Short Communication

Synthesis of Racemic 3,5-O-Benzylidene-2-deoxypentoses from 2-Phenyl-1,3-dioxan-5-one Hydrate

Trond Ulven, Karsten A. Sørbye and Per H. J. Carlsen*

Institute of Organic Chemistry, Norwegian University of Science and Technology, N-7034 Trondheim, Norway

A recent publication reported the convenient synthesis of 2-phenyl-1,3-dioxan-5-one (BDHA, benzylidenedihydroxyacetone),[1] which formed a stable hydrate, 1. This is a potentially useful synthon for a number of polyhydroxy compounds of biological interest, e.g., modified carbohydrates, azasugars, nucleosides and glycosides. We here report the syntheses of the racemic 3,5-O-benzylidene protected 2-deoxyxylose, 2, and 2-deoxyribose, 3. These compounds may be of interest in the synthesis of modified nucleosides, e.g., 3'-substituted 2',3'-dideoxynucleosides such as AZT.[2]

Results and discussion

The syntheses of the desired deoxysugars were accomplished as outlined in Scheme 1. This involved allylation of BDHA followed by reduction of the ketone and ozonolysis of the alkene. Direct alkylation of the 1,3-O-acetal protected dihydroxyacetone has been reported to be troublesome, as, in most cases, reduction and self-condensation products were formed in considerable amounts.[3] As a consequence, the allylation was carried out using the corresponding dimethylhydrazone, 4, which for similar systems has been reported to work satisfactorily.[4] The reaction proceeded smoothly forming the axial product, 5, in agreement with the literature.[5] This structure was fully confirmed by NOE experiments. The hydrazone 5 may be used directly in the subsequent step without further purification, or it can be purified by flash chromatography through a short silica column, however, not without some loss of product, mainly due to hydrolysis of the hydrazone group.

The conversion of hydrazones into the corresponding ketones may be performed by acidic hydrolysis or by ozonolysis,[6] neither of which was suitable for the transformation of 5 into 6. A hydrolytic method was preferred

over an oxidative one. However, because of the acid labile acetal, conditions had to be carefully selected. As it turned out, treatment with a saturated aqueous ammonium dihydrogen phosphate buffer at ambient temperature smoothly converted 5 into 6 in an essentially quantitative yield.

The equatorially substituted BDHA derivative 7 was predicted[7] to be sterically more stable than the axially substituted 6. Epimerisation of 6 to the equatorially substituted BDHA with aqueous sodium hydroxide was investigated, but resulted in complex reaction mixtures. However, upon treatment with ammonium hydroxide (25%) at ambient temperature, the epimerisation was executed satisfactorily, cleanly yielding compound 7 together with 6 in up to 23:1 ratio, as determined by GC.

Reduction of unsubstituted BDHA with sodium borohydride has been shown to lead to the formation of the corresponding equatorial alcohol with >99% selectivity.[8] The reduction of compound 6 with sodium borohydride gave the equatorial alcohol 8 together with approximately 10% of the corresponding axial alcohol. Compound 7 was readily converted into alcohol 9 in a one-pot procedure from 6 by addition of sodium boro hydride to the aqueous ammonium hydroxide–THF epimerization reaction mixture, with a selectivity of >95% over the axial alcohol.

The syntheses of the benzylidene protected 2-deoxy-DL-xylose, 2, and the 2-deoxy-DL-ribose, 3, were completed by ozonolysis of compounds 8 and 9, respectively. In this step slow elevation of the temperature after addition of methyl sulfide appeared to be essential. The benzylidene protected deoxyxylose 2 was isolated as a mixture of α- and β-furanose anomers. The corresponding deoxyribose 3, however, did unexpectedly retain the aldoribose form. This may be due to steric constraints caused by the small dihedral angles of the C–C bonds and the shorter C–O bond lengths generally characteristic

