2,6-Dihydroxynaphthalene (10). Method A. The standard procedure was followed. Reagents added into the reaction flask were sodium methoxide (77 mg, 1.42 mmol, 2.5 equiv), 2,6-dimethoxynaphthalene (**9**, 107 mg, 0.567 mmol, 1.0 equiv), hexamethyldisilathiane (305 mg, 1.42 mmol, 2.5 equiv), and 1,3-dimethyl-2-imidazolidinone (3.0 mL). After workup and purification by use of a chromatotron (1-mm plate, 50% EtOAc in hexanes as eluant), 2,6-dihydroxynaphthalene (**10**) was obtained as a white solid (mp 224.0–225.0 °C; lit.[29e] mp 223.0–225.0 °C) in 96% yield (87 mg, 0.54 mmol): GC (injector temperature 260 °C; column program: initial temperature 100 °C, duration 2.00 min; increment rate 15 °C/min; final temperature 250 °C) t_R 8.44 min; TLC R_f 0.35 (40% EtOAc in hexanes); ^{1}H NMR (DMSO-d_6 + $CDCl_3$, 80 MHz) δ 6.93–7.60 (m, 6 H, 2 C_6H_3), 8.21–8.85 (br, 2 H, 2 OH); IR (KBr) 3154 (s, OH), 3002 (s, =C—H), 2919 (s), 2872 (s), 1901 (w), 1664 (s), 1619 (s, C=C), 1519 (s, C=C), 1454 (s, C=C), 1449 (s), 1402 (m), 1367 (s), 1284 (s), 1243 (s, C—O), 1143 (m, C—O), 1120 (m, C—O), 1085 (w), 1038 (w), 967 (w), 934 (w), 873 (m), 808 (m), 773 (s), 744 (m), 685 (w) cm^{-1}. Its physical properties and spectroscopic characteristics are consistent with those of an authentic sample.[29e]

Phloroglucinol (12). Method A. The standard procedure was followed. Reagents added into the reaction flask were sodium methoxide (130 mg, 2.41 mmol, 2.5 equiv), 3,5-dimethoxyphenol (**11**, 149 mg, 0.963 mmol, 1.0 equiv), hexamethyldisilathiane (518 mg, 2.41 mmol, 2.5 equiv), and 1,3-dimethyl-2-imidazolidinone (3.0 mL). After workup, most of 1,3-dimethyl-2-imidazolidinone in the resulting mixture was removed by use of a column packed with basic aluminum oxide. Further purification was performed by use of a chromatotron (1-mm plate, 50% EtOAc in hexanes as eluant) to give phloroglucinol (**12**) as a yellow solid (mp 116.5–117.0 °C; lit.[28d] mp 117.0 °C) in 83% yield (101 mg, 0.799 mmol): GC (injector temperature 260 °C; column program: initial temperature 100 °C, duration 2.00 min; increment rate 15 °C/min; final temperature 250 °C) t_R 6.67 + 7.67 min; TLC R_f 0.37 (60% EtOAc in hexanes); ^{1}H NMR (DMSO-d_6 + $CDCl_3$, 80 MHz) δ 5.89 (s, 3 H, C_6H_3), 8.37 (br s, 3 H, 3 OH); IR (KBr) 3472 (s, OH) 3190 (br s, OH), 2931 (m), 2882 (w), 2684 (w), 1619 (s, C=C), 1531 (m), 1496 (s, C=C), 1414 (m), 1296 (m), 1155 (s, C—O), 1002 (s, C—O), 814 (m), 779 (m), 732 (m) cm^{-1}. Its physical properties and spectroscopic characteristics are consistent with those reported in literature.[31,32]

Method B. The standard procedure was followed. Reagents added into the reaction flask were sodium hydride (35 mg, 1.4 mmol, 1.5 equiv), 3,5-dimethoxyphenol (**11**, 149 mg, 0.963 mmol, 1.0 equiv), hexamethyldisilathiane (311 mg, 1.44 mmol, 1.5 equiv), and 1,3-dimethyl-2-imidazolidinone (3.0 mL). After workup and purification as described in method A, phloroglucinol (**12**) was obtained as a yellow solid in 75% yield (91 mg, 0.72 mmol). Its spectroscopic characteristics were identical with those listed above.

1-Methyl-2,6,7-trihydroxynaphthalene (14). Method A. The standard procedure was followed. Reagents added into the reaction flask were sodium methoxide (93 mg, 1.72 mmol, 2.5 equiv), 6,7-dimethoxy-1-methyl-2-naphthol (**13**, 150 mg, 0.688 mmol, 1.0 equiv), hexamethyldisilathiane (370 mg, 1.72 mmol, 2.5 equiv), and 1,3-dimethyl-2-imidazolidinone (3.0 mL). After workup, most of 1,3-dimethyl-2-imidazolidinone in the resulting mixture was removed by use of a column packed with neutral aluminum oxide. Further purification was performed by use of a chromatotron (1-mm plate, 50% EtOAc in hexanes as eluant) to give triol **14** as a yellow solid (mp 118.5–119.0 °C) in 78% yield (102 mg, 0.537 mmol): GC (injector temperature 260 °C; column program: initial temperature 140 °C, duration 2.00 min; increment rate 15 °C/min; final temperature 250 °C) t_R 8.22 min; TLC R_f 0.31 (50% EtOAc in hexanes); ^{1}H NMR (DMSO-d_6 + $CDCl_3$, 80 MHz) δ 2.41 (s, 3 H, CH_3), 6.60–7.46 (m, 4 H, $C_{10}H_4$), 7.85–8.61 (br s, 3 H, 3 OH); IR (KBr) 3401 (s, OH), 3295 (br s, OH), 3166 (s, =C—H), 2931 (m), 1643 (s, C=C), 1614 (s, C=C), 1537 (s, C=C), 1447 (w), 1411 (s), 1396 (s), 1342 (m), 1297 (w), 1264 (s), 1252 (s), 1204 (s, C—O), 1159 (m), 1076 (m, C—O), 1039 (w), 862 (m), 799 (m), 772 (w) cm^{-1}; exact mass calcd for $C_{11}H_{10}O_3$ 190.0630, found 190.0631.

