rated), 1.56 (2 H, m, CH_2CH_2COO saturated), 1.75 (3 H, t, Et), 1.99, 2.02 (3 H each, s, Me saturated), 2.71 (2 H, q, Et saturated), 3.02 (2 H, t, CH_2CH_2COO saturated), 3.29 (2 H, t, CH_2CH_2COO), 3.49, 3.50 (3 H each, s, ring Me), 3.51, 3.75 (3 H, s, CO_2Me), 3.93 (2 H, q, Et), 4.29 (2 H, t, CH_2CH_2COO), 9.05, 9.06 (1 H each, s, meso β,δ), 98.66 (1 H, s, meso γ), 9.74 (1 H, s, meso α), -2.78, -2.74 (1 H each, br s, NH); UV-vis λ_{max} (ϵ_M) 685 nm (95 000), 652 (7300), 622 (6800), 556 (10 700), 514 (8100), 486 (5700), 411 (187 000), 401 (164 000); MS, found m/e 627.3198 for $(M + H)^+$, $C_{36}H_{43}N_4O_6$ requires m/e 627.3185.

4,6-Mesoporphyrindione dimethyl ester or dimethyl 8,12-diethyl-3,7,12,17-tetramethyl-13,18-porphinedione-2,17-dipropionate (8): 7.0 mg (1.9%); NMR δ 0.61 (3 H, t, Et saturated), 1.70 (3 H, t, Et), 1.76 (2 H, t, CH_2CH_2COO saturated), 1.95, 1.96 (3 H each, s, Me saturated), 2.63 (2 H, q, Et), 2.94 (2 H, t, CH_2CH_2COO saturated), 3.13 (2 H, t, CH_2CH_2COO), 3.43, 3.44 (3 H each, s, ring Me), 3.46, 3.72 (3 H each, s, CO_2Me), 3.75 (2 H, q, Et), 4.14 (2 H, t, CH_2CH_2COO), 8.57, (1 H, s, meso α), 8.78 (1 H, s, meso β), 9.32 (1 H, s, meso γ), 9.52 (1 H, s, meso δ), -0.61 (2 H, br s, NH); UV-vis λ_{max} (ϵ_M) 637 nm (15 800), 592 (14 400), 583 (15 000) 544 (9100), 437 (92 000), 417 (90 000), 402 (72 000); MS (direct probe, 70 eV), m/e 626 (M^+).

4,5-Mesoporphyrindione dimethyl ester or dimethyl 8,12-diethyl-3,7,12,18-tetramethyl-13,17-porphinedione-2,18-dipropionate (9): 2.0 mg (0.5%); NMR δ 0.52 (3 H, m, Et saturated), 1.77 (3 H, m, Et), 1.82 (2 H, m, CH_2CH_2COO saturated), 1.98, 2.01 (3 H each, s, Me saturated), 2.68 (2 H, q, Et saturated), 3.00 (2 H, t, CH_2CH_2COO saturated), 3.17 (2 H, t, CH_2CH_2COO), 3.34, 3.37 (3 H each, s, ring Me), 3.57, 3.65 (3 H each, s, CO_2Me), 3.91 (2 H, q, Et), 4.25 (2 H, t, CH_2CH_2COO), 8.93 (1 H, s, meso α), 8.97 (1 H, s, meso γ), 9.66 (1 H, s, meso β), 9.80 (1 H, s, meso δ), -1.82 (2 H, br s, NH); UV-vis λ_{max} (ϵ_M) 623 nm (19 000), 592 (9500), 436 (100 000), 417 (135 000); MS, found m/e 627.3190 for $(M + H)^+$, $C_{36}H_{43}N_4O_6$ requires m/e 627.3185.

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Registry No. 1, 101954-76-1; 2, 101954-77-2; 3, 101954-78-3; 4, 101954-79-4; 5, 101954-80-7; 6, 101954-81-8; 7, 101954-82-9; 8, 101954-83-0; 9, 101954-84-1; mesoporphyrin IX dimethyl ester, 1263-63-4.