---

* To whom correspondence should be addressed.
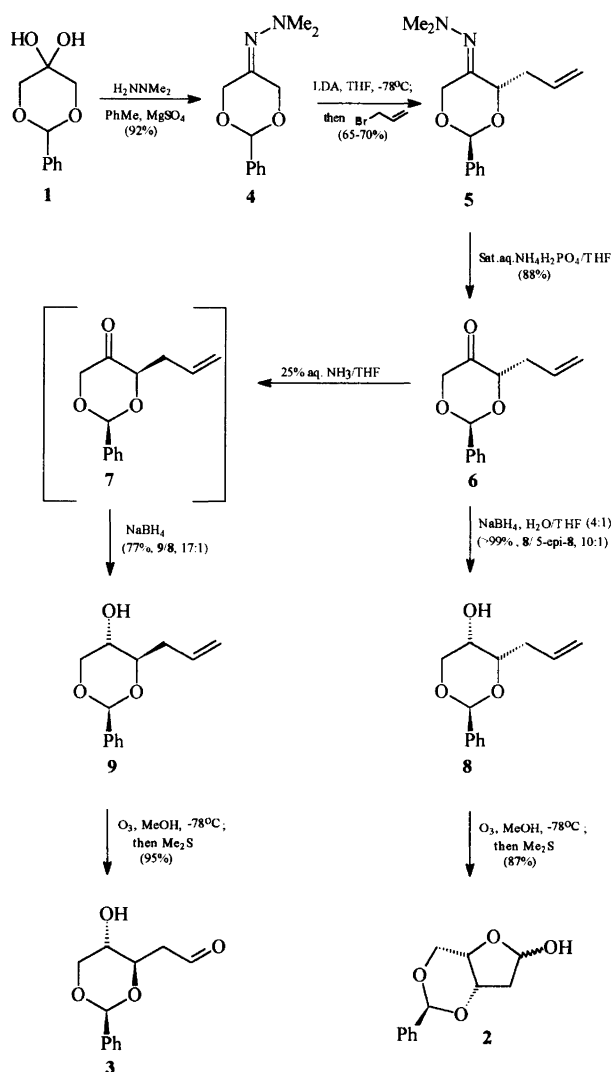
Scheme 1.

of 1,3-dioxanes.[9] The reactive centers may not fully satisfy the stereochemical requirements for the ring closure reaction as the angle of approach of the OH group to the aldehyde group differs substantially from the ideal Bürgi–Dunitz[10] trajectory of approximately 109°.

Hydrolysis of compounds 2 and 3 in aqueous trifluoroacetic acid (0.01 M) gave products whose ^{13}C NMR spectra were in total agreement with those reported for 2-deoxy-D-xylose and 2-deoxy-D-ribose respectively.[11] These NMR results and the synthetic pathways towards the products support the anticipated relative stereochemistries of compounds 2 and 3. Work towards the enantiomerically pure products is now in progress.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 300 or DPX 400. IR spectra were obtained with a Nicolet 200-SXC FT-IR or a Perkin–Elmer 684 spectrometer. Mass spectra were recorded on an AEI MS-902 spectrometer at 70 eV (IP) and 160–180 °C inlet temperature. GLC analyses were performed on a Chrompack CP 9000 gas chromatograph equipped with a CP-Sil 5CB 12.5 m column. Melting points are uncorrected. Tetrahydrofuran (THF) was distilled from sodium.

2-Phenyl-1,3-dioxan-5-one dimethylhydrazone 4. To a stirred solution of 1 (4.65 g, 24 mmol) in toluene (150 ml) at room temperature was added N,N-dimethylhydrazine (2.70 ml, 36 mmol), then $MgSO_4$ (ca. 7 g). After 48 h, the mixture was filtered and the solvent evaporated off under reduced pressure. The product was dried under vacuum (0.1 mmHg) to give 4 as white crystals, which turned yellow with time (4.93 g, >97% pure, 92% yield), m.p. 72–73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.47 (6 H, s, N,N-Me$_2$), 4.41 (1 H, d, J = 15.1 Hz, H-4), 4.53 (1 H, d, J = 14.2 Hz, H-6), 4.61 (1 H, d, J = 14.2 Hz, H-6), 5.26 (1 H, d, J = 14.7 Hz, H-4), 5.71 (1 H, s, H-2), 7.35–7.40 (3 H, m, Ph), 7.48–7.51 (2 H, m, Ph). ^{13}C NMR (400 MHz, $CDCl_3$): δ 47.6 (N,N-Me$_2$), 64.7, 69.3, 100.5 (C-2), 126.1 (Ph), 128.4 (Ph), 129.2 (Ph), 137.5 (Ph), 158.3 (C-5). IR (KBr): 3000, 2962, 2875, 2842, 1480, 1452, 1440, 1387, 1252, 1117, 1058, 1030, 970, 749, 741, 698 cm^{-1}. MS [m/z (% rel. int.)]: 220 (30, M^+), 146 (10), 114 (37), 106 (68), 105 (100), 77 (73).

