and methylene, respectively. Both ^1J(HC) and ^1J(CP) for the carbon at 60.9 ppm are substantially larger than the corresponding values for the carbon at 32.1 ppm, and clearly show that the two resonances arise from olefinic and aliphatic carbons, respectively.

The exchanging system is thus shown to comprise enamine–imine tautomers. Complete assignment of the magnetic resonance of all the atoms except oxygen (Table I) supports this interpretation. The very different ^{15}N chemical shifts, 211 and 79 ppm, require that they arise from imine and enamine groups, respectively.[8] The large vicinal coupling between the phosphorus and C-3 implies a *Z* configuration of the double bond of 8.[9] This configuration is consistent with the appearance in the infrared spectrum of an intramolecular hydrogen bond at 3318 cm^{-1}. Although the concentrations of 7 and 8 are nearly equal to 30 °C, at −60 °C the enamine, 8, predominates. There is no evidence for the occurrence of the *E* isomer of 8.

To provide further confirmation of these assignments, ^1H and ^{13}C spectra were obtained of the product after the $CDCl_3$ solution was shaken with D_2O. The peaks corresponding to the α-^1H and ^{13}C disappeared from the spectra immediately, with no other peaks affected.

Enamines are characterized by an upfield shift of the resonances of both the β-^1H and ^{13}C as a result of resonance contribution of $N^+{=}CCH^-$.[10] The further upfield shifts are evidently to be ascribed to the polarizability of the phosphonyl group, stabilizing the negative charge on the β carbon.[11]

Earlier studies have shown that the proportion of enamine and imine in these tautomeric systems is very sensitive to the effect of substituents.[12] In the examples quoted above, it is likely that the olefinic peaks which would have provided evidence for the existence of the enamine isomer of 6 were obscured in the 60-MHz spectrum by the ethoxyl resonances. The contrast of the facile exchange observed here with the apparent static character of the noncyclic systems noted above[2] is quite striking.

Experimental Section

Gas chromatographic analyses were carried out using a 30 m × 0.5-mm i.d. open DB-17 column (1-μm film thickness). The temperature for the analyses was programed from 60–215 °C at 10°/min, and the carrier gas flow rate was 15 mL/min. On a given day, retention temperatures were reproducible to 1 °C. Preparative gas chromatography was conducted with a 2 m × 5-mm i.d. column packed with 10% OV-17 on 100–120 mesh Supelcoport. ^1H and ^{13}C NMR spectra were obtained from $CDCl_3$ solutions at 4.7 and 7 T; ^{31}P NMR spectra were obtained at 4.7 T, while ^{15}N spectra were obtained at 7 T. Solutions for ^1H and ^{13}C spectra included tetramethylsilane as an internal reference (0 ppm); for ^{15}N, nitromethane (380 ppm, NH_3 = 0 ppm); for ^{31}P, external phosphoric acid (0 ppm). Assignments were made on the basis of homo- and heteronuclear correlation spectra, consistent with DEPT spectra. Multiplets ascribed to coupling with ^{31}P were confirmed by comparison of spectra obtained at 4.7 and 7.05 T. Electron-impact mass spectra were obtained using an GC/MS equipped with a 25 m × 0.31-mm i.d. HP-5 column. High-resolution mass spectra were obtained with a double-focusing mass spectrometer.

2-[(Diethylphosphono)methyl]-5-methyl-2-pyrroline (7). A solution containing 8.6 g (87 mmol) of 2,5-dimethylpyrrolidine in 100 mL of MeOH and 200 mL of 5% sodium hypochlorite solution was stirred for 2 h at room temperature. Following the addition of 10 g of NaOH, the mixture was heated on a steam bath for 1 h, cooled, and extracted with 3 × 70 mL of ether. The combined ether extracts were dried over anhydrous K_2CO_3 and carefully distilled to provide 4.0 g of 2,5-dimethyl-1-pyrroline (49% yield): bp 110–114 °C.[13] A solution containing 0.50 g (50 mmol) of 2,5-dimethyl-1-pyrroline in 2 mL of THF was added over 15 min to a solution containing 10 mmol of lithium diisopropylamide at −78 °C in 5 mL of THF (from 1.40 mL of diisopropylamine and 6.25 mL of 1.6 M *n*-butyllithium) under a nitrogen atmosphere. After 1 h, a solution containing 0.85 g (6.1 mmol) of diethyl chlorophosphate in THF was added slowly and the mixture was stirred for 3 h. The reaction was quenched with 1 mL of saturated aqueous $NaHCO_3$ and warmed to room temperature. After the addition of 10 mL of ether, the aqueous layer was separated, and the organic mixture was dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo provided 1.1 g of a mixture of which 85% was a single component with a long retention time, which was purified by preparative gas chromatography. Pure material so prepared had an NMR spectrum closely resembling that of the original crude product: IR (GC-FTIR or CCl_4) 3318, 1622, 1281, 1040, 951, and 787 cm^{-1}, unchanged by dilution of the sample. The IR of the neat liquid showed an additional band at 3220 cm^{-1}; MS *m/z* (rel intensity) 233 (21, M^+), 218 (29), 190 (15), 162 (14), 160 (15), 150 (11), 144 (18), 122 (53), 97 (100), 96 (29), 95 (19), 94 (37), 82 (44), 81 (15), 80 (62), and 54 (21); HRMS *m/z* 233.1184 M^+ ($C_{10}H_{20}O_3NP$, calcd 233.1181).

