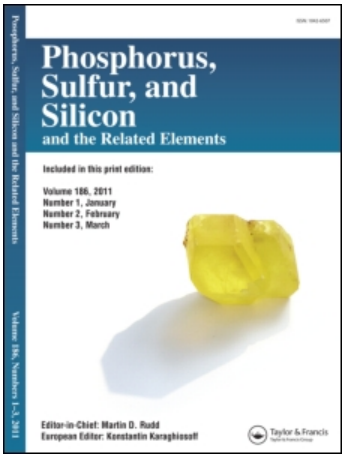

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"CARBATHIA" ANALOGUES OF PLATELET ACTIVATING FACTOR (PAF)

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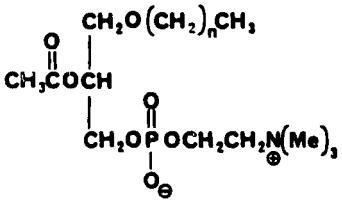
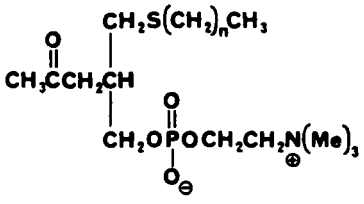
Sulfur analogues of "2-carba" PAF, **1a** and **1b**, were prepared by an 8-step synthesis using commercially available ethyl levulinate as a starting material.

INTRODUCTION

The report of the structure and biological activities of platelet activating factor (PAF)[2] or antihypertensive polar renomedullary lipid (APRL)[3] has prompted active research programs from these[4] and other laboratories[5,6]. The incorporation of an acetyl isostere which is not subject to enzymatic hydrolysis might presumably have a longer duration of action. Reports[5,6] of similar approaches to develop the structure activity relationships for PAF prompt us to report our results for the preparation of the sulfur analogues of the "2-carba" isostere of PAF.



PAF: n = 15 or 17



1a: n=15 1b: n=17

CHEMICAL SYNTHESIS

Our synthesis of the racemic target C_{16} and C_{18} compounds **1a** and **1b** utilized commercially available ethyl levulinate as the carbon backbone (Scheme 1). Ketalization with ethylene glycol led to **2** which was formylated to give **3** using sodium hydride and ethylformate in ether. Conversion of **3** to **4** was easily effected in yields of 70–75% using the procedure of Ireland[7] but, despite numerous attempts, **4** could

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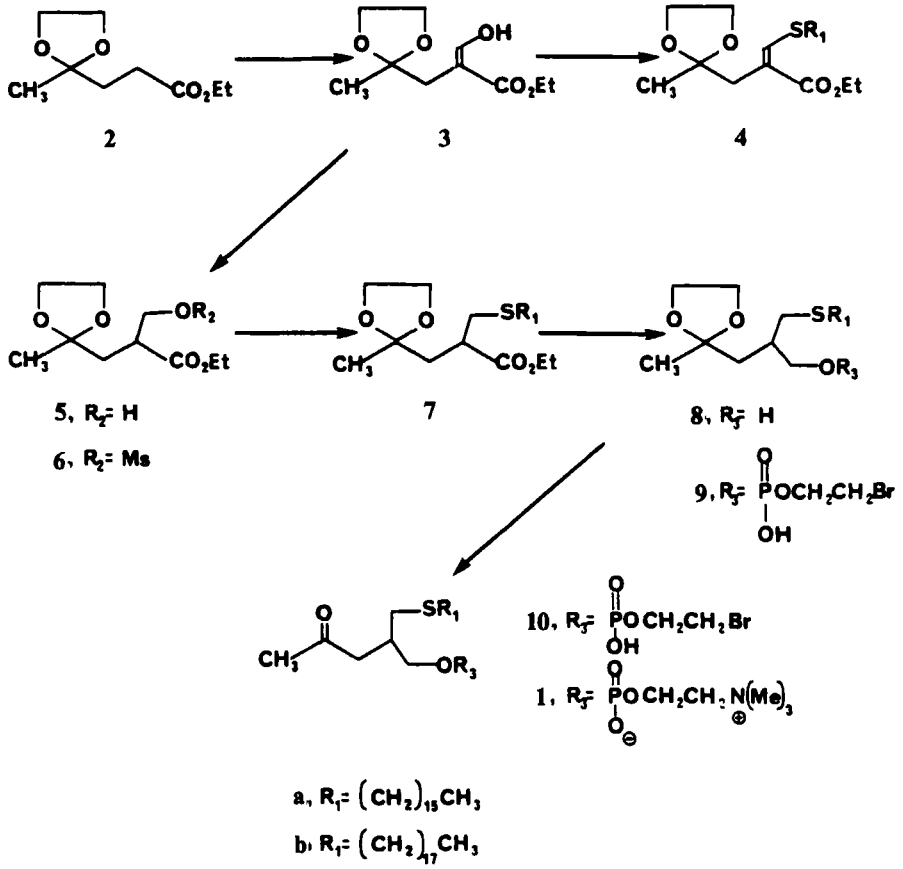
not be reduced to the desired saturated sulfide derivative **7** by either catalytic reduction or by the use of metal hydrides.[8] Frustrated by the surprising unreactivity of **4**, we further derivatized formyl ester **3** by reduction with sodium borohydride to alcohol **5**. Subsequent conversion of **5** to mesylate **6** with methanesulfonyl chloride and triethylamine and displacement by hexadecyl mercaptan in the presence of excess sodium hydride gave sulfide ester **7a** as a waxy solid.