trans-4-Allyl-2-phenyl-1,3-dioxan-5-one dimethylhydrazone 5. n-BuLi (1.6 M in hexane, 8.13 ml, 13 mmol) was added dropwise to a solution of diisopropylamine (1.82 ml, 13.0 mmol, distilled from CaH_2) in THF (40 ml) at 0 °C under an N_2 atm and stirred for 10 min to generate a solution of LDA. The LDA solution was added to a stirred solution of 4 (2.47 g, 11 mmol) in THF (30 ml) at −78 °C. After 30 min, allyl bromide (0.95 ml, 11 mmol) was added dropwise. After 40 min, the reaction was allowed to reach 0 °C and quenched with saturated $NaHCO_3$ (10 ml). To the mixture was added Et_2O (40 ml) and the organic phase was washed with brine (2 × 25 ml), dried ($MgSO_4$) and concentrated to give fairly pure 5 as a yellow oil (3.00 g, ca. 89% pure by GC, ca. 91% yield). Purification by flash chromatography (SiO_2, Et_2O–cyclohexane 1:2) led to some loss due to hydrolysis of the hydrazone on silica, but gave pure 5 as white crystals, which turned yellow on standing (65–70%): m.p. 50–53 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (6 H, s, N,N-Me$_2$), 2.62 (1 H, m, H-1′), 2.78 (1 H, m, H-1′), 4.46 (1 H, dd, J = 15.3, 1.3 Hz, H-6$_{ax}$), 4.61 (1 H, ddd, J = 9.2, 5.1, 1.2 Hz, H-4), 5.13 (1 H, d, J = 15.3 Hz, H-6$_{eq}$), 5.15 (2 H, m, H-3′), 5.90 (2 H, ddt, J = 17.1, 10.2, 7.0, H-2′), 5.95 (1 H, s, H-2), 7.34–7.41 (3 H, m, Ph), 7.47–7.51 (2 H, m, Ph). E-configuration of the hydrazone and the axial substitution of the allyl group were confirmed by an NOE-difference experiment. Irradiation of N,N-Me$_2$ gave an NOE of H-6$_{ax}$ and H-6$_{eq}$. Irradiation of H-1′ gave an NOE at H-2, H-2′ and H-4. Irradiation of H-6$_{ax}$ gave an NOE at H-6$_{eq}$ and

H-2. Irradiation of H-6$_{eq}$ gave an NOE at H-6$_{ax}$. ^{13}C NMR (300 MHz, CDCl$_3$): δ 36.6 (C-1′), 47.7 (N,N-Me$_2$), 62.9 (C-6), 74.4 (C-4), 95.6 (C-2), 117.8 (C-3′), 126.1 (Ph), 128.3 (Ph), 128.9 (Ph), 133.8 (C-2′), 137.9 (Ph), 162.2 (C-5). IR (KBr): 3067, 2987, 2960, 2867, 1642, 1453, 1393, 1215, 1132, 1100, 1034, 1022, 1001, 988, 964, 909, 749, 698 cm^{-1}. MS [m/z (% rel.int.)]: 260 (0.2, M$^+$), 218 (0.7), 210 (0.2), 204 (0.3), 202 (0.2), 149 (11), 148 (100), 147 (15), 133 (12), 120 (15), 119 (13), 118 (14), 107 (12), 106 (29), 105 (51), 90 (20), 77 (37).