Hydrogenation of 7/8. A small portion (ca. 200 mg) of the crude product above was taken up in hexane and hydrogenated over 0.4 g of 5% Rh/Al_2O_3 for 8 h. After filtration and removal of the solvent in vacuo gas chromatographic analysis revealed the presence of a single major component (85%): IR 2967, 2881, 1397, 1267, 1099, 949, and 806 cm^{-1}; ^1H NMR δ 4.1 (m, CH_2O), 3.3 (m, H-2), 3.1 (m, H-5), 2.0 (m, α-H, H-3), 1.6 (m, H-4), 1.29 (t, J = 7.0 Hz, CH_3CH_2O), 1.12 (d, J = 6.6, C-5 CH_3); ^{13}C NMR δ 61.4 (OCH_2, ^2J(CP) = 6 Hz), 53.9 (C-5), 53.6 (C-2, ^2J(CP) = 4 Hz), 32.9 (α, ^1J(CP) = 137 Hz), 32.6 (C-3, ^3J(CP) = 12 Hz), 32.5 (C-4), 21.6 (C-5 CH_3), 16.4 (CH_3CH_2O, ^3J(CP) = 6 Hz); MS *m/z* 235 (4, M^+), 220 (9), 192 (5), 179 (13), 164 (8), 98 (11), 97 (70), 85 (8), 84 (100), 83 (8), 82 (50), 81 (12), 70 (32), 68 (17), 57 (41), 55 (15), 43 (11); HRMS *m/z* 235.1336 M^+ ($C_{10}H_{22}O_3NP$, calcd 235.1337).

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Synthesis of Antibiotic Stilbenes Using Organomanganese Arene Complexes

Grant R. Krow,*[†] William H. Miles,*[‡,§] Patricia M. Smiley,[‡] Walden S. Lester,[†] and Yong J. Kim[†]

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122, and Department of Chemistry, Lafayette Collge, Easton, Pennsylvania 18042

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The two antibiotic metabolites isolated from strain H_b of Xenorhabdus, a genus of bacteria symbionts which live in the guts of parasitic nematodes,[1-3] have been identified as the homologous *trans*-hydroxystilbene derivatives **1a** and **1b**.[2,3] In order to conduct further biological testing of antibiotics **1a** and **1b**,[4] we sought an expedient synthesis based on the readily available 1,3-dimethoxy-2-alkylbenzenes. We envisioned that the direct nucleophilic at-

[†] Temple University.
[‡] Lafayette College.
[§] Portions of this work were investigated by W.H.M. at Seton Hall University, South Orange, NJ 07079.

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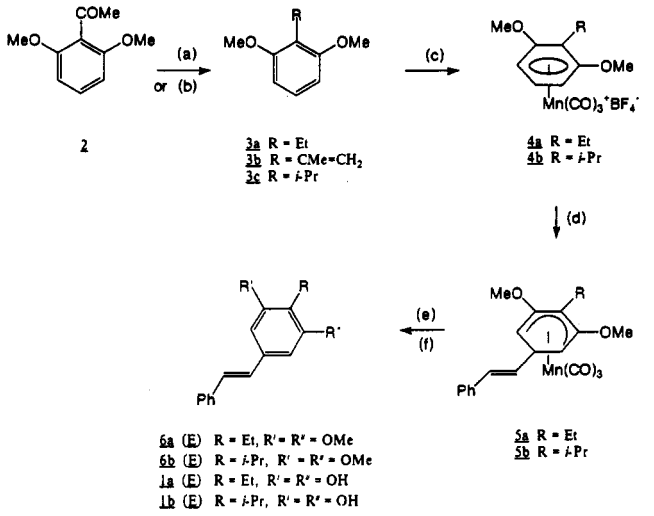
Scheme I[a]