Method B. The standard procedure was followed. Reagents added into the reaction flask were sodium hydride (25 mg, 1.03 mmol, 1.5 equiv), 6,7-dimethoxy-1-methyl-2-naphthol (**13**, 150 mg, 0.688 mmol, 1.0 equiv), hexamethyldisilathiane (222 mg, 1.03 mmol, 1.5 equiv), and 1,3-dimethyl-2-imidazolidinone (3.0 mL). After workup and purification as described in method A, triol **14** was obtained as a yellow solid in 72% yield (94 mg, 0.50 mmol). Its spectroscopic characteristics were identical with those listed above.

Acknowledgment. For financial support, we thank the donors of Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health for a Biomedical Research Support Grant S07 RR7041, as well as a grant supporting the purchase of a VG 70-S mass spectrometer.

Registry No. **1**, 91-16-7; **2**, 151-10-0; **3**, 150-78-7; **4**, 2132-80-1; **5**, 5486-55-5; **6**, 500-99-2; **7**, 1865-88-9; **8**, 120-80-9; **9**, 108-46-3; **10**, 123-31-9; **11**, 92-88-6; **12**, 581-43-1; **13**, 108-73-6; **14**, 129216-77-9; Me_3SiSNa, 2004-10-6; $Me_3SiSSiMe_3$, 3385-94-2.

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The Stereochemistry of the Aryl Phosphate/Aryl Phosphonate Rearrangement in 1,3,2-Oxazaphospholidine 2-Oxides

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Received April 16, 1990

On treatment with LDA/THF (aryloxy)phospholidines in the pseudoephedrine/ephedrine series undergo P–O to P–C rearrangement to afford arylphospholidines with retention of configuration at phosphorus. The stereochemistry of each product was assigned by ^{1}H NMR chemical shift and C-4/C-5 vicinal proton coupling constant analysis and comparison with known phenylphospholidines.

Introduction

The base (LDA or *n*-BuLi) induced rearrangement of arylphosphate **1** to arylphosphonate **2** shown in Figure 1 was first reported by Melvin in 1981.[1] Since that time Cambie and Palmer[2] as well as Dhawan and Redmore[3] have demonstrated the usefulness of this synthetic method. In an effort to probe the stereochemistry of this reaction at the phosphorus atom, the base-initiated rearrangement

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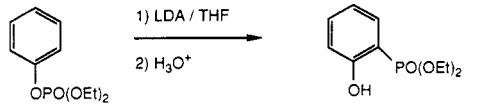


1 2

Figure 1.

Table I. ^{1}H NMR Chemical Shifts and Coupling Constants of Oxazaphospholidine 2-Oxides

compd	H-4	H-5	$J_{H4,H5}$	*N*-Me	*C*-Me
3	3.34	4.90	9	2.77	1.17
4	–	4.43	9	2.73	0.98
7	3.70	5.74	6	2.84	0.61
8	3.57	5.31	6	2.79	0.79
5	3.59	5.19	9	2.58	1.35
10	3.54	4.96	9	2.64	1.31
12	3.9–3.8	5.71	6	2.65	0.93
6	3.58	5.16	9	2.54	1.29
11	3.42	4.99	8	2.70	1.21
13	3.80	5.63	7	2.59	0.82
14	3.56	5.17	9	2.55	1.31
15	3.50	4.88	8	2.66	1.28
16[a]	3.83	5.95	6	2.74	0.80
17[a]	3.76	5.62	6	2.58	0.88

[a] Data obtained from ref 5.

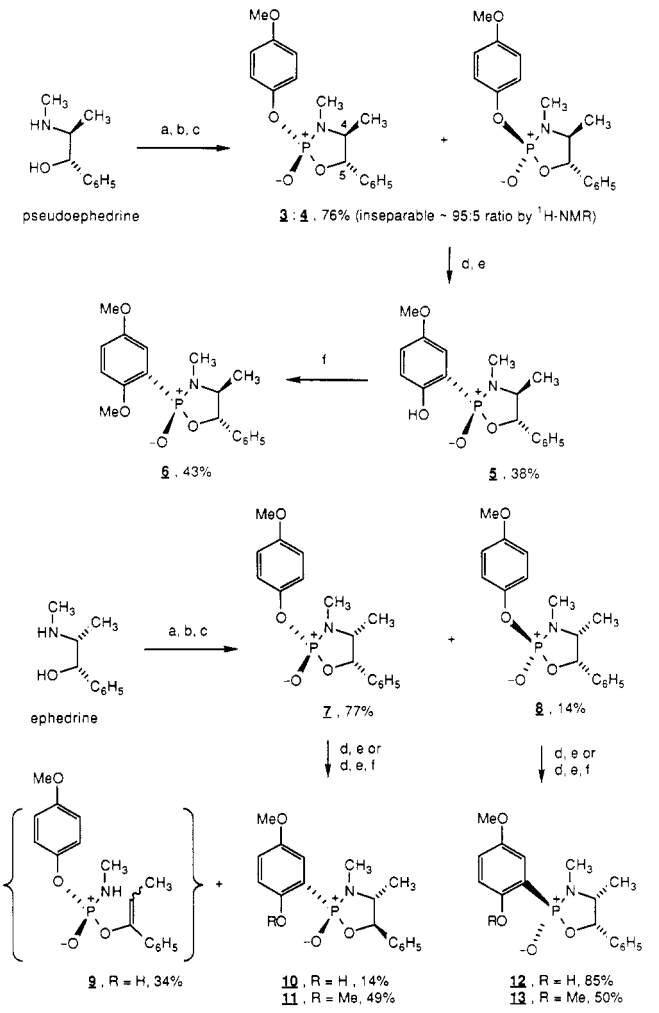
of 1,3,2-oxazaphospholidine 2-oxides in the pseudoephedrine/ephedrine series was examined. Stereochemical[4-6] and conformational[7] analyses of these 1,3,2-oxazaphospholane ring systems by NMR have been reported. The stereochemistry of phenoxy esters of 1,3,2-oxazaphospholidine 2-oxides in the pseudoephedrine/ephedrine series has been established by X-ray diffraction.[7]