This ester was cleanly reduced with diisobutylaluminum hydride to alcohol **8a** which was reacted with triethylamine and bromoethylphosphorochloride in carbon tetrachloride to give the ketal phosphate **9a**. Interestingly, use of chloro-2-oxo-1,3,2-dioxaphospholane[5] gave none of the desired analogous cyclic phosphate intermediate. Compound **9a** was converted without isolation to ketone **10a** by rapid hydrolysis using 3N hydrochloric acid in acetone. Preparation of the target compound **1a** from **10a** was accomplished by treatment with trimethylamine in acetonitrile. In a similar manner, mesylate **6** was reacted with octadecyl mercaptan to give **7b** which was reduced to **8b**. Phosphorylation to **9b** and subsequent hydrolysis gave **10b**. Reaction of **10b** with trimethylamine produced **1b**. The target compounds **1a** and **1b** were isolated as colorless glasses.



SCHEME 1

While this procedure is only described for the incorporation of sulfur into PAF analogues, clearly other nucleophiles could be used in this sequence.[9] These title compounds were prepared to investigate the effects of structural variation upon the biological effects of PAF. Using the methods in our laboratories described previously,[4] cardiovascular and platelet activities were evaluated. Derivative **1a** had only slight activity in platelets and in lowering blood pressure while **1b** was practically devoid of activity. These results are comparable to those recently reported for the "bioisosteric O-carba-analogue" of PAF.[6]

EXPERIMENTAL

Melting point determinations were made on a Mel-Temp capillary melting point apparatus and are uncorrected. NMR spectra were determined on a Varian Associates FT-80 spectrometer in deuterochloroform and chemical shifts are reported with TMS as an internal standard. Mass spectral determinations were made on a Finnegan MAT Model CH/spectrometer while field desorption (FD) and fast atom bombardment (FAB) mass spectra were determined on a Kratos MS 50 spectrometer.

2-Methyl-1,3-Dioxolane-2-Propanoic Acid Ethyl Ester (**2**). Ethyl levulinate (200 g, 1.4 mol), ethylene glycol (100 ml) and a catalytic amount of *p*-toluenesulfonic acid were heated to reflux in toluene (1 L) using a Dean-Stark apparatus. Additional amounts (20 ml) of ethylene glycol were added after the first and second hours of heating which was continued for a total of 5 h. The mixture was cooled to room temperature, washed with saturated aqueous sodium bicarbonate (2 × 250 ml) and water (100 ml), dried over magnesium sulfate, concentrated and the residue was distilled to give **2** as a colorless liquid, 197.3 g (81%), bp 110°C (10 mmHg). Mass spectrum m/z 188 (M^+); ^{1}H NMR: δ 4.10 (q, 2 H, C$\underline{H}_2$O), 3.90 (s, 4 H, OC$\underline{H}_2$C$\underline{H}_2$O), 2.32 (m, 2 H, C$\underline{H}_2$CO), 2.02 (m, 2 H, C$\underline{H}_2$CH$_2$CO), 1.68 (s, 3 H, C$\underline{H}_3$), 1.72 (t, 3 H, C$\underline{H}_3$).