trans-4-Allyl-2-phenyl-1,3-dioxan-5-one 6. The hydrazone 5 (5.10 g, 12 mmol) was dissolved in THF (25 ml), saturated aqueous ammonium dihydrogen phosphate (480 ml) was added and the solution was stirred at room temperature. After 7 h, the solution was extracted with CH$_2$Cl$_2$ (7 × 35 ml) and the extract was washed with brine (50 ml) and dried (MgSO$_4$). Concentration gave fairly pure 6 as the crude product (4.32 g, including traces of 5). The amount of 6 relative to 7 was determined by GC to be 14:1. Crystallization from n-pentane at −20 °C gave 6 (>95%, GC) as white needles (3.75 g, 88%): m.p. 41–42 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.60 (2 H, m, H-1′), 4.42 (2 H, m, H-6), 4.44 (1 H, dd, J = 7.8, 4.7 Hz, H-4), 5.14 (1 H, ddd, J = 10.2, 2.9, 1.2 Hz, H-E-3′), 5.16 (1 H, ddd, J = 17.1, 3.1, 1.6 Hz, H-Z-3′), 5.84, (1 H, ddt, J = 17.1, 10.2, 6.9 Hz, H-2′), 6.05 (1 H, s, H-2), 7.37–7.44 (3 H, m, Ph), 7.49–7.55 (2 H, m, Ph). ^{13}C NMR (300 MHz, CDCl$_3$): δ 33.9 (C-1′), 70.7 (C-6), 96.1, 96.8, 118.4 (C-3′), 126.1 (Ph), 128.4 (Ph), 129.1 (Ph), 132.8 (C-2′), 137.3 (Ph), 207.1 (C-5). IR (neat): 3074, 2877, 1749, 1211, 1116, 1041, 1028, 995, 920, 745, 698 cm^{-1}. MS [m/z (% rel. int.)]: 218 (1.3, M$^+$), 177 (16), 148 (67), 120 (42), 119 (31), 106 (60), 105 (100), 92 (26), 91 (30), 90 (27).

threo-4-Allyl-5-hydroxy-2-phenyl-1,3-dioxane 8. To a stirred solution of 6 (307 mg, 1.4 mmol) in THF–water (1:4, 45 ml) at 0 °C was added NaBH$_4$ (100 mg, 2.6 mmol). After 30 min the mixture was extracted with CH$_2$Cl$_2$ (5 × 10 ml). The organic phase was washed with brine (15 ml), dried (MgSO$_4$) and concentrated under reduced pressure. Flash chromatography (SiO$_2$, Et$_2$O–cyclohexane 2:3) gave 8, together with minor amounts of diastereomers, which were inseparable by flash chromatography, as a colorless oil (308 mg, >99% combined yield, 8:5-epi-8, 10:1 from GC). ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.38 (1 H, m, H-1′), 2.53 (1 H, m, H-1′), 2.75 (1 H, d, J = 11.0 Hz, OH), 3.38 (1 H, dd, J = 11.0, 1.5 Hz, H-5), 3.82 (1 H, m, H-4), 3.87 (1 H, dd, J = 11.8, 2.7 Hz, H-6), 3.93 (1 H, dd, J = 11.8, 1.7 Hz, H-6), 5.14 (1 H, dm J = 10.1 Hz, H-E-3′), 5.19 (1 H, ddd, J = 17.1, 3.2, 1.5 Hz, H-Z-3′), 5.86 (1 H, ddt, J = 17.2, 10.1, 7.1 Hz, H-2′), 6.11 (1 H, s, H-2), 7.33–7.48 (>5 H, m, Ph). ^{13}C NMR (400 MHz, CDCl$_3$): δ 35.4 (C-1′), 65.6, 66.0, 71.8 (C-5), 96.7 (C-2), 118.1 (C-3′), 126.8 (Ph), 128.8 (Ph), 133.6 (C-2′), 136.5 (Ph). IR (neat): 3440 (br), 2926, 1642, 1452, 1391, 1331, 1205, 1097, 1026, 916, 793, 736,

700, 698 cm^{-1}. MS [m/z (% rel.int.)]: 220 (6, M$^+$), 219 (7), 179 (20), 177 (4), 150 (7), 149 (6), 107 (100), 106 (28), 105 (57), 91 (14), 79 (27), 77 (35).

