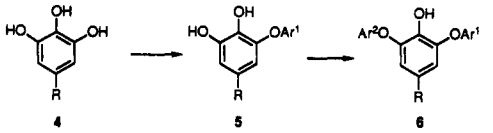
we address three questions:[4] (1) selectivity during the reaction of chloroarene–manganese complexes with some polyhydric phenols; (2) arylation of protected tyrosines and dipeptide derivatives; (3) the preparation of arylglycines derived from the *O*-aryltyrosines.

Results and Discussion

Selectivity during Arylation of Polyhydric Phenols. One of the requirements for preparation of subunits of the vancomycin family is that we should be able to arylate selectively phenolic compounds of general structure **4** to give unsymmetrical triaryl diethers **6**. We therefore examined selectivity during the reactions of gallic esters and 3,4-dihydroxybenzaldehyde derivatives with arene–$Mn(CO)_3$ cations.

Scheme I. Reversible Steps during the Reaction of 7 with 8 (Partial Mechanism)





Treatment of 3,4-dihydroxybenzaldehyde (**7**) with 1 equiv of sodium hydride, followed by reaction of the so-formed phenoxide with chlorotoluene–$Mn(CO)_3$ hexafluorophosphate (**8**) followed by in situ decomplexation, gave an approximately 95:5 mixture (by NMR) of the monoarylated compounds **9** and **10**. No diarylated product was observed. That the major product was **9** was confirmed by conversion to the methyl ether **11** and comparison of the NMR spectrum with authentic samples of **11** and the isomeric compound **12**, prepared by arylation of commercially available 4-hydroxy-3-methoxybenzaldehyde and 3-hydroxy-4-methoxybenzaldehyde, respectively.

The regioselectivity of arylation of **7** is somewhat surprising, based on the expectation that the more stable aryloxide **13** would be formed by deprotonation of the 4-hydroxy group. A plausible explanation is embodied in Scheme I, in which a series of reversible steps is envisioned

(1) For related work, see: (a) Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063. (b) Pant, N.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 2002. (c) Hobbs, D. W.; Still, W. C. *Tetrahedron Lett.* **1987**, *28*, 2805. (d) Evans, D. A.; Britton, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 6881. (e) Suzuki, Y.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 6043. (f) Evans, D. A.; Ellman, J. A.; DeVries, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 8912. (g) Mann, M. J.; Pant, N.; Hamilton, A. D. *J. Chem. Soc., Chem. Commun.* **1986**, 158. (h) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1989**, *54*, 2498; *Tetrahedron Lett.* **1989**, *30*, 2053 and 5061. (i) Crimmin, M. J.; Brown, A. G. *Tetrahedron Lett.* **1990**, *31*, 2017 and 2021. (j) Jung, M. E.; Jachiet, D.; Rohloff, J. C. *Tetrahedron Lett.* **1989**, *30*, 4211. (k) Pearson, A. J.; Park, J. G.; Yang, S. H.; Chuang, Y.-H. *J. Chem. Soc., Chem. Commun.* **1989**, 1363.

(2) Reviews: Williams, D. H.; Rajananda, V.; Williamson, M. P.; Bojesen, G. In *Topics in Antibiotic Chemistry*; Sammes, P. G., Ed.; John Wiley & Sons, Inc.: New York, 1980; Vol. 5, p 119. Barna, J. C. J.; Williams, D. H. *Ann. Rev. Microbiol.* **1984**, *38*, 339.

(3) Pauson, P. L.; Segal, J. A. *J. Chem. Soc., Dalton Trans.* **1975**, 1677. See also: Mawby, A.; Walker, P. J. C.; Mawby, R. J. *J. Organomet. Chem.* **1973**, *55*, C39. Winkhaus, G.; Pratt, L.; Wilkinson, G. *J. Chem. Soc.* **1961**, 3807. Walker, P. J. C.; Mawby, R. J. *Inorg. Chem.* **1971**, *10*, 404; *Inorg. Chim. Acta* **1973**, *7*, 621; *J. Chem. Soc., Dalton Trans.* **1973**, 622.

(4) For earlier related studies from this laboratory, see: Pearson, A. J.; Bruhn, P. R.; Hsu, S. Y. *J. Org. Chem.* **1986**, *51*, 2137.

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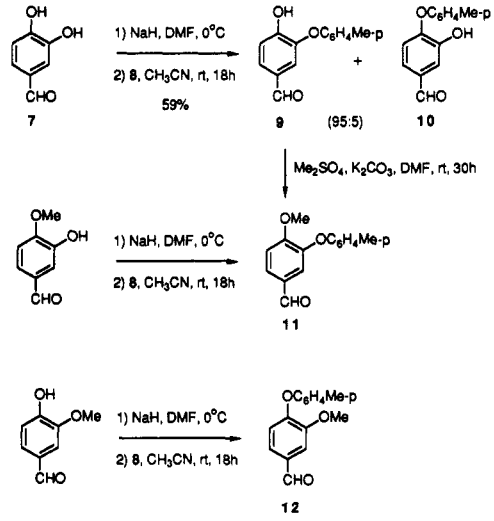
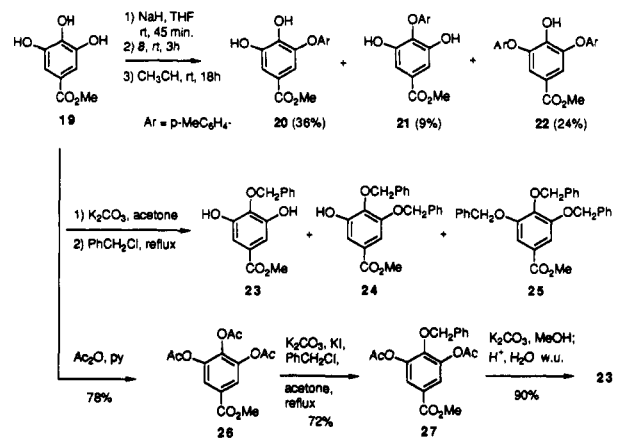


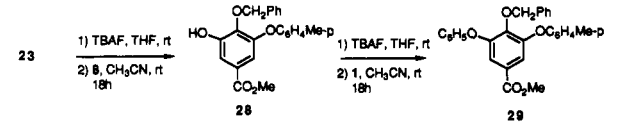
for this conversion. The resonance stabilization of **13** makes it less reactive than **14** and also a better leaving group in the reverse step (**15** → **13**). Consequently, the overall conversion of **14** to the complex **18** is much faster than **13** to **17**. (It should be noted that **17** and **18** were not isolated from these reactions but were decomplexed in situ).

We next turned our attention to the arylation of methyl gallate (**19**). Treatment of **19** with 1 equiv of sodium hydride, followed by complex **8** (1 equiv) and subsequent demetalation (CH_3CN), gave a mixture of three products. Chromatographic separation and NMR analysis revealed that the major monoarylated product **20** (36% yield) was again that resulting from reaction of the 3-hydroxy group, but larger amounts (9% yield) of 4-hydroxy arylation product **21** were formed. Also, the diarylated product **22** was produced in substantial amounts, indicating that the overall selectivity during this reaction was rather poor. Consequently, the arylation of monoprotected methyl gallate was investigated. Selective benzylation of **19** to give **23** has been reported previously,[5] but in our hands this procedure consistently gave a 2:2:1 mixture of **23**, **24**, and **25**. Chromatographic purification afforded **23** in 17% yield. Better selectivity was observed when fluoride was used as the base during the benzylation reaction (in DMF solvent), giving 40% yield of **23** and varying amounts of **24**. A cleaner method was therefore sought. The reaction of **19** with acetic anhydride in pyridine is reported to give methyl 3,5-diacetoxy-4-hydroxybenzoate, which can be alkylated and hydrolyzed to give methyl 4-alkoxy-3,5-dihydroxybenzoate derivatives.[6] In our hands, acetylation of **19** gave the triacetate **26**. However, treatment of **26** with K_2CO_3, KI, and benzyl chloride in refluxing acetone produced the diacetoxy benzyl ether **27** in good yield, which was readily hydrolyzed to the desired monobenzylated compound **23** in a reliable 50% overall yield from **19**.