2

3a R = Et
3b R = CMe=CH2
3c R = i-Pr

4a R = Et
4b R = i-Pr

6a (E) R = Et, R' = R'' = OMe
6b (E) R = i-Pr, R' = R'' = OMe
1a (E) R = Et, R' = R'' = OH
1b (E) R = i-Pr, R' = R'' = OH

5a R = Et
5b R = i-Pr

[a] Reagents: (a) H_2, TsOH, Pd/C, 25 °C; (b) (i) MeMgI, ether/THF, 25 °C; (ii) H_2, Pd/C, 25 °C; (c) $(CO)_5MnBr$, $AgBF_4$, CH_2Cl_2, reflux; (d) (i) (*E*)-PhCH=CHBr, *t*-BuLi, THF/ether/pentane, -110 °C; (ii) $MgBr_2(OEt)_2$, -78 °C: add 4 and then warm to 0 °C; (e) DDQ, CH_3CN, reflux; (f) BBr_3–SMe_2, $ClCH_2CH_2Cl$, reflux.

tack by a β-metallostyryl reagent on the organomanganese arene complexes of 1,3-dimethoxy-2-alkylbenzenes would lead to the desired substitution pattern due to the strong meta-directing effect of the alkoxy substituents.[5,6] Herein, we report the regioselective and stereoselective synthesis of antibiotics **1a** and **1b** using organomanganese arene chemistry.

The requisite aryl ethers were prepared from the common precursor, 2,6-dimethoxyacetophenone (**2**). Catalytic dehydrogenation of **2** afforded 2-ethyl-1,3-dimethoxybenzene (**3a**) (90% yield).[7] Addition of methyl magnesium iodide to **2** followed by in situ dehydration of the initial alcohol product gave 1,3-dimethoxy-2-(1-methylethenyl)-benzene (**3b**) (93% yield), which was hydrogenated over Pd/C to give 2-isopropyl-1,3-dimethoxybenzene (**3c**) (98% yield).[8] The η^6-arene complexes **4** were readily prepared by the reaction of $(CO)_5MnBF_4$ (generated in situ from $(CO)_5MnBr$ and $AgBF_4$)[6b,e] with the corresponding aryl ether in methylene chloride (78% yield for **4a**, 61% yield for **4b**). The addition of (*E*)-C_6H_5CH=CHMgBr (prepared by the stereoselective lithiation of (*E*)-C_6H_5CH=CHBr with 2 equiv of *t*-BuLi followed by the addition of $MgBr_2(Et_2O)_2$)[9] to complexes **4a** and **4b** gave η^5 dienyl complexes **5a** (67% yield) and **5b** (60% yield), respectively.[10] The ^1H NMR spectrum for the η-dienyl complexes **5** were in accord with an exo-attack by the β-styryl reagent. We did not observe η^5-dienyl complexes possessing *E*-stereochemistry, nor did we observe products derived from attack at the ortho position. Oxidative-demetalation of the η^5-dienyl complexes **5a** and **5b** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in acetonitrile gave the corresponding methoxystilbene compounds **6a** (87% yield) and **6b** (70% yield). These were converted to the hydroxystilbenes **1a** and **1b** (89% and 87% yields) by demethylation using a large excess of boron tribromide–methyl sulfide complex in 1,2-dichloroethane.[11,12] The functionalization of electron-rich aromatic systems using this methodology offers an attractive alternative to the standard methods employing electrophilic reagents. We are continuing to explore the utility of cationic manganese arene complexes for the expedient synthesis of natural products and compounds of medicinal importance.

Experimental Section

NMR spectra were recorded at 300 MHz for ^1H NMR and at 75.5 MHz for ^{13}C NMR. Exact mass measurements were recorded at 70 eV. THF and ether were distilled from sodium; flash chromatography was performed using Baker Silica gel 250–400 mesh; TLC was performed using Analtech silica gel plates (GF) containing fluorescent indicator. Pentacarbonylmanganese bromide was obtained from Strem Chemicals, and $AgBF_4$ was obtained from Aldrich Chemical Co.

2-Ethyl-1,3-dimethoxybenzene (3a).[7] To a Parr flask containing methanol (200 mL) 10% Pd on carbon (1.0 g) was slowly added followed by 2,6-dimethoxyacetophenone (8.1 g, 0.045 mmol) and a catalytic amount of *p*-toluenesulfonic acid. The mixture was hydrogenated (60 psi) over 24 h in a Parr apparatus. The solution was filtered, and the solvent was removed in vacuo to produce 6.7 g (90%) of white crystalline **3a**: mp 58–59 °C (MeOH); ^1H NMR (300 MHz; Me_2SO-d_6) δ 7.29 (1 H, t, *J* = 8.4 Hz, H-5), 6.57 (2 H, d, *J* = 8.4 Hz, H-4 and H-6), 3.82 (6 H, s, OMe), 2.50 (3 H, s, CH_3).