Preparation of Diaryl Ethers from Tyrosine or 4-Hydroxyphenylglycine Using Organomanganese Chemistry

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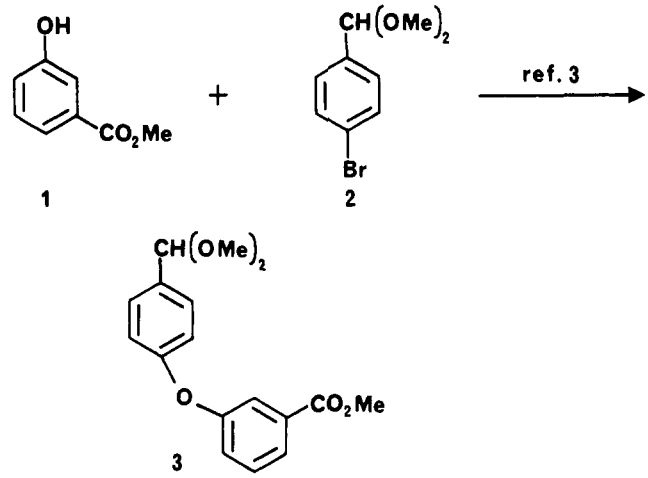
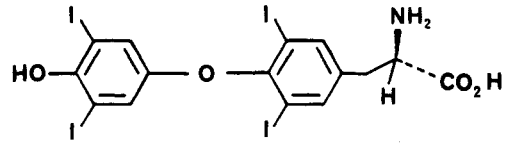
Diaryl and polyaryl ethers are important subunits in a wide variety of natural products,[1] but the commonly used method for constructing the ether linkage, i.e., Ullman coupling,[2] proceeds only under quite harsh conditions. One example, taken from the recent litearature,[3] is the coupling of phenolic compound 1 with haloaromatic 2 to give diaryl



ether 3. Although this reaction proceeds in good yield, the prolonged treatment required in basic solvent (pyridine) at elevated temperature (reflux, 24 h) is expected to lead to problems during similar coupling of molecules having base- and heat-sensitive side chains.

Several important natural products have polyaryl ether structures to which are attached, e.g., amino acid or peptide units. Examples are given by thyroxine (4) and the more



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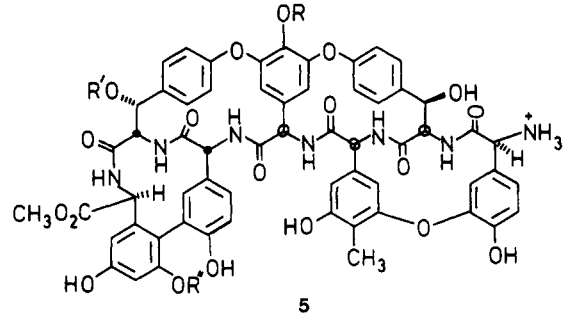
complex glycopeptide antibiotics related to ristocetin A (5),[4] and any projected synthesis of such compounds, in



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optically active, diastereomerically pure form, requires the development of milder procedures for diaryl ether formation. With respect to the ristocetin problem, it may be noted that phenylglycine derivatives are racemized quite readily under basic conditions.[5]

Several years ago, Pauson described the reaction of phenoxide anion with (chlorobenzene)$Mn(CO)_3$ cation (6) under mild conditions to give the complex 7. Decomplexation of this to give diphenyl ether was accomplished by heating in acetonitrile.[6] Since these conditions appear

(1) Selected examples: Alkaloids related to cularine, see: Gozler, B.; Shamma, M. *J. Nat. Prod.* **1984**, *47*, 753. Bisbenzylisoquinoline alkaloids, see: Guha, K. P.; Mukherjee, B.; Mukherjee, R. *J. Nat. Prod.* **1979**, *42*, 1. Schiff, P. L., Jr. *J. Nat. Prod.* **1983**, *46*, 1. Thyroxine: Harington, C. R.; Barger, G. *Biochem. J.* **1927**, *21*, 169. Harington, C. R.; McCartney, W. *Biochem. J.* **1927**, *21*, 852. Harington, C. R. *Biochem. J.* **1928**, *22*, 1429. Harington, C. R.; Salter, W. T. *Biochem. J.* **1930**, *24*, 457. Chalmers, J. R.; Dickson, G. T.; Elks, J.; Hems, B. A. *J. Chem. Soc.* **1949**, 3424. Vancomycin, and related glycopeptides; for reviews, see: Williams, D. H. *Acc. Chem. Res.* **1984**, *17*, 364. Barna, J. C. J.; Williams, D. H. *Annu. Rev. Microbiol.* **1984**, *38*, 339 and references cited therein.