The selective arylation of **23** with arene–manganese complexes proceeded very cleanly, although rather low yields resulted when sodium hydride was used as base. Better results were obtained using fluoride, under which conditions the monotolylated product **28** was obtained in 79% yield (at 60% conversion). Phenylation of **28**, using the chlorobenzene complex **1**, afforded the unsymmetrical triaryl diether **29** in 81% yield. These experiments serve to establish that selective arylation of dihydroxybenzene



derivatives is indeed feasible using chloroarene–manganese complexes.

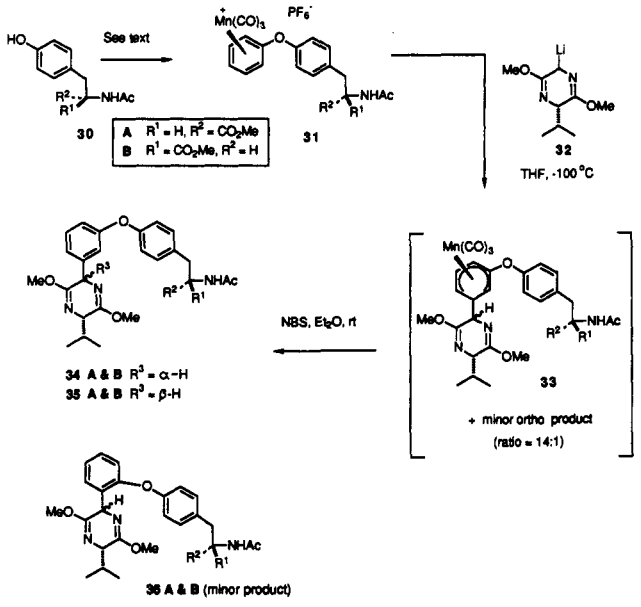


Arylation Reactions of Tyrosine Derivatives and Introduction of a Glycine Side Chain. The reaction of *N*-acetyltyrosine methyl ester with complex **1** was reported earlier by our group,[4] but appreciable decomplexation of the arene–manganese product occurred under the reaction conditions employed (CH_3CN, THF). Better yields of the complex have now been obtained by generating the sodium salt of protected tyrosine in THF, removal of the solvent, and then reaction of the aryloxide with complex **1** in acetone as solvent. In this manner, both enantiomers of protected tyrosine were converted to the manganese adducts **31A** and **31B** in good yield. We have previously shown[4] that no racemization occurs during this reaction.

Arene–$Mn(CO)_3$ cations are known[3] to react with carbanion nucleophiles to give stable dienyl–$Mn(CO)_3$ intermediates that can be oxidatively demetalated to give substituted aromated compounds. Alkoxy groups have been shown to be meta directing, due to electronic deactivation of the ortho and para positions toward nucleophilic attack, and this has been previously used by us to synthesize deoxyristomycinic acid derivatives.[7] In the present study we planned to introduce a glycine side chain via addition of Schöllkopf's chiral glycine enolate equivalent **32**[8] at the meta position of the manganese-complexed aromatic ring of enantiomerically pure complexes **31A** and **31B**. The reaction of **31A** and 1 equiv of **32** in tetrahydrofuran (THF) at −78 °C led to complete demetalation of **31A** to give *N*-acetyl-*O*-phenyltyrosine methyl ester as the major product. The decomplexation presumably occurs via addition of **32** to a carbonyl ligand, followed by deinsertion coupled with partial disengagement of the arene, which subsequently dissociates completely in the presence of THF as a donor ligand. When the nucleophile addition was carried out at −100 °C, demetalation was virtually eliminated and a mixture of dienyl–$Mn(CO)_3$ complexes was obtained (Scheme II). The reason for the temperature dependence of this reaction is presently not understood, although it is possible that a reduction in the rate of deinsertion, coupled with reversible nucleophile addition to CO ligand, is responsible.

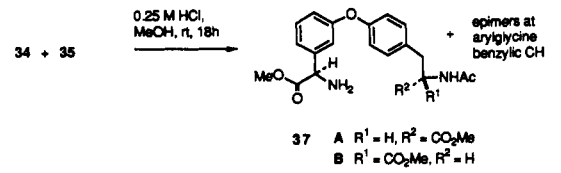
(5) ElSohly, H. N.; Ma, G. E.; Turner, C. E.; ElSohly, M. A. *J. Nat. Prod.* **1984**, *47*, 445.
(6) Sun, X.; Liang, X. *Huaxue Shiji* **1984**, *4*, 196; *Chem. Abstr.* **1982**, *97*, 197937t.
(7) Pearson, A. J.; Lee, S. H.; Gouzoules, F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2551. Pearson, A. J.; Bruhn, P. R.; Gouzoules, F.; Lee, S. H. *J. Chem. Soc., Chem. Commun.* **1989**, 659.

Scheme II. Reaction of Arene–$Mn(CO)_3$ Cations with Schöllkopf's Chiral Glycine Enolate Equivalent and Subsequent in Situ Decomplexation

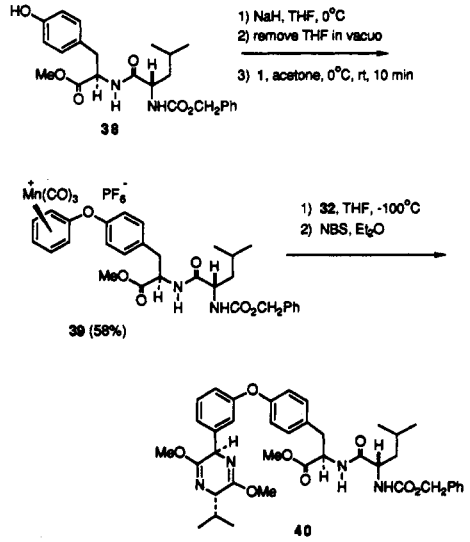


Owing to the fact that the dienyl–$Mn(CO)_3$ group is chiral in the immediate products, a complex mixture of diastereomers results from the reaction of **31A** or **31B** with **32**, and little useful information could be obtained from spectroscopic data. Therefore, the mixture was oxidized directly to the diaryl ether derivatives **34**, **35**, and **36**, obtained in ca. 65% combined overall yield. NMR analysis indicated a meta:ortho ratio of ca. 14:1 and a diastereomeric excess for **34** vs **35** of ca. 75%, somewhat lower than the de's obtained from simple alkylation reactions of **32**.[8] The major diastereomer was determined to be **34** by comparison of coupling constants with those observed for previously characterized derivatives.[7] Thus, the benzylic proton (R^3 in structures) is observed as a doublet (long range coupling) with consistently smaller coupling constant for the series $R^3 = \alpha$-H (δ 5.06, J = 3.6 Hz, for **34A**) compared to $R^3 = \beta$-H (δ 5.19, J = 4.8 Hz, for **35A**). This mixture was inseparable by TLC, and it was not possible to determine whether partial racemization had occurred in the tyrosine moiety during this reaction sequence. Accordingly, the mixture was hydrolyzed with 0.25 M hydrochloric acid in methanol, giving the amino ester derivatives **37A** and **37B** from the two series. These diastereomeric compounds could each be separated from the products of ortho addition by preparative TLC and showed identical R_f values. This is important because it shows that fractionation of diastereomers does not occur during purification, and an assessment could be made of the extent of racemization of the tyrosine moiety during the entire sequence. While the ^{1}H NMR spectra of **37A** and **37B** were identical, it was found that an equimolar mixture of these compounds showed a split CO_2Me signal for the tyrosine residue (by comparison with parent compounds) in the presence of $Eu(Hfbc)_3$ at a 0.8:1 ratio of shift reagent to substrate. An identical NMR experiment using **37B** alone indicated a split peak ratio of ca. 6.5:1, which is consistent with the 75% diastereomeric excess observed for **34** vs **35**. On this basis we conclude that no appreciable racemization of the tyrosine residue occurs.