1,3-Dimethoxy-2-(1-methylethenyl)benzene (3b). In a flask containing Mg (0.38 g, 0.016 mol) there was added dropwise over 30 min a solution of CH_3I (0.86 mL, 2.0 g, 0.014 mol) in ether (20 mL). After initiation of the Grignard reaction by addition of a few drops of the CH_3I solution, the addition was completed with refluxing. Then, 2,6-dimethoxyacetophenone (2.5 g, 0.014 mmol) in ether (40 mL) containing a minimum amount of THF to complete solubilization was added dropwise to the refluxing solution. After 20 min a grayish precipitate fell out of the solution, which was stirred an additional 12 h at 25 °C under N_2. The reaction was then poured into 20 mL of cracked ice and 20 mL of 3 M H_2SO_4 to yield a yellow green aqueous layer and a light brown organic phase. The organic layer was washed with H_2O, NaOH, and H_2O and dried ($MgSO_4$), and then solvent was removed in vacuo. The reaction was flash chromatographed to give 2.3 g (93%) of clear crystalline **3b**: R_f = 0.75 (5:1 hexane/ether); mp 38–40 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (1 H, t, *J* = 8.4 Hz, H-5), 6.61 (2 H, d, *J* = 8.4 Hz, H-4 and H-6), 5.37 (1 H, m, =CH), 4.92 (1 H, m, =CH), 3.84 (6 H, s, OMe), 2.06 (3 H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.47, 55.96, 104.07, 115.70, 121.44, 127.92, 139.23, 157.24; IR (neat) 3079, 2997, 2954, 2835, 1644, 1587, 1469, 1432, 1286, 1246, 1111, 896, 784, 733, 540 cm^{-1}. Anal. Calcd

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for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.40; H, 7.92.

1,3-Dimethoxy-2-(1-methylethyl)benzene (3c).[8] To a stirred solution of **3b** (2.0 g, 0.011 mol) and methanol (50 mL) was added 10% Pd/C (1.0 g) slowly with stirring. (Caution! Vapor ignition can occur.) The reaction was purged thoroughly and sealed under hydrogen in a balloon. After being stirred for 5 h, the mixture was filtered and the solvent was removed in vacuo to yield 1.9 g (98%) of a clear liquid **3c**: R_f = 0.90 (5:1 hexane/ether); ^{1}H NMR ($CDCl_3$) δ 7.14 (1 H, t, J = 8.4 Hz, H-5), 6.58 (2 H, d, J = 8.4 Hz, H-4 and H6), 3.84 (6 H, s, OMe), 3.66 (1 H, m, J = 7.2 Hz, CH), 1.33 (6 H, d, J = 7.2 Hz, Me); ^{13}C (75 MHz, $CDCl_3$) δ 20.93, 24.31, 55.71, 104.77, 124.65, 126.74, 158.88; IR (neat) 2988, 2955, 2871, 2836, 1592, 1474, 1361, 1249, 1141, 1113, 783, 727 cm^{-1}.

(1,3-Dimethoxy-2-ethylbenzene)manganese Tricarbonyl Tetrafluoroborate (4a). Pentacarbonylmanganese bromide (1.10 g, 4.00 mmol) was dissolved in CH_2Cl_2 (75 mL), and $AgBF_4$ (0.80 g, 4.00 mmol) was added in one portion. After the solution was refluxed for 45 min, 1,3-dimethoxy-2-ethylbenzene (**3a**; 2.00 g, 12.0 mmol) was added and the reaction mixture was refluxed for 2 h. CO was periodically vented from the reaction vessel during this time. The reaction mixture was filtered through a bed of Celite (to remove AgBr), and diethyl ether (400 mL) was added to the filtrate. Filtration gave yellow microcyrstalline **4a** (1.23 g, 78% yield; mp 156 °C dec). For **4a**: ^{1}H NMR (CD_3CN, 300 MHz) δ 6.77 (1 H, t, J = 6.8 Hz, H-5), 5.77 (2 H, d, J = 6.8 Hz, H-4 and H-6), 4.04 (6 H, s, OCH_3), 2.63 (2 H, q, J = 7.1 Hz, CH_2), 1.17 (3 H, t, J = 7.0 Hz, CH_3); IR (CH_2Cl_2) 2069, 2003 cm^{-1}. Anal. Calcd for $C_{13}H_{14}BF_4MnO_5$: C, 39.83; H, 3.60. Found: C, 39.71; H, 3.56.