(2) Ullmann, F.; Sponagel P. *Justus Liebigs Ann. Chem.* **1906**, *350*, 83. For a recent application of phase-transfer catalysis to the Ullmann diaryl ether synthesis, see: Soula, G. *J. Org. Chem.* **1985**, *50*, 3717. For other standard procedures, see: Harris, C. M.; Harris, T. M. *Tetrahedron* **1983**, *39*, 1661 and references cited therein. Bacon, R. G.; Hill, H. A. *J. Chem. Soc.* **1964**, 1100, 1108. Williams, A. L.; Kinney, R. E.; Bridger, R. F. *J. Org. Chem.* **1967**, *32*, 2501. See also ref 3.

(3) Iyoda, M.; Sakaitani, M.; Otsuka, H.; Oda, M. *Tetrahedron Lett.* **1985**, *26*, 4777.

(4) Philip, J. E.; Schenck, J. R.; Hargie, M. P. *Antibiot Annu.* **1957**, 699. Harris, C. M.; Kibby, J. J.; Fehlner, J. R.; Raabe, A. B.; Barber, T. A.; Harris, T. M. *J. Am.* Chem. *Soc.* **1979**, *101*, 437 and references cited therein. Williamson, M. P.; Williams, D. H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 949.

(5) Bodanszky, M.; Bodanszky, A. *Chem. Commun.* **1967**, 591. We have examined the racemization of *N*-acetyl-4-hydroxyphenylglycine methyl ester in hot pyridine. After 24 h at reflux, typical conditions for Ullmann coupling (see ref 3), complete racemization occurred.

(6) Pauson, P. L.; Segal, J. A. *J. Chem. Soc., Dalton Trans.* **1975**, 1677.

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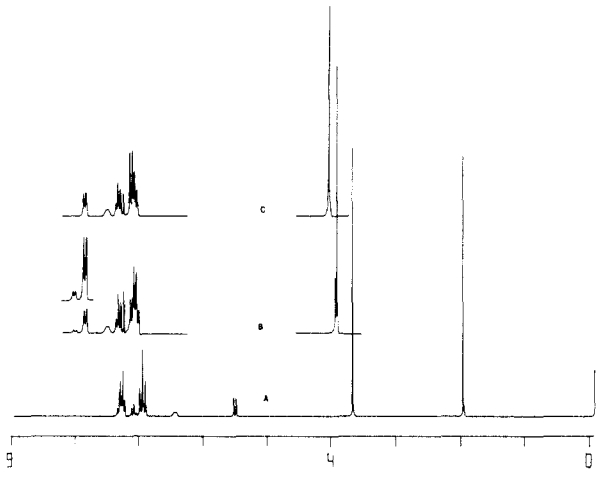


Figure 1. Effect of $Eu(dcm)_3$ on 200-MHz NMR spectra of compound **12** and its partially racemic analogue, at a mol ratio $Eu(dcm)_3$:**12** = 0.22. A, spectrum of **12** without added $Eu(dcm)_3$; B, spectrum of partially racemized **12** + $Eu(dcm)_3$; C, spectrum of **12** produced from reaction of single enantiomer of **9** with complex **6** + $Eu(dcm)_3$. (Chemical shifts are in δ downfield from Me_4Si internal reference.)

to be particularly favorable in the presence of fragile substituents, we have investigated the reaction of (chlorobenzene)tricarbonylmanganese hexafluorophosphate with protected tyrosine and 4-hydroxyphenylglycine, paying particular attention to any degree of racemization in the amino acid moiety during the coupling and decomplexation.

Protection of the amino acids as the *N*-acetyl methyl esters **8** and **9** was accomplished without racemization using standard techniques. Treatment of the sodium salt of **8** with complex **6** in THF/CH_3CN afforded the ether-insoluble complex **10** in 46% isolated yield. Evaporation of the mother liquors from precipitation of **10**, followed by chromatographic purification, afforded the ether **11** in 29% yield. This observation suggested that decomplexation of **10** by the acetonitrile present in the reaction mixture occurs readily even at room temperature, so a one-pot procedure was developed for the conversion of **8** to **11**, as described in the Experimental Section. In this way, direct conversion of **8** to **11** and of **9** and **12** was accomplished in 55–62% yield after purification of product.