These experiments, together with our earlier studies,[7] demonstrate that addition of carbanion nucleophiles, such



as **32**, to the arene–$Mn(CO)_3$ moiety can be carried out selectively in the presence of an acylamino ester group, having one acidic NH group which might compete by protonation of the nucleophile. We were interested in determining whether a high level of selectivity could also be obtained in the presence of two acidic NH groups. Accordingly, the protected dipeptide **38**, prepared by standard methods, was treated with complex **1** in the usual way, to afford complex **39** in 58% yield. Reaction of **39** with **32**, followed by oxidation of the intermediate dienyl complex with NBS, gave the aryl ether derivative **40** in 44% overall yield, which was stereoisomerically pure according to ^{1}H NMR spectroscopy (compare with **34A** and **35A**: the benzylic dihydropyrazine protons are easily distinguished).



In summary, these studies have established viable methodology for selective arylation of polyfunctional phenolic compounds and for the construction of diaryl ethers having amino acid and peptide side chains on both aromatic rings. This is particularly useful for synthesizing molecules with arylglycine functionality which is very easily racemized under mildly basic conditions.

For the selective arylation procedure described herein to be useful for constructing vancomycin building blocks, the preparation of arene–manganese complexes from 4-chlorophenylalanine and 4-chlorophenylserine derivatives is required. So far, all attempts to prepare such complexes in our laboratory have failed. The second approach described in this paper requires the preparation of manganese complexes of 2,6-dichlorophenol derivatives. This too has proven to be problematic. Consequently, a more promising approach, using arene–ruthenium complexes, has now been developed.[1k]

Experimental Section

NMR spectra were recorded at 200 MHz. Melting points are uncorrected. All reactions were conducted under an inert atmosphere of dry, oxygen-free Ar or N_2 and reaction vessels were flame- or oven-dried prior to use. Organic solvents were purified prior to use as follows: benzene and THF were freshly distilled from Na/benzophenone; Et_2O was freshly distilled from $LiAlH_4$; CH_3CN and CH_2Cl_2 were freshly distilled from CaH_2. Acetone

(8) Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem., Int. Ed. Engl.* 1981, *20*, 798.

was freshly distilled after being stirred over anhydrous Na_2SO_4 for 4 h. Dry methanol was prepared by distillation after drying with Na metal twice and stored over 4-Å molecular sieves under argon. DMF was vacuum distilled after being stirred over anhydrous Na_2SO_4 and stored over 4-Å molecular sieves under Ar. Aromatic compounds used in complexation reactions were purchased or preparaed by standard procedures and distilled or recrystallized prior to use. Chloroarene–manganese complexes were prepared by literature methods.[3]

Arylation of Methyl 3,4,5-Trihydroxybenzoate. Methyl 3,4,5-trihydroxybenzoate (**19**) (0.090 g, 0.49 mmol) was added to a suspension of 60% NaH/mineral oil (0.020 g, 0.49 mmol) in THF (5 mL). After stirring for 45 min at rt, complex **8** (0.200 g, 0.49 mmol) was added, and stirring was continued for 3 h. Acetonitrile (5 mL) was added and the mixture was stirred overnight, after which time it was poured into brine (20 mL) and extracted with ether (4 × 5 mL), dried ($MgSO_4$), and evaporated in vacuo to give a mixture of products. Flash chromatography (40% EtOAc–hexanes) gave 0.043 g (24%) of methyl 4-hydroxy-3,5-bis(tolyloxy)benzoate (**22**), and 0.060 g (45%) of a 4:1 mixture of methyl 3,5-dihydroxy-4-(tolyloxy)benzoate (**21**) and methyl 3,4-dihydroxy-5-(tolyloxy)benzoate (**20**), all obtained as colorless oils. Data for **22**. IR (CCl_4): ν_{max} 3530, 1720, 1595, 1500, 1428, 1320, 1200, 1017 cm^{-1}. ^1H NMR (D_2O): δ 7.32 (2 H, s, H2, H6); 7.08 (4 H, d, $J_{8,9}$ = 8.3 Hz, H9, H11, H9′, H11′); 6.87 (4 H, d, $J_{8,9}$ = 8.3 Hz, H8, H12, H8′, H12′); 6.07 (1 H, br s, OH); 3.75 (3 H, s, CO_2Me); 2.34 (6 H, s, 2 × CH_3). Data for **21**. IR (CCl_4): ν_{max} 3560, 1728, 1598, 1501, 1370, 1221, 1202, 1161 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.26 (2 H, s, H2, H6); 7.12 (2 H, d, $J_{8,9}$ = 8.7 Hz, H9, H11); 6.86 (2 H, d, $J_{8,9}$ = 8.7 Hz, H8, H12); 5.28 (2 H, s, OH); 3.90 (3 H, s, CO_2Me); 2.31 (3 H, s, CH_3). Data for **20**. IR (CCl_4): ν_{max} 3522, 1723, 1435, 1329, 1202 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.41 (1 H, d, $J_{2,6}$ = 1.9 Hz, H2); 7.29 (1 H, d, $J_{2,6}$ = 1.9 Hz, H6); 7.09 (2 H, d, $J_{8,9}$ = 8.6 Hz, H9, H11); 6.82 (2 H, d, $J_{8,9}$ = 8.6 Hz, H8, H12); 5.28 (2 H, s, OH); 3.79 (3 H, s, CO_2Me); 2.29 (3 H, s, CH_3).