(*E*)-[1,3-Dimethoxy-2-(1-methylethyl)benzene]manganese Tricarbonyl Tetrafluoroborate (4b). Pentacarbonylmanganese bromide (2.07 g, 7.50 mmol) was dissolved in CH_2Cl_2 (100 mL), and $AgBF_4$ (1.50 g, 7.65 mmol) was added in one portion. After the solution refluxed for 1 h, 1,3-dimethoxy-2-(1-methylethyl)-benzene (**3c**; 3.8 g, 21 mmol) was added and the reaction mixture was refluxed for 4 h with periodic venting. The reaction mixture was filtered through a bed of Celite, and diethyl ether (350 mL) was added to the filtrate. Filtration gave yellow, microcrystalline **4b** (1.86 g, 61% yield; mp 141 °C dec): ^{1}H NMR (CD_3CN, 300 MHz) δ 6.80 (1 H, t, J = 6.2 Hz, H-5), 5.69 (2 H, d, J = 6.1 Hz, H-4 and H-6), 4.02 (6 H, s, OCH_3), 3.41 (1 H, m, CH), 1.36 (6 H, d, J = 6.2 Hz, CH_3); IR (CH_2Cl_2) 2069, 2002 cm^{-1}. Anal. Calcd for $C_{14}H_{16}BF_4MnO_5$: C, 41.42; H, 3.97. Found: C, 41.25; H, 3.96.

(*E*)-3-Ethyl-2,4-dimethoxy-6-(2-phenylethenyl)cyclohexadienylmanganese Tricarbonyl (5a). A solution of (*E*)-β-bromostyrene (0.646 g, 3.53 mmol) in a 4:1:1 mixture of THF–Et_2O–pentane (10 mL) was stirred and cooled at −110 °C under Ar as *t*-BuLi (41.5 mL, 7.06 mmol) was added dropwise over 20 min. The solution was stirred an additional 1 h and then warmed to −78 °C. Additional THF (18 mL) was added followed by the addition of $MgBr_2(OEt_2)_2$ (1.34 g, 4.00 mmol), and then complex **4a** (0.635 g, 1.62 mmol) was added over 10 min at −78 °C. The solution was warmed to 0 °C and quenched with water (1 mL). Additional water was added, and the aqueous layer was extracted with ethyl acetate. Flash chromatography (silica gel; hexane–ethyl acetate, (9:1)) and recrystallization from hexane gave yellow, crystalline **5a** (0.44 g, 67% yield; mp 98–98.5 °C): ^{1}H NMR (C_6D_6, 300 MHz) δ 7.05–7.20 (5 H, m, C_6H_5), 5.91 (1 H, d, J = 15.8 Hz, =CHC_6H_5), 5.37 (1 H, dd, J = 7.1, 15.8 Hz, =CH), 3.15–3.26 (3 H, m, overlapping H-6 and CH_2), 2.91 (6 H, s, OCH_3), 2.73 (2 H, d, J = 6.0 Hz, H-1 and H-5), 1.58 (3 H, t, J = 7.4 Hz, CH_3); IR (CH_2Cl_2) 2007, 1923, 1600, 1516, 1470, 1267, 1262, 1134 cm^{-1}. Anal. Calcd for $C_{21}H_{21}MnO_5$: C, 61.77; H, 5.18. Found: C, 61.74; H, 5.21.

(*E*)-2,4-Dimethoxy-3-(1-methylethyl)-6-(2-phenylethenyl)cyclohexadienylmanganese Tricarbonyl (5b). Complex **5b** (mp 95–101 °C) was prepared in 60% yield from complex **4b** according to the procedure described above for the preparation of complex **5a**. For **5b**: ^{1}H NMR (C_6D_6, 300 MHz) δ 7.07–7.25 (5 H, m, C_6H_5), 5.93 (1 H, d, J = 15.8 Hz, =CHC_6H_5), 5.39 (1 H, dd, J = 6.9, 15.8 Hz, =CHC_6H_5), 3.94 (1 H, septet, J = 7.1 Hz, CH), 3.18 (1 H, q, J = 6.3 Hz, H-6), 2.88 (6 H, s, OCH_3), 2.71 (2 H, d, J = 6.0 Hz, H-1 and H-5), 1.78 (6 H, d, J = 7.2 Hz, CH_3); IR (CH_2Cl_2) 2008, 1923, 1600, 1513, 1494, 1470, 1424, 1265, 1260, 1135 cm^{-1}. Anal. Calcd for $C_{22}H_{23}MnO_5$: C, 62.56; H, 5.49. Found: C, 62.46; H, 5.51.