α-(Hydroxymethylene)-2-Methyl-1,3-Dioxolane-2-Propanoic Acid Ethyl Ester (**3**). Ketal **2** (80 g, 0.426 mol) and sodium hydride (62 g of 50% suspension prewashed with petroleum ether, 1.29 mol) were diluted with anhydrous ether (100 ml) and ethyl formate (70 ml, 0.87 mol) and ethanol (0.5 ml) were added over a period of 10 min with vigorous stirring. Low heat (ca. 35°C) was applied until vigorous hydrogen evolution began. After 0.5 h, additional anhydrous ether (400 ml) was added. After an additional 0.5 h, ethyl formate (20 ml) in anhydrous ether (300 ml) was added and the mixture was stirred overnight. The yellow solid was collected by filtration and carefully treated with acetic acid (100 ml) and ice (300 ml) using an ice-salt bath for cooling (T < 10°C). The aqueous mixture was extracted with chloroform (5 × 300 ml) and the organic layers were washed with saturated aqueous sodium bicarbonate (3 × 150 ml), dried over magnesium sulfate, concentrated and the residue was distilled to give **3** as a yellow liquid, 74.5 g (81%), bp 88°C (0.05 mmHg). Mass spectrum m/z 216 (M^+); ^{1}H NMR: δ 11.77 (d, 1 H, O$\underline{H}$), 7.10 (d, 1 H, C$\underline{H}$=), 4.25 (q, 2 H, C$\underline{H}_2$O), 3.98 (s, 4 H, OC$\underline{H}_2$C$\underline{H}_2$O), 2.48 (s, 2 H, C$\underline{H}_2$), 1.80 (m, 6 H, C$\underline{H}_3$). Anal. calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.56; H, 7.35.

α-[(Hexadecylthio)Methylene]-2-Methyl-1,3-Dioxolane-2-Propanoic Acid Ethyl Ester (**4a**). Formyl ester **3** (21.6 g, 0.1 mol) was dissolved in pyridine (75 ml) and methanesulfonylchloride (7.74 ml, 0.1 mol) was added. The mixture was stirred for 2 h. Hexadecylthiol (26 g, 0.1 mol) was added and the mixture was heated to 90°C for 4 d. The solvent was removed by evaporation and the residue was dissolved in chloroform (500 ml) and extracted with water and cold 25% aqueous potassium hydroxide (3 × 25 ml) and the organic layer was dried over magnesium sulfate. Concentration and subsequent dissolution of the residue in petroleum ether and elution through magnesium silicate gave a pale yellow solution which gave **4a** as an oil upon evaporation; the oil slowly crystallized, 34.5 g (75%), mp 25–27°C. Mass spectrum m/z 456 (M^+); ^{1}H NMR: δ 7.70 (s, 1 H, C$\underline{H}$=), 4.25 (q, 2 H, C$\underline{H}_2$O), 3.98 (s, 4 H, OC$\underline{H}_2$C$\underline{H}_2$O), 2.75 (t, 4 H, C$\underline{H}_2$C=, C$\underline{H}_2$S), 1.30 (m, 37 H, aliphatic $\underline{H}$). Anal. calcd for $C_{26}H_{48}O_4S$: C, 68.37; H, 10.59; S, 7.02. Found: C, 68.57; H, 10.52; S, 7.24.