Methyl 4-(Benzyloxy)-3,5-dihydroxybenzoate (23). A. A mixture of **19** (2.00 g, 10.9 mmol), K_2CO_3 (1.80 g, 13.0 mmol), and KI (0.30 g, 1.8 mmol) was stirred in acetone (200 mL) for 30 min. Benzyl chloride (1.65 g, 13.0 mmol) was added and the solution was heated under reflux for 8 h. The reaction mixture was then cooled, poured into water (200 mL), and extracted with ether (3 × 150 mL). The combined ether extracts were washed with brine (3 × 100 mL), dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography (30% ether in hexanes) gave ester **23**, 0.827 g (21%) of methyl 4,5-bis(benzyloxy-3-hydroxybenzoate (**24**), and 0.465 g (9%) of methyl 3,4,5-tris(benzyloxy)benzoate (**25**). Data for **23**. IR ($CHCl_3$): ν_{max} 3540, 1720, 1605, 1458, 1442, 1366, 1010 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.39 (5 H, s, ArH); 7.20 (2 H, s, H2, H6); 5.67 (2 H, s, OH (removed by exchange with D_2O)); 5.13 (2 H, s, CH_2); 3.87 (3 H, s, CO_2Me). mp 134–135 °C (lit.[5] mp 126–128 °C). Data for **24**. IR (CCl_4): ν_{max} 3536, 1720, 1446, 1177, 1097 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.38–7.28 (5 H, m, 5-CH_2Ph ArH); 7.23 (5 H, s, 4-CH_2Ph ArH); 7.19 (1 H, d, $J_{2,6}$ = 1.9 Hz, H2); 7.16 (1 H, d, $J_{2,6}$ = 1.9 Hz, H6), 5.63 (1 H, s, OH (exchanges with D_2O)); 5.10 (2 H, s, 5-CH_2Ar); 5.07 (2 H, s, 4-CH_2Ar); 3.80 (3 H, s, CO_2Me). mp 93–94 °C. Data for **25**. IR (CCl_4): ν_{max} 1720, 1427, 1330, 1198, 1072 cm^{-1}. ^1H NMR (CCl_4): δ 7.34 (10 H, m, 3-CH_2Ph ArH, 5-CH_2Ph ArH); 7.28 (2 H, s, H2, H6); 7.25 (5 H, m, 4-CH_2Ph ArH); 5.05 (4 H, s, 3-CH_2Ar, 5-CH_2Ar); 5.00 (2 H, s, 4-CH_2Ar); 3.81 (3 H, s, CO_2Me). mp 97–99 °C.

B. To a solution of **27** (1.60 g, 4.46 mmol) in MeOH (80 mL) was added a solution of K_2CO_3 (4.07 g) in water (40 mL). After being stirred at rt for 30 min, the reaction mixture was acidified with excess 10% HCl. The acidified aqueous solution was extracted with EtOAc (3 × 100 mL). The combined EtOAc extracts were washed with brine (2 × 100 mL) and water (1 × 100 mL), dired ($MgSO_4$), and evaporated in vacuo. Recrystallization ($CHCl_3$–pentane) gave 1.110 g (90%) of **23**, mp 133–134 °C. Spectral data are identical to those reported above.

Methyl 3,4,5-Triacetoxybenzoate (26). A mixture of **19** (5.00 g, 27.15 mmol) and acetic anhydride (9.98 g, 97.74 mmol) in pyridine (25 mL) was stirred overnight at rt. The reaction mixture was then poured into 10% HCl in brine (100 mL) and extracted with EtOAc (3 × 75 mL). The combined EtOAc extracts were washed with aqueous $NaHCO_3$ until the wash solution was basic, washed with brine (50 mL), dried ($MgSO_4$), and evaporated in vacuo. Recrystallization (EtOH) gave 6.56 g (78%) of **26**, mp 126.5–128 °C. IR ($CHCl_3$): ν_{max} 1781, 1726, 1433, 1372, 1328, 1166 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.81 (2 H, s H2, H6); 3.91 (3 H, s, CO_2Me); 2.31 (3 H, s, 4-OAc); 2.30 (6 H, s, 3-OAc, 5-OAc). Anal. Found: C, 54.35; H, 4.80. Calcd for $C_{14}H_{14}O_8$: C, 54.19; H, 4.56.

Methyl 3,5-Diacetoxy-4-(benzyloxy)benzoate (27). A mixture of **26** (2.00 g, 6.45 mmol), K_2CO_3 (2.70 g, 19.35 mmol), KI (0.165 g, 0.97 mmol), and benzyl chloride (1.63 g, 12.90 mmol) was heated in acetone (100 mL) under reflux for 18 h. The reaction mixture was then cooled, poured into water (150 mL), and extracted with Et_2O (3 × 100 mL). The combined Et_2O extracts were washed with brine (3 × 100 mL), dried ($MgSO_4$), and evaporated in vacuo. Recrystallization (EtOH) gave 1.67 g (72%) of **27**, mp 94–96 °C. IR ($CHCl_3$): ν_{max} 1774, 1723, 1500, 1437, 1371, 1327, 1180, 1040 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.69 (2 H, s, H2, H6); 7.36 (5 H, s, CH_2Ph ArH); 5.05 (2 H, s, CH_2); 3.89 (3 H, s, CO_2Me); 2.20 (6 H, s, 3-OAc, 5-OAc). Anal. Found: C, 63.54; H, 5.12. Calcd for $C_{19}H_{18}O_7$: C, 63.67; H, 5.07.

4-Hydroxy-3-(tolyloxy)benzaldehyde (9). To a stirred suspension of NaH (0.021 g, 0.49 mmol) in DMF (1 mL) at 0 °C was added 3,4-dihydroxybenzaldehyde (0.0673 g, 0.49 mmol). After 1 h, a solution of complex **8** (0.200 g, 0.49 mmol) in CH_3CN (10 mL) was added via syringe and stirring was continued overnight as the reaction mixture warmed slowly to room temperature. The reaction mixture was poured into 10% HCl in brine (20 mL) and extracted with Et_2O (4 × 20 mL). The combined Et_2O extracts were washed with brine (3 × 20 mL), dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography (60% EtOAc–hexanes) gave 0.054 g (49%) of **9** and 0.012 g of unreacted 3,4-dihydroxybenzaldehyde. The yield, calculated on the basis of the recovered starting material, was 59%, mp 77–78 °C (CCl_4–petroleum ether). IR (CCl_4): ν_{max} 3555, 1702, 1603, 1510, 1447, 1296, 1280, 1227, 1166 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.75 (1 H, s, CHO); 7.54 (1 H, dd, $J_{5,6}$ = 8.3 Hz, $J_{2,6}$ = 1.8 Hz, H6); 7.31 (1 H, d, $J_{2,6}$ = 1.8 Hz, H2); 7.19 (2 H, d, $J_{8,9}$ = 8.6 Hz, H9, H11); 7.15 (1 H, d, $J_{5,6}$ = 8.3 Hz, H5); 6.96 (2 H, d, $J_{8,9}$ = 8.6 Hz, H8, H12); 6.33 (1 H, s, OH); 2.36 (3 H, s, CH_3). Anal. Found: C, 73.69; H, 5.2. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30.

4-Methoxy-3-(tolyloxy)benzaldehyde (11). A. The procedure was identical to that for **9**, using NaH (0.49 mmol), 3-hydroxy-4-methoxybenzaldehyde (0.074 g, 0.49 mmol), DMF (1.5 mL), complex **8** (0.200 g, 0.49 mmol), and CH_3CN (10 mL). Flash chromatography (25% EtOAc–hexanes) gave 0.052 g (44%) of **11**, mp 108–110 °C (CCl_4–petroleum ether). IR (CCl_4): ν_{max} 1700, 1603, 1510, 1276, 1228, 1120 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.79 (1 H, s, CHO); 7.61 (1 H, dd, $J_{5,6}$ = 8.5 Hz, $J_{2,6}$ = 1.9 Hz, H6); 7.37 (1 H, d, $J_{2,6}$ = 1.9 Hz, H2); 7.13 (2 H, d, $J_{8,9}$ = 8.5 Hz, H9, H11); 7.09 (1 H, d, $J_{5,6}$ = 8.5 Hz, H5); 6.89 (2 H, d, $J_{8,9}$ = 8.5 Hz, H8, H12); 3.96 (3 H, s, OCH_3); 2.34 (3 H, S, CH_3). Anal. Found: C, 73.37; H, 5.78. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82.