(*E*)-2-Ethyl-1,3-dimethoxy-5-(2-phenylethenyl)benzene (6a). Complex **5a** (0.218 g, 0.534 mmol) was dissolved in CH_3CN (4.0 mL), and DDQ (0.182 g, 0.802 mmol) was added in one portion. The reaction mixture was refluxed for 4 h. Flash chromatography (hexane–ethyl acetate (9:1)) gave white crystalline **6a** (0.125 g, 87% yield, mp 73.5–74.5 °C): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51 (2 H, d, J = 7.6 Hz, H-2′ and H-6′), 7.36 (2 H, t, J = 7.5 Hz, H-3′ and H-5′), 7.25 (1 H, t, J = 7.2 Hz, H-4′), 7.07 (2 H, s, CH=CH), 6.70 (2 H, s, H-42 and H-6), 3.87 (6 H, s, OCH_3's), 2.66 (2 H, q, J = 7.4 Hz, CH_2), 1.09 (3 H, t, J = 7.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.2, 137.4, 135.9, 129.2, 128.7, 127.8, 127.5, 126.4, 120.9, 102.1, 55.7, 16.4, 13.8; IR (CH_2Cl_2) 2964, 2936, 2871, 2838, 1600, 1575, 1454, 1417, 1267, 1139, 818, 755, 732 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.41; H, 7.52.

(*E*)-1,3-Dimethoxy-2-(1-methylethyl)-5-(2-phenylethyl)-benzene (6b). Stilbene **6b** (mp 65–66 °C) was prepared in 70% yield from complex **5b** according to the procedure given for the synthesis of **6a**. For **6b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51 (2 H, d, J = 7.7 Hz, H-2′ and H-6′), 7.35 (2 H, t, J = 7.5 Hz), 7.24 (1 H, t, J = 7.2 Hz, H-4′), 7.05 (2 H, s, CH=CH), 6.69 (2 H, s, H-4 and H-6), 3.84 (6 H, s), 3.59 (1 H, septet, J = 7.0 Hz, CH), 1.29 (6 H, d, J = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.7, 137.3, 135.9, 129.0, 128.7, 128.0, 127.5, 126.4, 124.4, 102.8, 24.2, 20.7; IR (CH_2Cl_2) 2957, 2934, 2872, 2838, 1600, 1576, 1568, 1450, 1416, 1362, 1237, 1142, 1108, 1056, 961, 819, 758, 748, 745 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.70; H, 7.88.

(*E*)-2-Ethyl-1,3-dihydroxy-5-(2-phenylethenyl)benzene (1a).[2] To a 25-mL round-bottom flask was added **6a** (19.4 mg, 0.071 mmol) dissolved in freshly distilled 1,2-dichloroethane (2 mL) followed by boron tribromide–methyl sulfide (192 mg, 0.614 mmol) dissolved in 1,2-dichloroethane (2 mL). The mixture was heated at reflux under N_2 for 24 h. After the disappearance of starting material as monitored by TLC and cooling, the reaction mixture was hydrolyzed by adding H_2O (5 mL), followed by stirring for 20 min and diluting with 5 mL of ether. The organic layer was separated, and the remaining layer was repeatedly extracted with ether. The combined extracts were then washed several times with H_2O, 10% $NaHCO_3$, and H_2O and dried ($MgSO_4$), and the solvent was removed in vacuo to yield a brown solid, which was further purified by flash column chromatography on silica gel (3:1 petroleum ether–ether) to give 15.4 mg (89%) of white crystalline **1a**: R_f = 0.36 (3:1 petroleum ether–ether); mp 143–145 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.50 (2 H, d, J = 7.2 Hz, H-2′ and H-6′), 7.37 (2 H, t, J = 7.2 Hz, H-3′ and H-5′), 7.27 (1 H, t, J = 7.2 Hz, H-4′), 7.02 (1 H, d, J = 16.5 Hz, =CH), 6.94 (1 H, d, J = 16.2 Hz, =CH), 6.59 (2 H, s, H-4 and H-6), 4.81 (2 H, s, OH), 2.69 (2 H, q, J = 7.5 Hz, CH_2), 1.21 (3 H, t, J = 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 16.5, 106.2, 116.6, 126.5, 127.6, 127.9, 128.6, 128.7, 136.4, 137.1, 154.5; IR (KBr pellet) 3390, 3026, 2971, 2928, 1618, 1582, 1445, 1427, 1246, 1091, 982, 960, 827, 755, 700 cm^{-1}; HRMS m/z calcd for $C_{16}H_{16}O_2$ 240.1151, found 240.1144.