3,5-O-Benzylidene-2-deoxy-DL-threo-pentofuranose 2. Through a solution of 8 (400 mg, 1.80 mmol) in MeOH (50 ml) at −78 °C was passed a stream of ozone until persistent blue color was achieved. The solution was flushed with N$_2$ until no further ozone was detected. Me$_2$S (1.3 ml) was added and the solution was allowed slowly to reach room temperature (overnight). Concentration under reduced pressure and crystallization from Et$_2$O gave an anomeric mixture of 3 as white crystals (232 mg). Flash chromatography of the concentrated mother liquors (SiO$_2$; Et$_2$O–cyclohexane 1:1; then EtOAc) yielded another batch of 3 (140 mg, total yield of 93%): m.p. 107–109 °C. Major anomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.15 (1 H, dt, J = 14.1, 4.8 Hz, H-2), 2.28 (1 H, d, J = 14.1 Hz, H-2), 3.81 (1 H, q J = 3.3 Hz, H-4), 4.03 (1 H, dd, J = 12.7, 3.1 Hz, H-5), 4.14 (1 H, dd, J = 12.6, 3.5 Hz, H-5), 4.43 (1 H, t, J = 3.8 Hz, H-3), 5.49 (1 H, d, J = 5.1 Hz, H-1), 6.11 (1 H, s, H-6), 7.34–7.51 (5 H, m, Ph). ^{13}C NMR (400 MHz, CDCl$_3$): δ 40.1 (C-2), 61.5 (C-5), 69.1 (C-3), 75.6 (C-4), 95.7 (C-1), 99.5 (C-6), 126.8 (Ph), 128.7 (Ph), 128.9 (Ph), 136.1 (Ph). Minor anomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.10 (1 H′, ddd, J = 14.5, 5.8, 3.4 Hz, H′-2), 2.47 (1 H′, ddd, J = 14.4, 5.6, 1.9 Hz, H′-2), 3.99 (1 H′, dd, J = 12.5, 2.8 Hz, H′-5), 4.07 (1 H′, q J = 3.3 Hz, H-5), 4.14 (1 H′, dd, J = 12.6, 3.5 Hz, H′-5), 4.54 (1 H′, ddd, J = 5.7, 3.5, 2.1 Hz, H′-3), 5.87 (1 H′, dd, J = 5.6, 3.4 Hz, H′-1), 5.99 (1 H′, s, H′-6), 7.37–7.51 (5 H′, m, Ph′). ^{13}C NMR (400 MHz, CDCl$_3$): δ 41.2 (C′-2), 60.9 (C′-5), 70.3 (C′-3), 73.0 (C′-4), 95.1 (C′-1), 98.4 (C′-6), 126.7 (Ph′), 128.5 (Ph′), 128.7 (Ph′), 136.9 (Ph′). IR (neat) 3410 (br), 2970, 1338, 1210, 1129, 1086, 1061, 1012, 999, 791, 731, 698 cm^{-1}. MS [m/z (% rel. int.)]: 222 (1.5, M$^+$), 221 (5.5), 220 (1.5), 204 (1.5), 176 (4), 175 (6), 107 (44), 106 (52), 105 (100), 79 (12), 77 (51).

erythro-4-Allyl-5-hydroxy-2-phenyl-1,3-dioxane 9. To the ketone 6 (270 mg, 1.2 mmol) dissolved in THF (10 ml) was added 25% aq. NH$_3$ (40 ml) and the mixture was stirred at room temperature for 4 h. The temperature was lowered to 0 °C and NaBH$_4$ (24 mg, 0.6 mmol) was added. The temperature was slowly allowed to reach room temperature, and the mixture was extracted with CH$_2$Cl$_2$ (5 × 12 ml). The extract was washed with brine (15 ml), dried (MgSO$_4$) and concentrated under reduced pressure. The product was purified by flash chromatography [SiO$_2$; Et$_2$O–cyclohexane (2:3)] to give 9 as a colorless oil together with trace amounts of the inseparable isomer 8 (211 mg, 77%; 9/8, 17:1 from GC). Recrystallization from Et$_2$O afforded 9 (>98%, GC) as white needles: m.p. 64 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.69 (1 H, d, J = 5.0 Hz, OH), 2.49 (1 H, m, H-1′), 2.64 (1 H, m, H-1′), 3.56–3.75 (3 H, m), 4.28 (1 H, dd, J = 10.6, 4.9 Hz, H-5), 5.13 (1 H, dm, J ≈ 10 Hz, H-3′),