B. A mixture of **9** (0.033 g, 0.096 mmol), K_2CO_3 (0.014 g, 0.10 mmol), dimethyl sulfate (0.014 g, 0.11 mmol), and DMF (2 mL) was stirred at rt for 30 h. The reaction mixture was poured into brine (20 mL) and extracted with Et_2O (3 × 20 mL). The combined Et_2O extracts were washed with brine (3 × 20 mL), dried ($MgSO_4$), and evaporated in vacuo. Preparative layer chromatography (30% EtOAc–hexanes) gave 0.013 g (56%) of material which was spectroscopically identical to **11**.

3-Methoxy-4-(tolyloxy)benzaldehyde (12). The procedure was identical to that above, using 0.24 mmol of 4-hydroxy-3-methoxybenzaldehyde. Flash chromatography (25% EtOAc–hexanes) afforded 0.026 g (45%) of **12**, mp 76–77 °C (CCl_4–petroleum ether). IR (CCl_4): ν_{max} 1701, 1591, 1503, 1271, 1235, 1153 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.87 (1 H, s, CHO); 7.51 (1 H, d, $J_{2,6}$ = 1.9 Hz, H2); 7.35 (1 H, dd, $J_{5,6}$ = 8.2 Hz, $J_{2,6}$ = 1.9 Hz, H6); 7.18 (2 H, d, $J_{8,9}$ = 8.3 Hz, H9, H11); 6.96 (2 H, d, $J_{8,9}$ = 8.3 Hz, H8, H12); 6.86 (1 H, d, $J_{5,6}$ = 8.2 Hz, H5); 3.97 (3 H, s, OCH_3); 2.36 (3 H, s, CH_3). Anal. Found: C, 74.60; H, 5.79. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82.

Methyl 4-(Benzyloxy)-5-hydroxy-3-(tolyloxy)benzoate (28). A 1.0 M solution of tetra-*n*-butylammonium fluoride (TBAF, 1.0 mL) was added to a solution of **23** (0.134 g, 0.49 mmol) in THF (5 mL). After stirring for 15 min at rt, a solution of **8** (0.200 g, 0.49 mmol) in CH_3CN (10 mL) was added, and stirring was continued at rt for 30 h. The reaction mixture was then poured into 10% HCl in brine (20 mL) and extracted with Et_2O (3 × 20

mL). The combined Et_2O extracts were washed with brine (3 × 20 mL), dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography (25% EtOAc–hexanes) gave 0.083 g (47%) of **28** and 0.055 g of recovered **23**. The yield of **28** based upon recovered **23** is 79%, mp 90–91 °C (CCl_4–pentane). IR (CCl_4): ν_{max} 3525, 1732, 1354, 1207, 1053 cm^{-1}. ^1H NMR (CCl_4): δ 7.25 (1 H, d, $J_{2,6}$ = 2.0 Hz, H6); 7.21 (5 H, s, CH_2Ph ArH); 7.05 (1 H, d, $J_{2,6}$ = 2.0 Hz, H2); 7.03 (2 H, d, $J_{8,9}$ = 8.3 Hz, H9, H11); 6.79 (2 H, d, $J_{8,9}$ = 8.3 Hz, H8, H12); 5.73 (1 H, br s, OH), 5.09 (2 H, s, CH_2Ph); 3.73 (3 H, s, CO_2Me); 2.29 (3 H, s, CH_3). Anal. Found: C, 72.32; H, 5.38. Calcd for $C_{22}H_{20}O_5$: C, 72.50; H, 5.54.

Methyl 4-(Benzyloxy)-5-(phenyloxy)-3-(tolyloxy)benzoate (29). The procedure was identical to that for **28**, using 0.070 g (0.192 mmol) of **28**. Flash chromatography (10% EtOAc–hexanes) gave 0.069 g (81%) of **29**, mp 74–75 °C (CCl_4–pentane). IR ($CHCl_3$): ν_{max} 1721, 1502, 1492, 1433, 1422, 1339, 1168, 1009 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.40–6.86 (10 H, m, ArH); 5.15 (2 H, s, CH_2Ph); 3.79 (3 H, s, CO_2Me); 2.34 (3 H, s, CH_3). Anal. Found: C, 75.98; H, 5.50. Calcd for $C_{28}H_{24}O_5$: C, 76.34; H, 5.50.

L-Tyrosine Methyl Ester. This was prepared according to the literature procedure[9] and gave the product, mp 135–136 °C. $[\alpha]^{26}_D$ = +27.1° (c = 2, MeOH) (lit.[9] mp (EtOAc) 135–6 °C, $[\alpha]^{26}_D$ = +26.75° (MeOH)).

D-Tyrosine Methyl Ester. The procedure was identical to that for L-tyrosine and gave the product, mp 134–136 °C (EtOAc), $[\alpha]^{24}_D$ = −27.1° (c = 2, MeOH). IR ($CHCl_3$): ν_{max} 3495, 3380, 3310, 1738, 1617, 1603, 1514, 1430, 1174 cm^{-1}. ^1H NMR ($CDCl_3$–DMSO-d_6): δ 8.70 (1 H, br s, OH); 6.99 (2 H, d, $J_{2,3}$ = 8.4 Hz, H2, H6); 6.77 (2 H, d, $J_{2,3}$ = 8.4 Hz, H3, H5); 3.71 (3 H, s, CO_2Me); 3.67 (1 H, dd (partially obscured), $J_{7a,8} + J_{7b,8}$ = 12.9 Hz, H8); 2.99 (1 H, ABX q, $J_{7a,7b}$ = 13.6 Hz, $J_{7a,8}$ = 5.3 Hz, H7a); 2.77 (1 H, ABX q, $J_{7a,7b}$ = 13.6 Hz, $J_{7b,8}$ = 7.6 Hz, H7b); 1.45 (2 H, br s, NH_2).

***N*-Acetyl-L-tyrosine Methyl Ester (30A).** The literature procedure[10] gave an 85% yield of **30A**, mp 134–135 °C, $[\alpha]^{26}_D$ = +27.3° (c = 2, MeOH) (lit.[10] mp 132 °C, $[\alpha]^{25}_D$ = +27.8° (c = 2, MeOH)). IR ($CHCl_3$): ν_{max} 3503, 3435, 1744, 1675, 1503, 1440, 1377 cm^{-1}. ^1H NMR ($CDCl_3$–DMSO-d_6): δ 8.58 (1 H, br s, OH); 6.93 (2 H, d, $J_{2,3}$ = 8.5 Hz, H2, H6); 6.76 (2 H, d, $J_{2,3}$ = 8.5 Hz, H3, H5); 6.45 (1 H, br d, $J_{8,NH}$ = 7.6 Hz, N*H*Ac); 4.78 (1 H, dt, $J_{8,NH}$ = 7.6 Hz, $J_{7,8}$ = 6.0 Hz, H8); 3.71 (3 H, s, CO_2Me); 3.00 (2 H, d, $J_{7,8}$ = 6.0 Hz, H7); 1.98 (3 H, s, NHAc).

***N*-Acetyl-D-tyrosine Methyl Ester (30B).** A procedure identical to the above, using 1.95 g of D-tyrosine methyl ester, gave after recrystallization (EtOAc–petroleum ether) 1.60 g (68%) of **30B**, mp 134–135.5 °C. $[\alpha]^{25}_D$ = −26.6° (c = 2, MeOH).