The optical purities of compounds **11** and **12** were established by using chiral shift reagent [$Eu(dcm)_3$ or $Eu(hfbc)_3$] NMR studies. Figure 1 shows the results obtained for the phenylglycine derivative **12**, compared to the same compound prepared from partly racemized starting material **9**. In this way it is established that *no detectable racemization* occurs throughout the entire sequence leading to both **11** and **12**. Consequently, provided appropriate (arene)$Mn(CO)_3$ complexes can be prepared, this becomes an extremely attractive coupling method for the construction of molecules related to, e.g., ristocetin **9**.

Experimental Section

L-(+)-*N*-Acetyltyrosine Methyl Ester (8). *O*-Benzyl-L-tyrosine methyl ester hydrochloride salt (1.7 g, 5.3 mmol) was dissolved in 10% aqueous sodium hydroxide solution (20 mL), and acetic anhydride (1 mL, 11 mmol) was added. The mixture was stirred for 10 min at room temperature, during which time *N*-acetyl-*O*-benzyl-L-tyrosine methyl ester precipitated out and was immediately filtered. The crude product was dried in vacuo and then hydrogenated in methanol over 5% palladium on charcoal catalyst (0.39 g) for 1 h at room temperature. The mixture was filtered, solvent was removed by evaporation in vacuo, and the product was purified by flash chromatography (ethyl acetate solvent) (yield 0.90 g, 72%), mp 120–121 °C: IR ($CHCl_3$) ν_{max} 3583, 3423, 1743 and 1673 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 6.94 (2 H, d, J = 8.2 Hz), 6.73 (2 H, d, J = 8.2 Hz), 6.10 (1 H, d, J = 8.1 Hz, N*H*), 4.86 (1 H, m), 3.74 (3 H, s), 3.07 and 2.99 (2 H, ABX, J_{AB} = 14, J_{AX} = 6.4, J_{BX} = 5.5 Hz), 1.99 (3 H, s); $[\alpha]^{20}_D$ +97.0° (*c* 0.60 in $CHCl_3$, *l* = 1.0 dm, α = 0.579). Anal. C, H, N.

***N*-Acetyl-D-(−)-*p*-hydroxyphenylglycine Methyl Ester (9).** A solution of D-(−)-*p*-hydroxyphenylglycine (5.0 g, 29.9 mmol) and *p*-toluenesulfonic acid monohydrate (11.9 g, 62.8 mmol) in methanol (100 mL) was boiled under reflux for 24 h.[7] The mixture was cooled, and the volume was reduced to ca. 10 mL on the rotary evaporator. The *p*-toluenesulfonate ammonium salt was precipitated by addition of diethyl ether (200 mL), filtered, washed thoroughly with ether, and dried in vacuo. The product was stirred in aqueous $NaHCO_3$ solution (0.5 M, 100 mL), and *p*-nitrophenyl acetate (6.5 g, 35.9 mmol) was added.[8] After having been stirred at room temperature for 16 h, the product was extracted with ethyl acetate (3 × 200 mL), washed with water and then brine, and dried over $MgSO_4$. Evaporation of the solvent, followed by flash chromatography (ethyl acetate solvent) and then recrystallization (EtOAc), afforded **9** as a white crystalline solid, mp 179–180 °C (3.1 g, 46% overall). That no racemization had occurred throughout this operation was shown by NMR studies using chiral lanthanide shift reagent (see later): IR (THF) ν_{max} 3553, 3493, 3293, 1750, and 1683 cm^{-1}; NMR (acetone-d_6, 200 MHz) δ 7.73 (1 H, br, NH), 7.21 (2 H, d, J = 8.6 Hz), 6.81 (2 H, d, J = 8.6 Hz), 5.37 (1 H, d, J = 7 Hz plus singlet at center, presumably due to hydrogen bonding effects. This proton is observed as a doublet for O-acetyl and O-phenyl derivatives.), 3.65 (3 H, s), 1.95 (3 H, s); $[\alpha]^{20}_D$ −171.8 °C (*c* 0.50 in acetone, *l* = 1.0 dm, α = −0.85). Anal. C, H, N.