(*E*)-1,3-Dihydroxy-2-(1-methylethyl)-5-(2-phenylethenyl)benzene (1b).[2,3] To a dry 25-mL round-bottom flask was added boron tribromide–methyl sulfide complex (1.2 g, 3.8 mmol) in freshly distilled 1,2-dichloroethane (4 mL). Stilbene **6b** (24 mg, 0.084 mmol) was dissolved in 1,2-dichloroethane (4 mL) and added to the reaction vessel. The reaction was stirred at reflux for 24 h, and H_2O (5 mL) was added. Workup as described for **1a** yielded 18.7 mg (87%) of crystalline **1b**: R_f = 0.47 (3:1 petroleum ether/ether); mp 140–142 °C (heptane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (2 H, t, J = 7 Hz, H-2′ and H-6′), 7.37 (2 H, J = 7 Hz, H-3′ and H-5′), 7.28 (1 H, J = 7 Hz, H-4′), 7.01 (1 H, d, J = 16 Hz, =CH), 6.92 (1 H, d, J = 16 Hz, =CH), 6.52 (2 H, s, H-4 and H-6), 4.77 (2 H, bs, OH), 3.47 (1 H, m, J = 7 Hz, CH), 1.39 (6 H, d, J = 7 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 24.6, 106.8, 120.3, 126.5, 127.6, 127.7, 128.7, 136.2, 137.2, 154.9. IR (KBr pellet) 3547, 3508, 3393, 2962, 2928, 2874, 1636, 1579, 1425, 1347, 1259, 1135, 1069, 992 cm^{-1}; HRMS m/z calcd for $C_{17}H_{18}O_2$ 254.1307, found 254.1298.

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Registry No. **1a**, 79338-80-0; **1b**, 79338-84-4; **2**, 2040-04-2; **3a**, 18610-90-7; **3b**, 25108-61-6; **3c**, 16700-61-1; **4a**, 141509-22-0; **4b**, 141509-24-2; **5a**, 141509-25-3; **5b**, 141526-66-1; **6a**, 141509-19-5; **6b**, 141509-20-8; $Mg(CO)_5Br$, 14516-54-2; (*E*)-β-bromostyrene, 588-72-7.

A Ready Synthesis of Intermediates Containing the A-Ring Substructure of Taxol: A Diels–Alder Route to the B-*seco* Taxane Series

Yves Queneau,* Walter J. Krol, William G. Bornmann, and Samuel J. Danishefsky

Laboratory of Bio-Organic Chemistry, Sloan-Kettering Institute for Cancer Research, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10021

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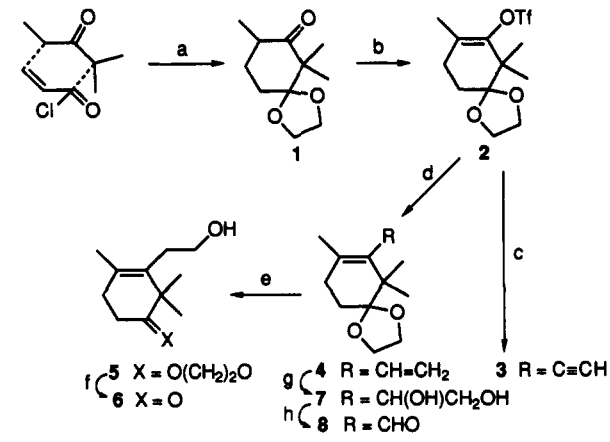
The tetracyclic diterpenoid taxol (**23**) has emerged in the past years as a very promising antitumor agent, especially against ovarian and breast cancers. Its extreme scarcity as well as its unusual mode of action, i.e., the acceleration of the polymerization of tubulin and the blocking of its depolymerization, have resulted in intense efforts toward its hemi and total synthesis.[1]

In the research described herein, we have developed chemistry which leads to A-ring equivalents en route to **23**. We focused on two kinds of goals. The first objective (see Schemes I and II) was to reach targets including the main features of the A-ring of **23** as well as access points for further extension.[2] It was further demonstrated that appropriately fashioned A-ring constructs can function as dienophiles to provide very rapid access to *seco*-B taxane analogues.