α-[(Octadecylthio)Methylene]-2-Methyl-1,3-Dioxolane-2-Propanoic Acid Ethyl Ester (**4b**). Formyl ester **3** (21.6 g, 0.1 mol) was treated with methanesulfonyl chloride and then octadecylthiol in a manner similar to that described above to give **4b** as an oil, 37.3 g (77%). Mass spectrum m/z 484 (M^+); ^{1}H NMR: δ 7.65 (s, 1 H, C$\underline{H}$=), 4.25 (q, 2 H, C$\underline{H}_2$O), 3.99 (s, 4 H, OC$\underline{H}_2$C$\underline{H}_2$O), 2.78 (m, 4 H, C$\underline{H}_2$C=, C$\underline{H}_2$S), 1.40 (m, 41 H, aliphatic $\underline{H}$). Anal. calcd for $C_{28}H_{52}O_4S$: C, 69.37; H, 10.81; S, 6.61. Found: C, 69.61; H, 10.53; S, 6.74.

α-(Hydroxymethyl)-2-Methyl-1,3-Dioxolane-2-Propanoic Acid Ethyl Ester (**5**).. Formyl ester **3** (50.0 g, 0.232 mol) in ethanol (500 ml) was treated with sodium borohydride (7 g, 0.185 mol) portionwise over a 1 h period. The mixture was concentrated after 2 h and the residue was dissolved in water (50 ml) and extracted with methylene chloride (2 × 50 ml). The organic layers were dried over magnesium sulfate and evaporated to give a liquid, 44.3 g (88%) which was used without further purification. An analytical sample was prepared by evaporative distillation using a Kugelrohr apparatus. Mass spectrum m/z 218 (M^+); ^{1}H NMR: δ 4.19 (q, 2 H, C$\underline{H}_2$O), 3.98 (s, 4 H, OC$\underline{H}_2$C$\underline{H}_2$O), 3.78 (t, 2 H, C$\underline{H}_2$OH), 2.4 (m, 3 H, C$\underline{H}_2$, C$\underline{H}$), 1.25 (m, 6 H, C$\underline{H}_3$). Anal. calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.16; H, 8.06.

α-(Mesyloxymethyl)-2-Methyl-1,3-Dioxolane-2-Propanoic Acid Ethyl Ester (**6**).. Alcohol **5** (34.7 g, 0.16 mol) was dissolved in methylene chloride (800 ml) and triethylamine (35 ml) was added; the mixture was cooled in an ice bath and methanesulfonyl chloride (14 ml, 0.18 mol) was added dropwise over 15 min. The mixture was stirred at room temperature for 1.5 h and extracted with ice water (125 ml), cold 6N hydrochloric acid (125 ml) and saturated aqueous sodium bicarbonate (125 ml). The organic layer was dried over magnesium sulfate and concentrated to give **6** as a green oil, 47 g (97%) which was used without additional purification.

2-Methyl-α-[(Octadecylthio)Methyl]-1,3-Dioxolane-2-Propanoic Acid Ethyl Ester (**7b**). Mesylate **6** (8.5 g, 0.029 mol) and octadecylthiol (8.6 g, 0.030 mol) were combined in dry tetrahydrofuran (20 ml) and the mixture was cooled to 0°C under an argon atmosphere. Sodium hydride (1.5 g of a 50% suspension prewashed with petroleum ether, 0.032 mol) was added and the mixture was stirred for 18 h. Water (50 ml) was added and the mixture was extracted with methylene chloride (2 × 100 ml). The combined organic layers were dried over magnesium sulfate, evaporated and the residue was dissolved in hexanes and eluted through magnesium silicate. The eluate was concentrated and purified on silica gel (250 g) using hexanes (1 L), 10% ether in hexanes (2 L) and 20% ether in hexanes (2 L). Pure **7b** was isolated from the latter fractions by concentration and distillation using a Kugelrohr apparatus, 7.0 g (50%). Mass spectrum m/z 486 (M^+); ^{1}H NMR: δ 4.20 (q, 2 H, C$\underline{H}_2$O), 3.98 (s, 4 H, OC$\underline{H}_2$C$\underline{H}_2$O), 2.48 (m, 4 H, C$\underline{H}_2$S), 1.35 (m, 44 H, aliphatic $\underline{H}$). Anal. calcd for $C_{28}H_{54}O_4S$: C, 69.08; H, 11.18; S, 6.59. Found: C, 69.68; H, 11.14; S, 6.54.