***N*-(Benzyloxycarbonyl)-L-leucine.** L-Leucine (13.1 g, 100 mmol) was dissolved in water (300 mL) and 5 N NaOH (20 mL) and cooled to 0 °C. Small portions of benzyl chlorocarbonate (18.77 g, 110 mmol total) and 2 N NaOH (55 mL total) were added alternately over 1.5 h. After warming to rt and stirring for an additional 30 min, the pH was adjusted to 10 with 2 N NaOH, the solution was extracted with Et_2O (4 × 50 mL), and the organic layer was discarded. The aqueous layer was acidified to pH 2 with 5 N HCl and extracted with Et_2O (3 × 40 mL). The Et_2O extracts were combined, dried ($MgSO_4$), and evaporated in vacuo to give 24 g (90%) of product as a colorless oil, which was not further purified. This material was stored as a 0.54 M solution in EtOAc. IR ($CHCl_3$): ν_{max} 3432, 1720, 1510 cm^{-1}. ^1H NMR ($CDCl_3$): δ 10.10 (1 H, br s, CO_2H); 7.35 (5 H, s, ArH); 5.20 (1 H, br s (obscured), NH); 5.13 (2 H, s, OCH_2Ph); 4.43 (1 H, br s, H1); 1.73 (3 H, m, H2, H3); 0.96 (6 H, d, J = 3.3 Hz, H4, H5).

***N*-(Benzyloxycarbonyl)-L-leucyl-L-tyrosine Methyl Ester (38).** A mixture of L-tyrosine methyl ester (0.976 g, 5.00 mmol), *N*-(benzyloxycarbonyl)-L-leucine (1.327 g, 5.00 mmol), and hydroxybenzotriazole (0.676 g, 5.00 mmol) in THF (20 mL) was cooled to 0 °C, and DCC (1.013 g, 5.0 mmol) was added. After stirring for 1 h at 0 °C, the solution was allowed to warm to rt and let stand for 4 h. EtOAc (10 mL) was added and the precipitated dicyclohexylurea was filtered off and washed with EtOAc (3 × 35 mL). The combined filtrates were washed with aqueous $NaHCO_3$ (2 × 10 mL), dried ($MgSO_4$), and evaporated in vacuo. Recrystallization (EtOAc–petroleum ether) gave 1.54 g (69%) of **38**, mp 108–110 °C, $[\alpha]^{25}_D$ = −16.2° (c = 2.5, MeOH) (lit.[11] mp 88–92 °C $[\alpha]_D$ = −15.5° (c = 2.5 MeOH)). IR ($CHCl_3$): ν_{max} 3592, 3430, 1740, 1720, 1672, 1603, 1504, 1490 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.34 (5 H, s, CH_2Ph ArH); 6.91 (2 H, d, $J_{2,3}$ = 8.3 Hz, H2, H6); 6.66 (2 H, d, $J_{2,3}$ = 8.3 Hz, H3, H5); 6.58 (1 H, d, $J_{8,NH}$ = 8.0 Hz, NH_{tyr}); 6.20 (1 H, br s, OH); 5.20 (1 H, d, $J_{11,NH}$ = 8.8 Hz, NH_{leu}); 5.10 (2 H, s, CH_2Ar); 4.83 (1 H, m, H8); 4.18 (1 H, m, H11); 3.73 (3 H, s, CO_2Me); 3.05 (2 H, center ABX q, H7); 1.63 (3 H, m, H12, H13); 0.89 (6 H, d, J_{13,CH_3} = 5.8 Hz, 2 × CH_3). Decoupling–irradiation at δ 4.83 collapses δ 6.58 d and simplifies δ 3.05 m. Irradiation at δ 4.18 collapses δ 5.20 d and simplifies δ 1.63 m. Anal. Found: C, 65.24; H, 7.0. Calcd for $C_{24}H_{30}N_2O_6$: C, 65.15; H, 6.79.

Tricarbonyl[*N*-acetyl-4-[(1–6-η)-phenyloxy]-L-tyrosine methyl ester]manganese(1+) Hexafluorophosphate (31A). An ice-cold solution of **30A** (0.356 g, 1.50 mmol) in THF (5 mL) was added dropwise to an ice-cold stirred suspension of NaH (1.40 mmol) in THF (20 mL). After stirring for 0.5 h at 0 °C, the THF was removed in vacuo; acetone (20 mL) was added and the mixture was cooled to 0 °C. Complex **1** as the BF_4^- salt[3] (0.396 g, 1.0 mmol) was added in one portion and the ice bath removed. After 10 min, excess aqueous NH_4PF_6 was added and the product was extracted with CH_2Cl_2 (2 × 50 mL). The combined CH_2Cl_2 extracts were washed with water, dried ($MgSO_4$), concentrated in vacuo to ~10 mL, and added dropwise to rapidly stirred Et_2O (300 mL) to precipitate the product. The yellow crystals were collected by filtration, washed with Et_2O, and dried in vacuo overnight to give 0.431 g (72%) of **31A**, mp 120–122 °C dec, $[\alpha]^{26}_D$ = +3.8° (c = 1, CH_3CN). IR (CH_3CN): ν_{max} 3373, 2081, 2024, 1747, 1682, 1267, 850 cm^{-1}. ^1H NMR (CD_3CN): δ 7.41 (2 H, d, $J_{8,9}$ = 8.0 Hz, H9, H11); 7.18 (2 H, d, $J_{8,9}$ = 8.0 Hz, H8, H12); 6.75 (2 H, t, J = 6.9 Hz, H3, H5); 6.75 (1 H, obscured, NH); 6.00 (2 H, d, $J_{2,3}$ = 6.9 Hz, H2, H6); 5.94 (1 H, t, obscured, J = 6.9 Hz, H4); 4.69 (1 H, m, H14); 3.67 (3 H, s, CO_2Me); 3.12 (2 H, m, center of unresolved ABX q, H13); 1.88 (3 H, s, NHAc). Anal. Found: C, 37.07; H, 2.93. Calcd for $C_{21}H_{19}F_6MnNO_2P$: C, 37.23; H, 3.21.

Tricarbonyl[*N*-acetyl-4-[(1–6-η)-phenyloxy]-D-tyrosine methyl ester]manganese(1+) Hexafluorophosphate (31B). The procedure was identical to that for **31A**. Yield: 0.430 g (72%), mp 115–117 °C dec, $[\alpha]^{26}_D$ = −4.3° (c = 1.0, CH_3). IR (CH_3CN): ν_{max} 3380, 2083, 2030, 1750, 1683, 1268, 854 cm^{-1}. ^1H NMR (CD_3CN): δ 7.41 (2 H, d, $J_{8,9}$ = 8.3 Hz, H9, H11); 7.18 (2 H, d, $J_{8,9}$ = 8.3 Hz, H8, H12); 6.75 (2 H, m, H3, H5); 6.75 (1 H, obscured, NH); 6.00 (3 H, m, H2, H4, H6); 4.65 (1 H, m, H14); 3.67 (3 H, s, CO_2Me); 3.12 (2 H, center of unresolved ABX q, H14); 1.87 (3 H, s, NHAc). Anal. Found: C, 38.51; H, 3.09. Calcd for $C_{21}H_{19}F_6MnNO_7P$: C, 38.23; H, 3.29.