Results and Discussion

Sequential treatment of pseudoephedrine with phosphorus oxychloride in benzene in the presence of triethylamine followed by 4-methoxyphenol and chromatography on silica gel gives an inseparable mixture of (aryloxy)phospholidines **3** and **4** (Scheme I) in 76% yield as a 95:5 ratio, respectively. These assignments are in agreement with the revised structures for the intermediate 2-chloro-1,3,2-oxazaphospholidin-2-ones[6,7] and the fact that these corresponding acid chlorides undergo subtitution with phenoxide anions with retention of configuration.[5] The relative stereochemistry of the isomers **3** and **4** is confirmed by comparison of the ^{1}H NMR chemical shifts of the C-5 methine protons as well as the C-4 methyl groups in Table I.[4] It has been reported that in phosphorus-containing heterocycles, C-5 protons which are in a 1,3-cis orientation to the P=O bond are deshielded relative to the respective 1,3-trans protons.[4,5] We have also observed this deshielding effect for a 1,3-cis orientation of the C-4 methyl group to the P=O bond relative to the respective 1,3-trans C-4 methyl group in the pseudoephedrine/ephedrine series (Table I).

Base-induced rearrangement (LDA/THF; NH_4Cl/H_2O)[1-3] of this 95:5 mixture of **3** and **4**, respectively, affords a single isolatable product **5** in 38% yield[8] (Scheme I).

Scheme I[a]



[a] (a) $POCl_3/Et_3N/C_6H_6$; (b) $4\text{-}MeOC_6H_4OH/Et_3N/C_6H_6$; (c) chromatography on silica gel; (d) LDA/THF/−78 °C; (e) NH_4Cl/H_2O; (f) NaH/MeI/THF/DMF.

Methylation of phenol **5** (NaH/MeI/THF/DMF)[9] produces arylphospholidine **6** in 43% yield. The structure of **5** (and **6**) is consistent with retention of configuration in the P–O to P–C rearrangement of **3** to **5** since no other stereoisomer was observed or isolated.[8] This assignment was made on the basis of comparison of the ^{1}H NMR chemical shifts and C-4/C-5 vicinal coupling constants of **5** and **6** with known phenylphospholidine **14** (Table I).[7] The four known diastereomeric phenylphospholidines **14–17** were prepared from the reaction of either pseudoephedrine or ephedrine with phenylphosphonic dichloride in benzene in the presence of triethylamine according to the procedures of Inch and co-workers[5] as well as Setzer and co-workers.[7] The structural assignments for phenylphospholidines **14** and **15** were confirmed by single-crystal X-ray structural analysis.[7]

Sequential treatment of ephedrine with phosphorus oxychloride in benzene in the presence of triethylamine followed by 4-methoxyphenol and chromatography on silica gel gives a separable mixture of (aryloxy)-phospholidines **7** and **8** (Scheme I) in 77% and 14% yields, respectively. Alternatively, according to the procedure of

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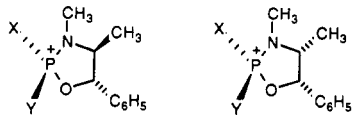
(5) Cooper, D. B.; Hall, C. R.; Harriman, J. M.; Inch, T. D. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1969.
(6) Devillers, J.; Navech, J. *Bull. Chim. Soc. Fr.* **1970**, 4341. The respective acid chlorides that form **3** and **4** are not separable either.
(7) Setzer, W. N.; Black, B. G.; Hovanes, B. A.; Hubbard, J. L. *J. Org. Chem.* **1989**, *54*, 1709. The data presented in Table I and the results contained within the present study (X-ray analysis of **15**) confirm the stereochemical assignments of **14** and **15** by Setzer and co-workers (structures **4** and **5** their paper).
(8) Presumably **5** is formed from **3**; however, since **3** and **4** could not be separated, the question of some of **5** forming from **4** cannot be completely ruled out.
(9) Stoochnoff, B. A.; Benoiton, N. L. *Tetrahedron Lett.* **1973**, 21.



14 X = C_6H_5, Y = O⁻ 16 X = C_6H_5, Y = O⁻

15 X = O⁻, Y = C_6H_5 17 X = O⁻, Y = C_6H_5

Inch and co-workers,[5] treatment of ephedrine with phosphorus oxychloride in benzene followed by chromatography on silica gel gives a separable mixture of 2-chloro-1,3,2-oxazaphospholidin-2-ones in 71% and 12% yields, respectively. The major isomer has the chlorine substituent cis to the C-4 methyl group and the minor isomer has the chlorine atom trans to the C-4 methyl group. Separate esterifications of these major and minor phoshoryl chlorides with 4-methoxyphenol in benzene in the presence of triethylamine gives (aryloxy)phospholidines **7** and **8** in 60% and 61% yields, respectively, with retention of configuration in each case. These results are in agreement with the stereochemical observations reported by Inch and co-workers with phenol.[5] The relative stereochemistry of isomers **7** and **8** is assigned on the basis of the deshielding the C-4 and C-5 methine protons in **7** vs **8** as well as the deshielding of the C-4 methyl group in **8** vs **7** as shown in Table I.[4,5]

Base-induced rearrangement (LDA/THF; NH_4Cl/H_2O)[1-3] of isomer **7** affords a very labile, nonrearranged, eliminative ring-open compound **9** in 34% yield and a single stable, isolatable product **10** in 14% yield (Scheme I). Presumably deprotonation of the C-5 benzylic proton of **7** is faster than P–O to P–C rearrangement to afford **10**. Stereochemical congestion with a *cis*-methyl group at C-4 and a *cis*-phenyl substituent at C-5 may account for the decreased rate of P–O to P–C rearrangement and the relatively large amount of elimination product produced from isomer **7**. Methylation of phenol **10** (NaH/MeI/THF/DMF)[9] produces arylphospholidine **11** in 49% yield. The structure of **9** is based solely upon ^1H NMR, ^{13}C NMR, and HRMS data. The presence of a vinylic proton at δ 5.82 (dq, $J_{H,Me}$ = 7 Hz and $J_{H,P}$ = 3 Hz), a NH*Me* group at δ 2.51 (dd, $J_{H,Me}$ = 6 Hz and $J_{H,P}$ = 13 Hz), and an allylic-*Me* group at δ 1.75 (dd, $J_{H,H}$ = 7 Hz, $J_{H,P}$ = 2 Hz, =CHC*H*$_3$) indicates compound **9** is a ring-opened eliminative structure. This conclusion is supported by appearance of two alkene carbons at 146 (OC=) and 111 ppm (=*C*HCH$_3$) in the ^{13}C NMR spectrum. Examination of the ^1H NMR spectra of products **10** and **11** shows an unexpected anomoly. Generally the ^1H NMR (aryloxy)-phospholidines and arylphospholidines in the ephedrine series display a C-4 methyl resonance of less than δ 1.0 and a C-4/C-5 vicinal proton coupling constant near 5–7 Hz (Table I). Products **10** and **11** clearly show C-4 methyl resonances of δ 1.31 and 1.21, respectively, with large vicinal coupling constants of 9 and 8 Hz, respectively. These data are consistent with a base-initiated (LDA/THF) epimerization of the C-5 proton to the pseudoephedrine series (Table I) followed by rearrangement with retention of configuration in the P–O to P–C bond-forming process to give **10**. These stereochemical assignments were made on the basis of comparison of the ^1H NMR chemical shifts and C-4/C-5 vicinal coupling constants of **10** and **11** with phenylphospholidine **15** (Table I).[5,7]