2-Methyl-α-[(Octadecylthio)Methyl]-1,3-Dioxolane-2-Propanol (**8b**). Ester **7b** (8.9 g, 0.018 mol) dissolved in dry tetrahydrofuran (40 ml) was treated with diisobutylaluminum hydride (40 ml, 1.5M in toluene, 0.06 mol) dropwise over a 20 min period with temperature maintained at 0–5°C. The mixture was stirred at room temperature for 18 h. The mixture was cooled to 0°C, quenched with methanol (100 ml) and the solid that formed after 1 h was collected by filtration. The solid was washed with methanol (100 ml) and methylene chloride (100 ml) and the filtrates were concentrated to a wax (8.2 g). The wax was purified on a silica gel column (400 g) using 50% ether in hexanes to give **8b** as a wax, 3.9 g (54%). Mass spectrum m/z 416 (M^+); ^{1}H NMR: δ 5.11 (brd, 1 H, O$\underline{H}$), 4.00 (m, 6 H, C$\underline{H}_2$O), 2.5 (m, 4 H, C$\underline{H}_2$S), 1.35 (m, 41 H, aliphatic $\underline{H}$). Anal. calcd for $C_{26}H_{52}O_3S$: C, 70.21; H, 11.78. Found: C, 69.88; H, 11.69.

Phosphoric Acid, 2-Bromoethyl 2-[(Octadecylthio)Methyl]-4-Oxopentyl Ester (**10b**). Alcohol **8b** (3.7 g, 0.0083 mol) was dissolved in dry carbon tetrachloride (15 ml) and treated with dry triethylamine (4.5 ml, 0.033 mol) and bromoethylphosphorochloride (4.5 ml, 0.037 mol). After 2 h at room temperature, the mixture was cooled to 0°C and 0.5M aqueous sodium acetate (7 ml) was added with vigorous stirring. The mixture was stirred at room temperature for 0.5 h, extracted with methylene chloride (3 × 25 ml) and the combined extracts were dried over magnesium sulfate and concentrated to a paste. The paste was treated with acetone (30 ml) and 3N hydrochloric acid (3 ml) was added and the mixture was heated to reflux for 15 min. The acetone was evaporated without heat and the residue was extracted with methylene chloride (3 × 25 ml). The combined extracts were concentrated to a foam (5.3 g) which was purified on a florosil column (70 g) eluted first with chloroform (150 ml) and then with 10% methanol in chloroform (300 ml). The latter fractions were combined to give **10b** as a tan foam, 2.6 g (54%). ^{1}H NMR: δ 4.30 (m, 4 H, C$\underline{H}_2$OP), 3.6 (brt, 2 H, C$\underline{H}_2$Br), 2.5 (m, 6 H, C$\underline{H}_2$S, C$\underline{H}_2$CO), 2.25 (s, 3 H, C$\underline{H}_3$), 1.25 (m, 36 H, aliphatic $\underline{H}$). Anal. calcd for $C_{26}H_{52}O_5SPBr \cdot H_2O$: C, 51.56; H, 8.99; S, 5.29; P, 5.11; Br, 13.19. Found: C, 51.37; H, 8.10; s, 5.56; P, 5.24; Br, 13.41.

4-Hydroxy-N,N,N-Trimethyl-7-(2-Oxopropyl)-3,5-Dioxa-9-Thia-4-Phosphoheptacoxan-1-Aminium-4-Oxide, Hydroxide Inner Salt (**1b**). Bromide **10b** (2.0 g, 0.0035 mol) was dissolved in chloroform (20 ml) and 33% trimethylamine in acetonitrile (20 ml) and the mixture was heated to reflux for 2 h. Additional 33% trimethylamine in acetonitrile (10 ml) was added and heating was continued for 18 h. Silver carbonate (1 g, 0.0036 mol) was added and heating was continued for 2 h. The mixture was cooled, filtered through Celite and evaporated to a residue (2.7 g) which was purified on silica gel using first 10%