5.21 (1 H, dm $J = 17$ Hz, H-3'), 5.49 (1 H, s, H-2), 6.01 (1 H, ddt, $J = 17.2$, 10.1, 7.4 Hz, H-2'), 7.32–7.42 (3 H, m, Ph), 7.46–7.52 (2 H, m, Ph). ^{13}C NMR δ 36.7 (C-1'), 65.7, 71.0, 81.0, 100.9 (C-2), 117.6 (C-3'), 126.1 (Ph), 128.3 (Ph), 128.9 (Ph), 134.2 (C-2'), 137.7 (Ph). IR (KBr): 3447, 3074, 2974, 2902, 1644, 1456, 1407, 1110, 1069, 1025, 953, 917, 756, 700 cm^{-1}. MS [m/z (% rel. int.)]: 220 (8, M^+), 219 (4), 179 (23), 107 (100), 105 (21), 79 (14), 77 (12).

3,5-O-Benzylidene-2-deoxy-DL-*erythro-pentose* **3**. Through a solution of **9** (55 mg, 0.25 mmol) in MeOH (9 ml) at −78 °C was passed a stream of ozone until a persistent blue color was achieved. The solution was flushed with N_2 until no further ozone was detected. Me_2S (0.16 ml) was added and the solution was allowed slowly to reach room temperature (overnight). The solution was concentrated and the product purified by flash chromatography (SiO$_2$; Et$_2$O–cyclohexane 1:1; then ethyl acetate) to give **2** as a colorless oil (53 mg, 95%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.34 (1 H, d, $J = 5.4$ Hz, OH), 2.86 (1 H, ddd, $J = 16.9$, 6.9, 2.1 Hz, H-2), 2.94 (1 H, ddd, $J = 16.9$, 5.1, 1.6 Hz, H-2), 3.58–3.71 (2 H, m), 4.12 (1 H, ddd, $J = 8.7$, 6.9, 5.1, H-3), 4.30 (1 H, m, H-5), 5.52 (1 H, s, benzylidene), 7.33–7.40 (3 H, m, Ph), 7.42–7.49 (2 H, m, Ph), 9.85 (1 H, t, $J = 1.9$, H-1). ^{13}C NMR (400 MHz, CDCl$_3$): δ 46.5 (C-2), 65.4, 71.4, 77.0, 101.0 (benzylidene), 126.0 (Ph), 128.2 (Ph), 129.0 (Ph),

137.2 (Ph), 200.8 (C-1). IR (neat): 3448 (br), 2858, 1723, 1455, 1397, 1076, 1026, 757, 699 cm^{-1}. MS [m/z (% rel. int.)] 222 (13, M^+), 221 (10), 150 (6), 149 (8), 108 (8), 107 (100), 106 (28), 105 (57), 91 (9), 79 (22), 77 (35).

References

1. Carlsen, P. H .J., Sørbye, K. A., Ulven, T. and Aasbø, K. *Acta Chem. Scand. 50* (1996) 185.
2. Dueholm, K. L. and Pedersen, E. B. *Synthesis* (1992) 1, and references cited therein.
3. Majewski, M., Gleave, D. M. and Nowak, P. *Can. J. Chem. 73* (1995) 1616.
4. Enders, D. and Bockstiegel, B. *Synthesis* (1989) 493.
5. Collum, D. B., Kahne, D., Gut, S. A., DePue, R. T., Mohamadi, F., Wanat, R. A., Clardy, J. and Van Duyne, G. *J. Am. Chem. Soc. 106* (1984) 4865.
6. Enders, D., Eichenauer, H., Baus, U., Shubert, H. and Kremer, K. A. M. *Tetrahedron 40* (1984) 1345.
7. PCMODEL/MMX, Serena Software.
8. Unpublished results.
9. Eicher, T. and Hauptmann, S. *The Chemistry of Heterocycles*, Thieme, New York 1995, p.383.
10. Bürgi, H. B., Dunitz, J. D., Lehn, J.-M. and Wipff, G. *Tetrahedron 30* (1974) 1563.
11. Wong, M. Y. H. and Gray, G. R. *J. Am. Chem. Soc.* (1978) 3548.