Finally, base-induced rearrangement (LDA/THF; NH_4Cl/H_2O)[1-3] of **8** smoothly affords a single isolatable product **12** in 85% yield (Scheme I). In this isomer the P–O to P–C rearrangement is stereochemically unencumbered by any methyl or phenyl substituent. This probably accounts for the relative ease of the rearrangement as well as the high yield for the reaction. Methylation of phenol **12** (NaH/MeI/THF/DMF)[9] produces arylphospholidine **13** in 50% yield. The structures of **12** and **13** are consistent with retention of configuration in the P–O to P–C rearrangement. The structures of **12** and **13** were assigned on the basis of comparison of the ^1H NMR chemical shifts and C-4/C-5 vicinal coupling constants with model phenylphospholidine **17** (Table I).[5,7]

Summary

On treatment with LDA/THF (aryloxy)phospholidines in the pseudoephedrine/ephedrine series undergo P–O to P–C rearrangement to afford arylphospholidines with retention of configuration at phosphorus. Interestingly enough the stereochemically least congested (*p*-$MeOC_6H_5O$ trans to both the C-4 methyl and C-5 phenyl) rearrangement, namely, **8** to **12**, proceeds smoothly in 85% yield; the intermediately congested (*p*-$MeOC_6H_5O$ trans to the C-4 methyl and cis to the C-5 phenyl) rearrangement **3** to **5** proceeds in a modest 38% yield; and most congested (*p*-$MeOC_6H_5O$ cis to both the C-4 methyl group and the C-5 phenyl group) rearrangement **7** to **10** goes slowly in a poor 14% yield with epimerization at C-5 together with a considerable amount of elimination to very labile **9** (34%). The stereochemistry of each product was assigned by ^1H NMR chemical shift and C-4/C-5 vicinal coupling constant analysis and comparison with known phenylphospholidines **14–17** (Table I).[5,7]

Experimental Section

Materials and Techniques. Melting points were determined on a Buchi melting point apparatus and are uncorrected. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. Microanalyses were performed by Spang Microanalytical Laboratory. Silica gel 60 (E. Merck No. 9385, 230–400 mesh) and Analtech silica gel GHLF (No. 21521) were used for medium-pressure (MPLC)[10] and thin-layer chromatography, respectively.

All solvents were purified by distillation of anhydrous commercial solvents under N_2 immediately before use in all reactions according to standard procedures.[11] For all anhydrous reactions performed under an atmosphere of dry N_2 the equipment was dried in an oven at 120 °C for several hours and then allowed to cool in an atmosphere of dry N_2. All liquid transfers were made with N_2 filled syringes. The standard workup procedure is to wash the organic layer with water and then saturated NaCl, dry over anhydrous Na_2SO_4, and remove the solvent in vacuo.

(2*S*,4*S*,5*S*)- and (2*R*,4*S*,5*S*)-3,4-Dimethyl-2-(4-methoxyphenoxy)-5-phenyl-1,3,2-oxazaphospholidine 2-Oxides (3 and 4).[5] To a solution of pseudoephedrine (5.01 g, 30.3 mmol) and freshly distilled Et_3N (12 mL, 15 g, 150 mmol) in dry benzene (100 mL) is added freshly distilled $POCl_3$ (2.8 mL, 4.6 g, 30 mmol). The mixture is stirred under a dry atmosphere at room temperature for 18 h, followed by the addition of 4-methoxyphenol (4.48 g, 36.1 mmol). Stirring is continued for another 24 h. The mixture is filtered to remove the Et_3N·HCl, and the solvent and excess Et_3N are removed in vacuo. The residue is taken up in benzene (ca. 50 mL) and chromatographed by MPLC. Elution with 25% EtOAc/hexanes to remove excess 4-methoxyphenol, followed with 50% EtOAc/hexanes, gives 7.64 g (76%) of **3** as a colorless syrup (single spot by analytical TLC). ^1H NMR analysis indicates that the product consists of **3** (95%), contaminated with a small amount (~5%) of **4**. Compound **3**: ^1H NMR ($CDCl_3$) δ 7.36–7.33 (m, 5, ArH), 7.24–6.84 (AA'BB', 4, ArH), 4.90 (dd, 1, $J_{H5,P}$ = 2 Hz, $J_{H4,H5}$ = 9 Hz, OCHAr), 3.77 (s, 3, OCH_3), 3.34 (dq, 1, $J_{H4,Me}$ = 6 Hz, $J_{H4,H5}$ = 9 Hz, C*H*CH$_3$), 2.77 (d, 3, $J_{H,P}$ = 11 Hz, NCH_3), 1.17 ppm (d, 3, $J_{H4,Me}$ = 6 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$) 156.5, 144.8, 136.2, 129.0, 128.4 (2), 126.9 (2), 121.2 (2),

(10) MPLC refers to medium-pressure liquid chromatography. See: Meyers, A. L.; Slade, J.; Smith, R. K.; Mihelich, E. D.; Hershenson, F. M.; Liang, C. D. *J. Org. Chem.* **1979**, *44*, 2247.