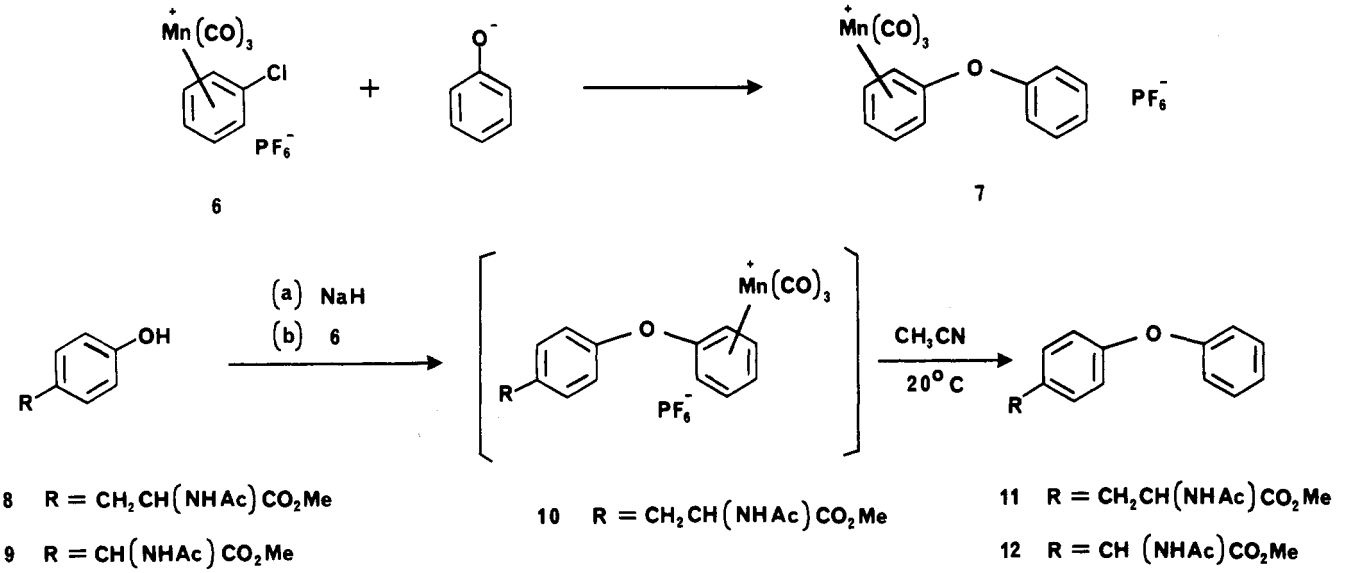
Reaction of (Chlorobenzene)tricarbonylmanganese Hexafluorophosphate (6) with 8. (A) Isolation of Complex 10. To a stirred suspension of sodium hydride (0.252 mmol, from NaH dispersion in mineral oil, washed by decantation with dry THF) in 1:1 THF–acetonitrile (2 mL), under nitrogen at 0 °C, was added **8** (0.252 mmol) in THF–acetonitrile (2 mL). The mixture was stirred at room temperature for 30 min, and complex **6** (0.10 g, 0.252 mmol) was added (reaction vessel opened with back flushing of N_2 during addition). After having been stirred 2 h at room temperature, the reaction mixture was poured into 5 mL of aqueous ammonium hexafluorophosphate, and products were extracted with dichloromethane (2 × 10 mL). To the dried ($MgSO_4$) concentrated (t o 10 mL) dichloromethane extract was added ether, and the complex **10** was collected by filtration as a pale yellow solid (0.074 g, 46%): IR (CH_3CN) ν_{max} 2082, 2023, 1740, 1679, and 853 cm^{-1}; NMR (CD_3CN, 200 MHz) δ 7.41 (2 H, d, J = 8.3 Hz), 7.18 (2 H, d, J = 8.3 Hz), 6.78–6.68 (3 H, m, ArH complex, and NH), 6.02–5.93 (3 H, m), 4.64 (1 H, m), 3.67 (3 H, s), 3.09 (2 H, ABX, J_{AB} = 14, J_{AX} = 5, J_{BX} = 8 Hz), 1.96 (3 H, s); $[\alpha]^{20}_D$ +5.3° (*c* 0.55 in CH_3CN, *l* = 1.0 dm, α = 0.029). Anal. C, H, N.