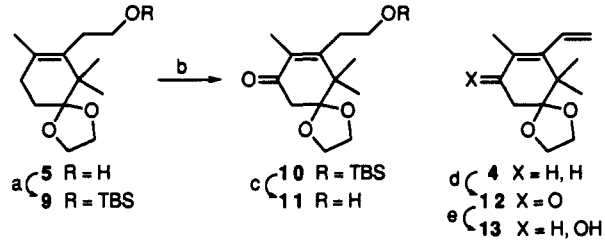
The keto ketal **1** was obtained in three steps from 2-methyl-3-pentanone and acryloyl chloride following known protocols.[3] Reaction of the potassium enolate of **1** with *N*-phenyltrifluoromethanesulfonimide[4] provided **2** in 82% yield. The enol triflate linkage of **2**, though hindered, is amenable to palladium-mediated cross-coupling reactions[5] with acetylenic as well as vinylic stannanes. Thus coupling of **2** with ethynyltri-*n*-butylstannane afforded a 69% yield of **3**. Similar reaction with vinyltri-*n*-butylstannane afforded a 91% yield of **4**. Compound **4** served as a starting material for a variety of interesting sequences leading to **5–8** as shown in Scheme I.

Scheme I[a]



[a] (a) Reference 3; (b) KHMDS, $PhNTf_2$, THF, 0 °C, 82%; (c) $Bu_3SnC{\equiv}CH$, cat. $Pd(PPh_3)_4$, LiCl, THF, reflux, 69%; (d) $Bu_3SnCH{=}CH_2$, cat. $Pd(PPh_3)_4$, LiCl, THF, reflux, 91%; (e) 9-BBN, THF, reflux, 97%; (f) *p*-TsOH, THF–water, 45 °C, 100%; (g) cat. OsO_4, NMO, acetone–water, r.t., 100%; (h) cat. TPAP,[6] NMO, powdered 4-Å molecular sieves, CH_2Cl_2, rt, 56%.

Scheme II[a]



[a] (a) TBDMSCl, Et_3N, cat. DMAP, CH_2Cl_2, rt, 82%; (b) CrO_3–3,5-DMP, CH_2Cl_2, −23 °C, 48%; (c) *p*-TsOH, aqueous acetone 82%; (d) CrO_3–3,5-DMP, CH_2Cl_2, −23 °C, 70%; (e) $CeCl_3$, $NaBH_4$, MeOH, 0 °C, 85%.

The feasibility of achieving allylic oxidation as a route to establish the vital C-13[7] functionality of **23** was demonstrated at several stages. Thus silylation of **5** afforded **9** which upon oxidation with chromium oxide–3,5-dimethylpyrazole[8] gave rise to **10** and thence **11** (cf. Scheme II). Similar oxidation of **4** afforded a 70% yield of **12**. The latter could be reduced under Luche conditions[9] to provide **13**. Alternatively, reduction of **12** under the protocols of Corey[10] provided **13** albeit at this writing in only 70% ee.

Alcohol **5** was smoothly oxidized to provide **14** which, upon reaction with isopropenylmagnesium bromide, afforded **15** and thence, by Swern oxidation,[11] the ketone **16**. This compound serves as a branch point to reach inter-

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(2) Studies in the synthesis of intermediates containing the CD substructure of taxol are in progress in our laboratory. For a preliminary communication, see: Magee, T. V.; Bornmann, W. G.; Isaacs, R. C. A.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 3274.

(3) (a) Detering, J.; Martin, H.-D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 695. (b) Hargreaves, J. R.; Hickmott, P. W.; Hopkins, B. J. *J. Chem. Soc. C* **1968**, 2599.

(4) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47. Examples of potassium enolates for enol triflate formation include the following. Corey, E. J.; Houpis, I. N. *J. Am. Chem. Soc.* **1990**, *112*, 8997. Tius, M. A.; Kannangara, G. S. K. *J. Org. Chem.* **1990**, *55*, 5711.

(5) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.

(6) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625. Cleavage of the diol linkage of **7** was observed during an attempted selective monooxidation to the corresponding hydroxy aldehyde using tetrapropylammonium perruthenate. Selective oxidation of primary alcohols in the presence of an allylic alcohol have been described, see: Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957. In the case of diol **7**, the various ratios of the two possible products were consistent with the results observed by Swern et al.; however the mixture thus obtained was converging to the undesired hydroxy ketone.

(7) Numbering refers to the usual numbering of taxol (**23**).

(8) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057. CrO_3–3,5-dimethylpyrazole has already been successively used on a taxane derivative, see: Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 3513.

(9) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(10) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. In this reaction, we used as chiral catalyst the (*R*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole. Therefore, by analogy with Corey's findings, the absolute configuration for the major enantiomer of **13** was assigned to be *S*. The ee was determined by NMR study of the mixture using (+)-$Eu(hfc)_3$ as chiral shift reagent.

(11) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

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