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114.5 (2) (Ar), 85.4 (OCHAr), 61.3 ($NCHCH_3$), 55.4 (OCH_3), 28.2 (NCH_3), 15.3 ppm ($CHCH_3$). Anal. Calcd for $C_{17}H_{20}NO_4P$: C, 61.26; H, 6.05; P, 9.29. Found: C, 61.16; H, 6.20; P, 9.25. Compound **4**: ^1H NMR ($CDCl_3$) only resonances resolved are δ 4.43 (dd, $J_{H5,P}$ = 2 Hz, $J_{H4,H5}$ = 9 Hz, OCHAr), 2.73 (d, $J_{H,P}$ = 10 Hz, NCH_3), 0.98 ppm (d, $J_{H4,Me}$ = 6 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$) the only resonances resolved are 126.3 (Ar), 85.0 (OCHAr), 16.1 ppm ($CHCH_3$).

(2*R*,4*S*,5*S*)-3,4-Dimethyl-2-(2-hydroxy-5-methoxyphenyl)-5-phenyl-1,3,2-oxazaphospholidine 2-Oxide (5). To a stirred solution of **3** (550 mg, 1.65 mmol) in dry THF (15 mL) at −78 °C under N_2 is added 1.5 M LDA·THF in cyclohexane (2.4 mL, 3.6 mmol, Aldrich) over a 10-min period. The mixture is allowed to come to room temperature, and is then quenched by addition of saturated NH_4Cl (10 mL). The product is extracted into EtOAc (50 mL + 25 mL), and the combined extracts are worked up in the standard way. The residue taken up in a small quantity of benzene and chromatographed by MPLC. Elution with 40% EtOAc/hexanes gives 208 mg (38%) of **5** as a colorless foam. Recrystallization from Et_2O/pentane gives a light solid **5**: mp 129–131 °C; ^1H NMR ($CDCl_3$) δ 10.41 (s, 1, OH), 7.4 (m, 5, ArH), 7.09 (dd, 1, J_{ortho} = 9 Hz, J_{meta} = 3 Hz, ArH), 6.96 (dd, 1, J_{ortho} = 9 Hz, $J_{H,P}$ = 7 Hz, ArH), 6.71 (dd, 1, J_{meta} = 3 Hz, $J_{H,P}$ = 18 Hz, ArH), 5.19 (d, 1, $J_{H4,H5}$ = 9 H, OCHAr), 3.74 (s, 3, OCH_3), 3.59 (dq, 1, $J_{H4,H5}$ = 9 Hz, $J_{H4,Me}$ = 6 Hz, $CHCH_3$), 2.58 (d, 3, $J_{H,P}$ = 11 Hz, NCH_3), 1.35 ppm (d, 3, $J_{H4,Me}$ = 6 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$) 157.6, 152.2, 136.4, 129.1, 128.7 (2), 126.3 (2), 122.2, 118.9, 113.9, 108.5 (d, $J_{C,P}$ = 165 Hz) (Ar), 85.3 (OCHAr), 63.7 ($NCHCH_3$), 55.8 (OCH_3), 28.0 (NCH_3), 15.7 ppm ($CHCH_3$). Anal. Calcd for $C_{17}H_{20}NO_4P$: C, 61.26; H, 6.05; P, 9.29. Found: C, 61.18; H, 6.19; P, 9.32.

(2*R*,4*S*,5*S*)-2-(2,5-Dimethoxyphenyl)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-Oxide (6). To a solution of **5** (277 mg, 0.83 mmol) in dry THF (2.5 mL) is added dry DMF (0.25 mL), iodomethane (0.41 mL, 0.93 g, 6.6 mmol), and then granular NaH (42 mg, 1.8 mmol), and the mixture is stirred at reflux under a dry atmosphere ($CaSO_4$ drying tube) for 1 h. The mixture is diluted with EtOAc (25 mL), and the excess NaH is destroyed by careful addition of water (25 mL), followed by saturated NH_4Cl (10 mL). The organic phase is separated, and the aqueous phase is extracted with additional EtOAc (25 mL). The combined organic extract is worked up in the standard way. Recrystallization from hexanes, in the presence of a small amount of CH_2Cl_2 (ca. 1 mL) gives 124 mg (43%) of **6** as colorless plates: mp 173–175 °C; ^1H NMR ($CDCl_3$) δ 7.69 (dd, 1, J_{meta} = 3 Hz, $J_{C,P}$ = 13 Hz, ArH), 7.4–7.3 (m, 5, ArH), 7.07 (dd, 1, J_{ortho} = 9 Hz, J_{meta} = 3 Hz, ArH), 6.89 (dd, 1, J_{meta} = 9 Hz, $J_{C,P}$ = 8 Hz, ArH), 5.16 (d, 1, $J_{H4,H5}$ = 9 Hz, OC*H*Ar), 3.83 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 3.58 (dq, 1, $J_{H4,H5}$ = 9 Hz, $J_{H4,Me}$ = 6 Hz, NC*H*Ar), 2.54 (d, 3, $J_{H,P}$ = 11 Hz, NCH_3), 1.29 (d, 3, $J_{H4,Me}$ = 6 Hz, $CHCH_3$); ^{13}C NMR 154.9, 153.4, 137.6, 128.5, 128.3 (2), 126.7 (2), 121.9, 121.0, 116.3 (d, $J_{C,P}$ = 170 Hz), 111.6 (Ar), 85.7 (OCHAr), 62.6 ($NCHCH_3$), 55.9 (OCH_3), 55.4 (OCH_3), 27.9 (NCH_3), 15.5 ppm ($CH4CH_3$). Anal. Calcd for $C_{18}H_{22}NO_4P$: C, 62.24; H, 6.38; P, 8.92. Found: C, 62.04; H, 6.45; P, 8.87.