The liquors and washings from precipitation of **10** were washed with water, dried ($MgSO_4$), evaporated, and subjected to preparative TLC, to afford the ether **11** (0.0236 g, 29% yield), identical with that obtained from the one-pot procedure described next.

(B) One-Pot Conversion of 8 to 11. The protected amino acid **8** (59.7 mg) in THF solution (1 mL) was added to a stirred suspension of sodium hydride (0.265 mmol, 6.4 mg) in THF (2 mL) at 0 °C under N_2. The mixture was stirred for 30 min, and the complex **6** (0.100 g) was added, as above. Stirring was continued at room temperature for 30 min, after which time acetonitrile (2 mL) was added, and the mixture was stirred overnight, then diluted with ether (10 mL). Filtration through Celite followed by washing with water (2 × 10 mL), drying ($MgSO_4$), and evaporation of solvent afforded the crude compound **11** (59 mg, 75%), quite pure by NMR spectroscopy. Further purification by preparative TLC (silica gel, ethyl acetate) afforded the pure ether **11**, mp 92–93 °C (44 mg, 55%): IR ($CHCl_3$) ν_{max} 3435, 1745, 1682 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 7.36–6.90 (9 H, m), 5.95 (1 H, br d, J = 7.8 Hz, NH), 4.88 (1 H, dt, J = 7.8, 5.6 Hz), 3.74 (3 H,

(7) Bodanszky, M. *Int. J. Pept. Protein Res.* **1984**, *23*, 111 and references cited therein. Remarkably, we observed no racemization of the phenylglycine under these conditions.

(8) Bodanszky, M. *Nature (London)* **1955**, *175*, 685. Bodanszky, M. *Int. J. Pept. Protein Res.* **1980**, *16*, 402.



8 R = $CH_2CH(NHAc)CO_2Me$

9 R = $CH(NHAc)CO_2Me$

10 R = $CH_2CH(NHAc)CO_2Me$

11 R = $CH_2CH(NHAc)CO_2Me$

12 R = $CH(NHAc)CO_2Me$

s), 3.13 and 3.09 (2 H, ABX, J_{AB} = 12, J_{AX} = 2.8, J_{BX} = 2.7 Hz), 2.01 (3 H, s); $[\alpha]^{20}_D$ +91.6° (c 0.50 in $CHCl_3$, l = 1.0 dm, α = 0.458). Anal. C, H.

D-(-)-*N*-Acetyl-4-(phenyloxy)phenylglycine Methyl Ester (12). The procedure was identical with that described for the preparation of 11, using *N*-acetyl-4-hydroxyphenylglycine methyl ester (223 mg, 1 mmol), sodium hydride (44 mg), and (chlorobenzene)manganesetricarbonyl hexafluorophosphate (401 mg, 1.01 mmol). Extractive workup, followed by flash chromatography (silica gel, ethyl acetate), gave the product 12 as a hygroscopic white foam (194 mg, 65%): IR ($CHCl_3$) ν_{max} 3435, 1743, and 1682 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 7.39–6.95 (9 H, m), 6.46 (1 H, br d, J = 7.2 Hz), 5.56 (1 H, d, J = 7.2 Hz), 3.75 (3 H, s), 2.05 (3 H, s). The optical rotation was measured immediately upon isolation of the vacuum-dried sample: $[\alpha]^{20}_D$ - 70.6° (c 0.50 in acetone, l = 1.0 dm, α = -0.353). Due to the hygroscopic nature of this compound, satisfactory combustion analysis was not obtained. Anal. Calcd for $C_{17}H_{17}NO_4$ M^+ = 299.1158, found M^+ = 299.1149.