Tricarbonyl[*N*-(benzyloxycarbonyl)-L-leucinyl-4-[(1–6-η)-phenyloxy]-L-tyrosine methyl ester]manganese(1+) Hexafluorophosphate (39). The procedure was identical to that for **31**, using **38** (0.663 g, 1.50 mmol) to give 0.446 g (58%) of **39**, mp 131–133 °C, $[\alpha]$ = +2.4° (c = 1, acetonitrile). IR (CH_3CN): ν_{max} 3365, 2080, 2023, 1745, 1727, 1689, 1265, 853 cm^{-1}. ^1H NMR (CD_3CN): δ 7.39 (2 H, d, $J_{8,9}$ = 8.6 Hz, H9, H11); 7.34 (5 H, s, CH_2Ph ArH); 7.13 (2 H, d, $J_{8,9}$ = 8.6 Hz, H8, H12); 6.95 (1 H, br d, $J_{14,NH}$ = 8.3 Hz, NH_{tyr}); 6.72 (2 H, m, H3, H5); 5.97 (3 H, m, H2, H4, H6); 5.81 (1 H, br d, $J_{17,NH}$ = 8.3 Hz, NH_{leu}); 4.66 (1 H, ddd, $J_{14,NH}$ = 8.3 Hz, $J_{13a,14}$ = 8.3 Hz, $J_{13b,14}$ = 5.4 Hz, H14); 4.05 (1 H, dt, $J_{17,NH}$ = 8.3 Hz, $J_{17,18}$ = 7.6 Hz, H17); 3.68 (3 H, s, CO_2Me); 3.22 (1 H, ABX q, $J_{13a,13b}$ = 13.8 Hz, $J_{13b,14}$ = 5.4 Hz, H13b); 3.02 (1 H, ABX q, $J_{13a,13b}$ = 13.8 Hz, $J_{13a,14}$ = 8.3 Hz, H13a); 1.62 (3 H, m, H17, H18); 0.90 (6 H, $J_{19,20}$ = 6.4 Hz, 2 × CH_3). Anal. Found: C, 48.39; H, 4.16. Calcd for $C_{33}H_{34}F_6MnN_2O_9P$: C, 49.39; H, 4.27.

Nucleophilic Additions to Diaryl Ether–Manganese Complexes. Preparation of 34A, 35A, and 36A. A solution of the lithium anion **32** was prepared by treating 3(*S*)-2,5-dimethoxy-3-isopropyl-3,6-dihydropyrazine[8] (0.92 g, 0.50 mmol) in THF (2.5 mL) with *n*-BuLi (0.36 mL of 1.4 M solution in hexanes) at −78 °C for 30 min. This solution was cooled to −100 °C and added via canula to a stirred suspension of **31A** (0.149 g, 0.25 mmol) in THF (2.0 mL) also at −100 °C. After 2 h the reaction

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mixture was quenched at −100 °C by the addition of aqueous NH_4Cl (10 mL). The reaction mixture was warmed to rt and extracted with ether (3 × 15 mL). The combined extracts were dried ($MgSO_4$) and treated with NBS (0.044 g, 0.25 mmol). After being stirred at rt for 30 min, the ether solution was washed with water (25 mL) and brine (25 mL). Drying ($MgSO_4$), evaporation of the solvent in vacuo, and flash chromatography (60% EtOAc–hexanes) gave 0.060 g (49%) of a mixture of products as colorless oils. These products were assigned on the basis of the characteristic doublets in the NMR spectrum as **34A** (δ 5.01, J = 3.6 Hz), **35A** (δ 5.19, J = 5.0 Hz), and **36A** (δ 5.36, J = 3.8 Hz), present in a ratio of 12.5:2:1. This represents a diastereomeric excess, **34A** over **35A** of 72% and a ratio of ortho:meta addition of *ca.* 1:14. Spectroscopic data for the major product: IR ($CHCl_3$) ν_{max} 3430, 1741, 1683, 1503, 1486, 1440, 1013 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.29 (1 H, m, H5); 7.15–6.84 (7 H, m, ArH); 5.93 (1 H, br d, $J_{21,NH}$ = 7.7 Hz, NH_{tyr}); 5.06 (1 H, d, $J_{7,10}$ = 3.6 Hz, H7); 4.87 (1 H, dt, $J_{21,NH}$ = 7.7 Hz, $J_{20a,21} + J_{20b,21}$ = 11.0 Hz, H21); 4.07 (1 H, dd, $J_{3,10}$ = 3.6 Hz, $J_{10,13}$ = 3.6 Hz, H10); 3.74 (3 H, s, CO_2Me); 3.72 (3 H, s, OCH_3); 3.64 (3 H, s, OCH_3); 3.13 (1 H, ABX q, $J_{20a,20b}$ = 13.6 Hz, $J_{20a,21}$ = 5.4 Hz, H20a); 3.08 (1 H, ABX q, $J_{20a,20b}$ = 13.6 Hz, $J_{20b,21}$ = 5.6 Hz, H20b); 2.38 (1 H, m, H13); 2.01 (3 H, s, NHAc); 1.10 (3 H, d, J_{13,CH_3} = 6.8 Hz, CH_3); 0.75 (3 H, d, J_{13,CH_3} = 6.8 Hz, CH_3). HRMS: found (M^+) 495.2384, calcd for $C_{27}H_{33}N_3O_6$ 495.2371. MS: m/e 495 (80), 493 (44), 436 (83), 434 (74), 365 (100), 363 (66).

Preparation of 34B. The procedure was identical to that for **34A**, using **32** (0.074 g, 0.40 mmol), THF (2 mL), complex **31B** (0.119 g, 0.20 mmol), and NBS (0.35 g, 0.20 mmol). Flash chromatography (60% EtOAc–hexanes) gave 0.322 g (65%) of a mixture of diastereomers and regioisomers in the ratio of **34B** (δ 5.06, J = 3.6 Hz):**35B** (δ 5.19, J = 5.0 Hz):**36B** (δ 5.36, J = 3.8 Hz) = 10.33:1.67:1.00. This represents a diastereomeric excess of 72% and a ratio of ortho:meta addition of 1:12. The major product represents 81% of the product mixture. Spectroscopic data for the major product: IR ($CHCl_3$) ν_{max} 3430, 1740, 1678, 1503, 1489, 1438 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.29 (1 H, m, H5); 7.07–6.91 (7 H, m, ArH); 5.93 (1 H, br d, $J_{21,NH}$ = 7.8 Hz, NH_{tyr}); 5.06 (1 H, d, $J_{7,10}$ = 3.6 Hz, H7); 4.88 (1 H, dt, $J_{21,NH}$ = 7.8 Hz, $J_{20a,21} + J_{20b,21}$ = 11.1 Hz, H21); 4.07 (1 H, dd, $J_{7,10}$ = 3.6 Hz, $J_{10,13}$ = 3.6 Hz, H10); 3.74 (3 H, s, CO_2Me); 3.72 (3 H, s, OMe); 3.64 (3 H, s, OMe); 3.13 (1 H, ABX, $J_{20a,20b}$ = 14.1 Hz, $J_{20a,21}$ = 5.4 Hz, H20a); 3.09 (1 H, ABX, $J_{20a,20b}$ = 14.1 Hz, $J_{20b,21}$ = 5.7 Hz, H20b); 2.38 (1 H, m, H13); 2.01 (3 H, s, NHAc); 1.10 (3 H, d, J = 6.8 Hz, CH_3); 0.75 (3 H, d, J = 6.8 Hz, CH_3). HRMS: found (M^+) 495.2364, calcd for $C_{27}H_{33}N_3O_6$ 495.2371. MS: m/e 495 (54), 493 (54), 436 (49), 434 (100), 365 (46), 363 (89).