(2*S*,4*R*,5*S*)-3,4-Dimethyl-2-(4-methoxyphenoxy)-5-phenyl-1,3,2-oxazaphospholidine 2-Oxide (7) and (2*R*,4*R*,5*S*)-3,4-Dimethyl-2-(4-methoxyphenoxy)-5-phenyl-1,3,2-oxazaphospholidine 2-Oxide (8).[5] These compounds were prepared from ephedrine·$^1/_2H_2O$ (5.25 g, 30.1 mmol, dried by azeotropic distillation of benzene) by a procedure similar to that used in the preparation of **3** and **4**. The less polar **8** is obtained as a white crystalline solid (1.36 g, 13.6%, R_f 0.58, EtOAc). The more polar **7** is obtained as a syrup (5.62 g, 56.2%, R_f 0.33, EtOAc). An additional 2.07 g (20.7%) of the more polar diastereomer **7** contains a minor impurity (R_f 0.48, UV active, EtOAC). Compound **8** was recrystallized from hexanes: mp 100–101 °C; ^1H NMR ($CDCl_3$) δ 7.40–7.31 (m, 5, ArH), 7.16–6.84 (AA'BB', 4, ArH), 5.31 (dd, 1, $J_{H4,H5}$ = 6 Hz, $J_{H5,P}$ = 4 Hz, OCHAr), 3.79 (s, 3, OCH_3), 3.57 [ddq (7 lines), 1, $J_{H4,H5}$ = $J_{H4,Me}$ = 6 Hz, $J_{H4,P}$ = 12 Hz, $CHCH_3$], 2.79 (d, 3, $J_{H,P}$ = 10 Hz, NCH_3), 0.79 ppm (d, 3, $J_{H4,Me}$ = 7 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$) 156.6, 144.5, 135.4, 128.3 (3), 125.9 (2), 121.4 (2), 114.6 (2) (Ar), 81.1 (OCHAr), 58.8 ($NCHCH_3$), 55.5 (OCH_3), 28.6 (NCH_3), 14.1 ppm ($CHCH_3$). Anal. Calcd for $C_{17}H_{20}NO_4P$: C, 61.26; H, 6.05; P, 9.29. Found: C, 61.26; H, 6.19; P, 9.20.

Compound **7**: ^1H NMR ($CDCl_3$) δ 7.50–7.18 (m, 5, ArH), 7.15–6.86 (AA'BB', 4, ArH), 5.74 (d, 1, $J_{H4,H5}$ = 6 Hz, OCHAr), 3.89–3.62 (ddq, 1, $J_{H4,H5}$ = $J_{H4,Me}$ = 6 Hz, $J_{H4,P}$ = 17 Hz, $CHCH_3$), 3.78 (s, 3, OCH_3), 2.84 (d, 3, J = 10 Hz, NCH_3), 0.61 ppm (d, 3, J = 6 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$) 156.5, 144.6, 135.4, 128.2 (2), 128.0, 125.4 (2), 121.5 (2), 114.4 (2) (Ar), 80.7 (OCHAr), 59.8 ($NCHCH_3$), 55.4 (OCH_3), 29.3 (NCH_3), 13.2 ppm ($CHCH_3$). Anal. Calcd for $C_{17}H_{20}NO_4P$: C, 61.26; H, 6.05; P, 9.29. Found: C, 61.16; H, 6.00; P, 9.35.

(2*R*,4*R*,5*R*)-3,4-Dimethyl-2-(2-hydroxy-5-methoxyphenyl)-1,3,2-oxazaphospholidine 2-Oxide (10) and (*S*)-4-Methoxyphenyl 1-Phenyl-1-propenyl *N*-Methylphosphoramidate (9). A solution of **7** (794 mg, 2.36 mmol) in dry THF (15 mL) is cooled to −78 °C under N_2. While stirring, 1.5 M LDA·THF in cyclohexane (3.5 mL, 5.2 mmol, Aldrich) is added via syringe over a 30-min period. The mixture is allowed to warm to room temperature, saturated NH_4Cl (10 mL) is added, and the mixture is partitioned between water (25 ML) and EtOAc (50 mL). The organic extract is worked up in the standard way. Chromatography (MPLC, 25% EtOAc/hexanes) gives 110 mg (14%) of **10** as a white solid (R_f 0.10, 25% EtOAc/hexanes) and 273 mg (34%) of elimination, ring-opened product **9** as a yellow oil. Compound **10**: mp 158–160 °C; ^1H NMR ($CDCl_3$) δ 10.33 (s, 1, OH), 7.5–7.4 (m, 5, ArH), 7.07 (dd, 1, J_{ortho} = 9 Hz, J_{meta} = 3 Hz, ArH), 6.93 (dd, 1, J_{ortho} = $J_{H,P}$ = 9 Hz, ArH), 6.88 (dd, 1, J_{meta} = 3 Hz, $J_{H,P}$ = 17 Hz, ArH), 4.96 (dd, 1, $J_{H,P}$ = 3 Hz, $J_{H4,H5}$ = 9 Hz, OCHAr), 3.80 (s, 3, OCH_3), 3.54 (dq, 1, $J_{H4,H5}$ = 9 Hz, $J_{H4,Me}$ = 6 Hz, $NCHCH_3$), 2.64 (d, 3, $J_{H,P}$ = 11 Hz, NCH_3), 0.93 ppm (d, 3, $J_{H,H}$ = 6 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$) 157.6, 152.2, 136.8, 129.0, 128.7 (2), 126.6 (2), 121.9, 118.6, 115.7, 109.2 (d, $J_{C,P}$ = 170 Hz) (Ar), 87.7 (OCHAr), 61.5 ($NCHCH_3$), 55.9 (OCH_3), 28.2 (NCH_3), 16.4 ppm ($CHCH_3$). Anal. Calcd for $C_{17}H_{20}NO_3P$: C, 61.26; H, 6.05; P, 9.29. Found: C, 61.38; H, 6.18; P, 9.26. Compound **9**: ^1H NMR ($CDCl_3$) δ 7.5–7.3 (m, 5, ArH), 7.13–6.80 (AA'BB', 4, ArH), 5.82 (dq, 1, $J_{H,H}$ = 7 Hz, $J_{H,P}$ = 3 Hz, $=CHCH_3$), 3.71 (s, 3, OCH_3), 2.51 ppm (dd, 3, $J_{H,H}$ = 6 Hz, $J_{H,P}$ = 13 Hz, $NHCH_3$; on treatment with D_2O, collapses to a doublet $J_{H,P}$ = 13 Hz), 1.75 (dd, 3, $J_{H,H}$ = 7 Hz, $J_{H,P}$ = 2 Hz, $=CHCH_3$), N*H* shift varies with concentration (br m, usually between 4 and 2.5 ppm) and disappears on treatment with D_2O; ^{13}C NMR ($CDCl_3$) 156.3 (Ar), 146.0 (OC=), 144.4, 128.4 (3), 128.2 (2), 127.8, 120.9 (2), 114.7 (2) (Ar), 111.3 ($=CCH_3$), 55.4 (OCH_3), 27.5 (NCH_3), 12.9 ppm ($=CCH_3$). The material was very labile and could not be purified for combustion analysis: HRMS (EI, 70 eV) m/z M^+, calcd for $C_{17}H_{20}NO_4P$ 333.1130, found 333.1125.