Determination of Enantiomeric Purity. (1) Racemic tyrosine was commercially available and was used to prepare authentic samples of racemic 8 and 11. (2) *N*-acetyl-D-(-)-*p*-hydroxyphenylglycine methyl ester was converted to its *N,O*-diacetyl derivative by standard procedure (acetic anhydride, pyridine, CH_2Cl_2, 20 °C, 1.5 h) due to its poor solubility in most commonly used NMR solvents for the chiral lanthanide shift reagent study. A partially racemized sample was prepared as follows.[9] D-(-)-*p*-hydroxyphenylglycine was treated with 2.5 N NaOH and acetic anhydride at 20 °C for 2 h, followed by extractive workup, to give *N,O*-diacetyl-D-(-)-*p*-hydroxyphenylglycine, which was then partially racemized with acetic anhydride and glacial acetic acid at reflux for 15 min. The racemized compound was isolated in the usual way and converted to its methyl ester by treatment with dimethyl sulfate and potassium carbonate in acetone at reflux for 7 h, to provide a partially racemic sample of *N,O*-diacetyl-*p*-hydroxyphenylglycine methyl ester. The *N,O*-diacetyl derivatives were used to establish that no racemization had occurred during the preparation of 9. Mild hydrolysis of the racemized diacetate[10] (MeOH, H_2O, saturated $NaHCO_3$, 0.75 h, room temperature) gave partly racemic *N*-acetyl-*p*-hydroxyphenylglycine methyl ester. Racemized and nonracemized materials prepared in this study were identical, apart from optical rotation. The partially racemic sample of 9 was converted to partially racemic diaryl ether 12 by using the procedure described above: $[\alpha]^{20}_D$ -45.2° (c 0.5 in acetone). (3) The enantiomeric purity of each chiral compound described in this paper was determined by using the chiral lanthanide shift reagents tris[3-[heptafluorobutyryl]-*d*-camphorato]europium(III), [Eu(hfbc)$_3$], or tris(*d,d*-dicampholylmethanato)europium(III), [Eu(dcm)$_3$], at a defined molar ratio. The appropriate shift reagent for each compound was determined by using racemic or partially racemic samples of that compound. Optimum conditions were as follows: compound 8 (rac) showed separation of ar*H* and CO_2CH_3 peaks in $CDCl_3$ (solution) by using a molar ratio of Eu(hfbc)$_3$:8 of 0.11. Compound 9 (rac) showed separation of Ar*H*, CO_2CH_3, and $NHCOCH_3$ peaks in $CDCl_3$ solution by using a molar ratio of Eu(dcm)$_3$:9 of 0.23. Compound 11 (rac) showed separation of CO_2CH_3 and $NHCOCH_3$ peaks in $CDCl_3$ solution by using a molar ratio Eu(dcm)$_3$:11 of 0.17. Compound 12 (rac) showed separation of Ar*H* and CO_2CH_3 in $CDCl_3$ solution by using a molar ratio (Eu(dcm)$_3$:12 of 0.22. By using the same ratios of shift reagent:substrate, no racemization could be detected for the compounds 8, 9, 11 and 12, and the results for the latter are shown in Figure 1.

Acknowledgment. We are extremely grateful to the National Institutes of Health and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. The Varian XL 200 NMR spectrometer used in this work was purchased in part with funds provided by the National Institutes of Health (RR-01689). High resolution mass spectra were measured at the Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln, NE. Combustion analyses were determined by Galbraith, Inc., Knoxville, TN.

Registry No. 6, 57812-91-6; 8, 2440-79-1; 9, 72691-40-8; 10, 101630-79-9; 11, 101630-75-5; 12, 101630-76-6; *O*-benzyl-L-tyrosine methyl ester hydrochloride, 34805-17-9; D-(-)-*p*-hydroxyphenylglycine, 22818-40-2; D-(-)-*p*-hydroxyphenylglycine *p*-toluenesulfonate, 101630-77-7; *N*-acetyl-*O*-benzyl-L-tyrosine methyl ester, 39613-68-8.

(9) Greenstein, J.-P.; Winitz, M. *Chemistry of the Amino Acids*; Wiley: New York, 1961; Vol. 3, p 2364 and references cited therein.
(10) Buchi, G.; Weinreb, S., M. *J. Am. Chem. Soc.* **1981**, *93*, 746.

Preparation of a New Type of Electron-Deficient Olefins: β-Phenylthio Nitro Olefins, β-Sulfinyl Nitro Olefins, and β-Sulfonyl Nitro Olefins

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Electron-deficient olefins substituted with nitro, sulfinyl, or sulfonyl groups are very important in the Michael addition reactions and cycloaddition reactions. In fact, ni-

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