Preparation of 40. The procedure was identical to that for **34A**, using **32** (0.92 g, 0.50 mmol), THF (2.5 mL), **39** (0.200 g, 0.25 mmol), and NBS (0.044 g, 0.25 mmol) to give, after flash chromatography, 0.076 g (44%) of isomerically pure **40**. IR ($CHCl_3$): ν_{max} 3430, 1740, 1720, 1675, 1603, 1503, 1490, 1438 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.31 (6 H, m, H5, ArH); 7.13–6.83 (7 H, m, ArH); 6.47 (1 H, br d, $J_{21,NH}$ = 7.7 Hz, NH_{tyr}); 5.09 (4 H, m, CH_2Ph, NH_{leu}, H7); 4.82 (1 H, m, H21); 4.14 (2 H, m, H10, H24), 3.72 (3 H, s, CO_2Me); 3.70 (3 H, s, OCH_3); 3.62 (3 H, s, OCH_3); 3.08 (2 H, m, H20); 2.30 (1 H, m, H10); 1.67 (3 H, m, H25, H26); 1.09 (3 H, d, J = 6.8 Hz, CH_3); 0.91 (6 H, d, J = 5.6, 2 × CH_3), 0.74 (3 H, d, J = 6.8 Hz, CH_3). Anal. Found: C, 66.76; H, 6.8; N, 8.3. Calcd for $C_{39}H_{48}N_4O_8$: C, 66.84; H, 6.9; N, 8.0.

Preparation of 37A. A solution of **34A** and isomers prepared above (0.050 g, 0.10 mmol) in 0.25 N HCl (5 mL) and MeOH (5 mL) was stirred for 18 h at rt. The reaction mixture was then shaken with Et_2O (10 mL) and the aqueous layer was separated and retained. Et_2O (10 mL) was added to the aqueous layer, aqueous ammonia was added in portions, and the mixture was shaken vigorously until pH reached 9. The Et_2O layer was collected, dired ($MgSO_4$), and evaporated in vacuo. Preparative layer chromatography (silica gel, 20% MeOH–EtOAc) gave 0.024 g (56%) of **37A** as a colorless oil. $[\alpha]^{24}_D$ = 5.5° (c = 0.6, MeOH). IR ($CHCl_3$): ν_{max} 3420, 1738, 1677, 1590, 1503, 1486, 1440 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.31 (1 H, t, J = 7.9 Hz, H5); 7.14–7.04 (4 H, m, H2, H6, H9, H11); 6.95–6.88 (3 H, m, H4, H8, H12); 5.94 (1 H, br d, $J_{14,NH}$ = 7.4 Hz, NHAc); 4.88 (1 H, dt, $J_{14,NH}$ = 7.4 Hz, $J_{13a,14} + J_{13b,14}$ = 11.0 Hz, H14); 4.59 (1 H, br s, H15); 3.74 (3 H, s, CO_2Me); 3.71 (3 H, s, CO_2Me); 3.14 (1 H, ABX q, $J_{13a,13b}$ = 13.9 Hz, $J_{13a,14}$ = 5.5 Hz, H13a); 3.08 (1 H, ABX q, $J_{13a,13b}$ = 13.9 Hz, $J_{13b,14}$ = 5.5 Hz, H13b); 2.01 (3 H, s, NHAc); 1.25 (2 H, br s, NH_2). HRMS: found (M^+) 400.1592, calcd for $C_{21}H_{24}N_2O_6$ 400.1635. MS: m/e 400 (1), 341 (100), 282 (55), 270 (34). Anal. Found: C, 62.55; H, 5.8; N, 7.1. Calcd for $C_{21}H_{24}N_2O_6$: C, 62.99; H, 6.04; N, 7.00.

Preparation of 37B. The procedure was identical to that for **37A**, using **34B** (0.025 g, 0.05 mmol) in 0.25 N HCl (2.5 mL) and MeOH (2.5 mL) to give, after preparative TLC (silica gel, 20% MeOH–EtOAc), 0.012 g (60%) of **37B**. $[\alpha]^{24}_D$ = −50.3° (c = 0.6, MeOH). IR ($CHCl_3$): ν_{max} 3425, 1738, 1675, 1588, 1503, 1485, 1437 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.31 (1 H, t, J = 7.9 Hz, H5); 7.16–7.04 (4 H, m, H2, H6, H9, H11); 6.95–6.89 (3 H, m, H4, H9, H13); 5.97 (1 H, br d, $J_{14,NH}$ = 7.4 Hz, NHAc); 4.88 (1 H, dt, $J_{14,NH}$ = 7.4 Hz, $J_{13a,14} + J_{13b,14}$ = 11.4 Hz, H14); 4.90 (1 H, br s, H15); 3.74 (3 H, s, CO_2Me); 3.71 (3 H, s, CO_2Me); 3.14 (1 H, ABX q, $J_{13a,13b}$ = 13.9 Hz, $J_{13a,14}$ = 5.8 Hz, H13a); 3.09 (1 H, ABX q, $J_{13a,13b}$ = 13.9 Hz, $J_{13b,14}$ = 5.6 Hz, H13b); 2.01 (3 H, s, NHAc); 1.25 (2 H, br s, NH_2). HRMS: found (M^+) 400.1517, calcd for $C_{21}H_{24}N_2O_7$ 400.1635. MS: m/e 400 (1), 282 (100), 270 (14). Anal. Found: C, 60.84; H, 5.9; N, 6.92. Calcd: C, 60.57; H, 5.81; N, 6.73.

Chiral Lanthanide Shift Reagent Study on 37A and 37B. An approximately equimolar solution of **37A** and **37B** in $CDCl_3$ was treated successively with $Eu(hfbc)_3$ in 0.1 M increments. At a concentration of 0.8:1 shift reagent:substrate, one CO_2Me signal was separated into two resonances. At the same concentration a pure sample of **37B** showed an approximately 6:1 ratio of peak intensities, indicating minimal racemization of the tyrosine moiety.

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Registry No. **1**, 57812-90-5; **1**·BF_4^-, 136805-30-6; **7**, 139-85-5; **8**, 57813-14-6; **9**, 136805-20-4; **11**, 93899-03-7; **12**, 57422-25-0; **19**, 99-24-1; **20**, 136805-21-5; **21**, 136805-22-6; **22**, 136805-23-7; **23**, 91925-82-5; **24**, 136805-24-8; **25**, 70424-94-1; **26**, 20189-90-6; **27**, 102019-30-7; **28**, 136805-25-9; **29**, 136805-26-0; **30A**, 2440-79-1; **30B**, 65160-71-6; **31A**, 101630-79-9; **31B**, 126108-94-9; **34A**, 126204-60-2; **34B**, 126372-78-9; **35A**, 136889-88-8; **35B**, 136889-89-9; **36A**, 136890-97-6; **36B**, 136889-90-2; **37A**, 126204-62-4; **37B**, 126204-63-5; **38**, 2541-25-5; **39**, 136805-29-3; **40**, 136805-27-1; ZCl, 501-53-1; L-Leu, 61-90-5; L-Tyr-OMe, 1080-06-4; D-Tyr-OMe, 3410-66-0; Z-L-Leu, 2018-66-8; $PhCH_2Cl$, 100-44-7; 3-OH-4-$OMeC_6H_3CHO$, 621-59-0; 4-OH-3-$MeOC_6H_3CHO$, 121-33-5; 3(*S*)-2,5-dimethoxy-3-isopropyl-3,6-dihydropyrazine, 78342-42-4.