(2*R*,4*R*,5*R*)-2-(2,5-Dimethoxyphenyl)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-Oxide (11). To a solution of **10** (134 mg, 0.40 mmol) in dry THF (1 mL) is added dry DMF (0.1 mL), iodomethane (0.13 mL, 0.30 g, 2.1 mmol), and then granular NaH (14 mg, 0.58 mmol), and the mixture is stirred at reflux under a dry atmosphere ($CaSO_4$ drying tube) for 1 h. The mixture is diluted with EtOAc (25 mL), and the excess NaH is destroyed by careful addition of water (25 mL), followed by saturated NH_4Cl (10 mL). The organic phase is separated and worked up in the standard way. Recrystallization from hexanes, in the presence of a small amount of CH_2Cl_2, gives 68 mg (49%) of **11** as a pale yellow crystalline solid: mp 143–144 °C; ^1H NMR ($CDCl_3$) δ 7.5–7.3 (m, 6, ArH), 7.02 (dd, 1, J_{ortho} = 9 Hz, J_{meta} = 3 Hz, ArH), 6.87 (dd, 1, J_{ortho} = $J_{H,P}$ = 9 Hz, ArH), 4.99 (dd, 1, $J_{H4,H5}$ = 8 Hz, $J_{H,P}$ = ca. 0.5 Hz, OC*H*Ar), 3.90 (s, 3, OCH_3), 3.81 (s, 3, OCH_3), 3.42 (dd, 1, $J_{H4,H5}$ = 8 Hz, $J_{H,Me}$ = 6 Hz, $NCHCH_3$), 2.70 (d, 3, $J_{H,P}$ = 11 Hz, NCH_3), 1.21 (d, 3, J = 6 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$) 155.1, 153.4, 137.8, 128.7, 128.5 (2), 126.7 (2), 119.7, 119.5, ~119 (d), 112.5 (Ar), 85.9 (OCHr), 62.9 ($NCHCH_3$), 56.1 (OCH_3), 55.9 (OCH_3), 29.6 (NCH_3), 16.4 ppm ($CHCH_3$). Anal. Calcd for $C_{18}H_{22}NO_4P$: C, 62.24; H, 6.38; P, 8.92. Found: C, 61.96; H, 6.46; P, 8.87.

(2*S*,4*R*,5*S*)-3,4-Dimethyl-2-(2-hydroxy-5-methoxyphenyl)-1,3,2-oxazaphospholidine 2-Oxide (12). To a stirred solution of 1.5 M LDA·THF in cyclohexane (1.7 mL, 2.6 mmol, Aldrich) and dry THF (10 L) at −78 °C is added a solution of **8** (387 mg, 1.16 mmol) in dry THF (5 mL) over a 5-min period. The mixture is allowed to come to room temperature and then quenched by addition of saturated NH_4Cl (10 mL). The product is extracted into EtOAc (50 mL + 25 mL), and the combined extracts are worked up in the standard way. The residue is

chromatographed by MPLC (25% EtOAc/hexanes) to give 329 mg (85%) of **12** as a light solid, which is recrystallized from Et_2O/pentane: mp 98–100 °C; ^1H NMR ($CDCl_3$) δ 10.36 (1, s, OH), 7.5–7.2 (m, 5, ArH), 7.07 (dd, 1, J_{ortho} = 9 Hz, J_{meta} = 3 Hz, ArH), 6.95 (dd, 1, J_{ortho} = 9 Hz, $J_{H,P}$ = 9 Hz, ArH), 6.86 (dd, 1, J_{meta} = 3 Hz, $J_{H,P}$ = 17 Hz, ArH), 5.71 (dd, 1, $J_{H4,H5}$ = $J_{H5,P}$ = 5 Hz, OCHAr), 3.9–3.8 (m, 1, NC*H*CH_3), 3.79 (s, 3, OCH_3), 2.65 (d, 3, $J_{H,P}$ = 10 Hz, NCH_3), 0.93 ppm (d, 3, $J_{H4,Me}$ = 6 Hz, CHC*H*$_3$); ^{13}C NMR 157.6, 152.2, 135.7, 128.5 (2), 128.4, 126.1 (2), 121.7, 118.8, 115.3, 109.2 (d, $J_{C,P}$ = 170 Hz) (Ar), 83.5 (OCHAr), 59.4 (NCH-CH_3), 56.0 (OCH_3), 28.5 (NCH_3), 14.8 ppm ($CHCH_3$). Anal. Calcd for $C_{17}H_{20}NO_4P$: C, 61.26; H, 6.05; P, 9.29. Found: C, 61.19; H, 6.14; P, 9.27.

(2*S*,4*R*,5*S*)-2-(2,5-Dimethoxyphenyl)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-Oxide (13). To a solution of **12** (106 mg, 0.32 mmol) in dry THF (1.0 mL) is added dry DMF (0.10 mL), iodomethane (0.10 mL, 0.23 g, 1.6 mmol), and then granular NaH (15 mg, 0.62 mmol), and the mixture is stirred at reflux under a dry atmosphere ($CaSO_4$ drying tube) for 1 h. The mixture is diluted with EtOAc (25 mL), and the excess NaH is destroyed by careful addition of water (10 mL), followed by saturated NH_4Cl (10 mL). The organic phase is worked up in the standard way to give 77 mg (70%) of a light crystalline solid **13**, which is recrystallized from CH_2Cl_2/hexanes to give 55 mg (50%) of **13**: mp 133–135 °C; ^1H NMR ($CDCl_3$) δ 7.56 (dd, 1, J_{meta} = 3 Hz, $J_{C,P}$ = 16 Hz, ArH), 7.5–7.3 (m, 5, ArH), 7.02 (dd, 1, J_{meta} = 3 Hz, J_{ortho} = 9 Hz, ArH), 6.88 (dd, 1, J_{ortho} = $J_{C,P}$ = 9 Hz, ArH), 5.63 (dd, 1, $J_{H4,H5}$ = $J_{H5,P}$ = 7 Hz, OC*H*Ar), 3.87 (s, 3, OCH_3), 3.8 (m, 1, NC*H*CH_3), 3.79 (s, 3, OCH_3), 2.59 (d, 3, $J_{H,P}$ = 10 Hz, NCH_3), 0.82 (d, 3, $J_{H4,Me}$ = 7 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$) 155.1, 153.4, 137.1, 128.2 (2), 128.0, 126.7 (2), 120.7, 119.9, ca. 116.0 (d), 112.4 (Ar), 82.4 (OCHAr), 68.6 (NCHCH$_3$), 56.3 (OCH_3), 55.9 (OCH_3), 28.6 (NCH_3), 15.4 ppm ($CHCH_3$). Anal. Calcd for $C_{18}H_{22}NO_4P$: C, 62.24; H, 6.38; P, 8.92. Found: C, 62.09; H, 6.48; P, 8.85.

(2*S*,4*S*,5*S*)- and (2*R*,4*S*,5*S*)-3,4-Dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidine 2-Oxide (14 and 15).[5,7] These compounds were prepared according to the procedure of Inch and co-workers. From pseudoephedrine (5.02 g, 30.4 mmol) was obtained 2.73 g (31%) of **15** as a white solid, 2.70 g (31%) of **14** as a yellow syrup, and 1.65 g (19%) of a mixture of both isomers.

Compound **15**: mp 150–153 °C (from EtOAc/hexane) [lit.[7] 124.6 °C (from EtOAc/EtOH)]; ^1H NMR ($CDCl_3$) δ 7.94–7.87 (m, 2, ArH), 7.57–7.36 (m, 8, ArH), 4.88 (dd, 1, $J_{H4,H5}$ = 8 Hz, $J_{H,P}$ = 1 Hz, OCHAr), 3.50 (dq, 1, $J_{H4,H5}$ = 8 Hz, $J_{H4,Me}$ = 7 Hz, C*H*CH_3), 2.66 (d, 3, $J_{H,P}$ = 11 Hz, NCH_3), 1.28 ppm (d, 3, $J_{H4,Me}$ = 7 Hz, CHC*H*$_3$). Anal. Calcd for $C_{16}H_{18}NO_2P$: C, 66.89; H, 6.32; P, 10.78. Found: C, 66.95; H, 6.28; P, 10.67.

Compound **14**: ^1H NMR ($CDCl_3$) δ 7.88–7.82 (m, 2, ArH), 7.59–7.40 (m, 8, ArH), 5.17 (d, 1, $J_{H4,H5}$ = 9 Hz, OCHAr), 3.56 (dq, 1, $J_{H4,H5}$ = 9 Hz, $J_{H4,Me}$ = 6 Hz, C*H*CH_3), 2.55 (d, 3, $J_{H,P}$ = 10 Hz, NCH_3), 1.31 ppm (d, 3, $J_{H4,Me}$ = 7 Hz, CHC*H*$_3$). Anal. Calcd for $C_{16}H_{18}NO_2P$: C, 66.89; H, 6.32; P, 10.78. Found: C, 66.95; H, 6.28; P, 10.82.

Acknowledgment. We thank the National Institutes of Health (Grant No. CA-43344) and the Robert A. Welch Foundation (Grant Nos. E-518 & E-594 to I.B.) for financial support and the National Science Foundation (Grant No. CHE-8616352) for the funds to purchase a General Electric QE-300 NMR spectrometer and for the funds to purchase the X-ray diffractometer.

Supplementary Material Available: X-ray structural data (final atomic parameters) and an ORTEP stereodrawing for **15** as well as ^{13}C NMR spectra of **3**:**4** and **9** (12 pages). Ordering information is given on any current masthead page.

A Novel Ring Expansion Observed during the Lithium Aluminum Hydride Reduction of 13-Nitrooxyberberine

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Received April 6, 1990

An unusual ring expansion was observed in the course of studies on the synthesis of berberine linked to oligonucleotides at the 13-position. Nitration of oxyberberine (**1**) gave 13-nitrooxyberberine (**2**) as the major product. Lithium aluminum hydride reduction of **2** gave ring-expansion product **4** in addition to the expected primary amine **5**. The structure of **4**, a novel B/C-cis fused ring system, was solved by X-ray crystallography.

The placement of an amino group at the 13-position of a protoberberine would provide a useful functional group for the covalent attachment of oligonucleotides through linker chains. During the investigation of a synthesis of *cis*-13-aminotetrahydroberberine (**5**) by lithium aluminum hydride reduction of intermediate **2** (Scheme I), an unusual ring expansion reaction was observed which resulted in the formation of compound **4**. The present paper details the synthetic route leading to substance **4**, provides evidence in support of the assigned structure, and attempts to shed some insight into the mechanism of the transformation leading to this novel ring system. A conformational analysis of **4** is also presented.

Oxyberberine (**1**), prepared from berberine chloride by a combination of established methods,[1,2] was readily nitrated with aqueous nitric acid to give **2** and **3** in 91.3 and 0.8% yields, respectively. The structure of the expected major product **2** was readily confirmed by spectral data, while the structure of the minor dinitro product **3** was less obvious. The ^1H NMR spectrum of **2** contained an AB quartet at δ 7.39 and 7.26 (J = 9.2 Hz) corresponding to the D ring protons and singlets at δ 7.00 and 6.77 corresponding to the A ring protons. The spectrum of **3** contained singlets at δ 7.90, 6.79, and 6.78. The absence of ortho coupling in **3** demonstrated that the second nitro group must be at position 11 or 12. Comparison of the carbon spectra of **2** and **3** provided no additional insight

† This paper is dedicated to Dr. Pennamuthiriar Chinnasamy, who performed the initial studies leading to the publication. He passed away unexpectedly on September 2, 1987.

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