methanol in chloroform (150 ml) and then chloroform-methanol-water (70:30:5, 300 ml) as eluants. The latter fractions were concentrated to a syrup which was dissolved in chloroform and precipitated with ether to give **1b** as a glass, 1.6 g (81%). Mass spectrum (FAB) m/z 566 (MH^+); ^1H NMR: δ 4.30 (brm, 4 H, $C\underline{H}_2OP$), 3.35 (brs, 11 H, $C\underline{H}_2NC\underline{H}_3$), 2.5 (m, 6 H, $C\underline{H}_2S$, $C\underline{H}_2CO$), 2.20 (s, 3 H, $C\underline{H}_3CO$), 1.20 (m, 36 H, aliphatic $\underline{H}$). Anal. calcd for $C_{29}H_{60}NO_5SP \cdot 2H_2O$: C, 57.88; H, 10.72; N, 2.33; S, 5.33; P, 5.15. Found: C, 57.52; H, 10.20; N, 1.97; S, 6.44; P, 5.38.

2-Methyl-α-[(Hexadecylthio)Methyl]-1,3-Dioxolane-2-Propanoic Acid Ethyl Ester (**7a**). Mesylate **6** (16.2 g, 0.055 mol) and hexadecylthiol (14.2 g, 0.05 mol) were dissolved in dry tetrahydrofuran (100 ml) and sodium hydride (4 g of 50% suspension prewashed with petroleum ether, 0.08 mol) was added as described for **7b**. Work-up and column chromatography gave **7a** as an oil, 10.0 g (44%) which was used without further purification. Mass spectrum m/z 458 (M^+); ^1H NMR: δ 4.20 (q, 2 H, $C\underline{H}_2O$), 3.98 (s, 4 H, $OC\underline{H}_2C\underline{H}_2O$), 2.5 (m, 4 H, $C\underline{H}_2S$), 1.25 (m, 40 H, aliphatic $\underline{H}$).

2-Methyl-α-[(Hexadecylthio)Methyl]-1,3-Dioxolane-2-Propanol (**8a**). Ester **7a** (10.0 g, 0.0218 mol) in dry tetrahydrofuran (50 ml) was treated with diisobutylaluminum hydride (40 ml, 1.5M in toluene, 0.06 mol) as described for **8b**. Work-up and chromatographic purification gave **8a** as a wax, 4.2 g (46%) which was used without additional purification. Mass spectrum m/z 444 (M^+); ^1H NMR: 5.11 (brd, 1 H, $O\underline{H}$), 4.00 (m, 6 H, $C\underline{H}_2O$), 2.5 (m, 4 H, $C\underline{H}_2S$), 1.35 (m, 37 H, aliphatic $\underline{H}$).

Phosphoric Acid, 2-Bromoethyl 2-[(Hexadecylthio)Methyl]-4-Oxopentyl Ester (**10a**). Alcohol **8a** (1.12 g, 0.003 mol) in dry carbon tetrachloride (5 ml) was treated with dry triethylamine (1.5 ml, 0.006 mol) and bromoethylphophorochloride (3 g, 0.006 mol) for 2 h. Addition of 0.5M aqueous sodium acetate (2.5 ml) and work-up as described for **10b** gave 2.0 g of a paste. Hydrolysis of the paste in acetone (10 ml) with 1N hydrochloric acid (1 ml) gave a crude yellow syrup (1.4 g) which was chromatographed in florosil (30 g) using chloroform (100 ml) and then 10% methanol in chloroform (200 ml) as eluant. The latter fractions gave **10a** as a tan foam, 1.1 g (69%), which was used without further purification. ^1H NMR: δ 4.20 (m, 4 H, $C\underline{H}_2OP$), 3.5 (m, 2 H, $C\underline{H}_2Br$), 2.5 (m, 6 H, $C\underline{H}_2S$, $C\underline{H}_2CO$), 2.20 (s, 3 H, $C\underline{H}_3$), 1.25 (m, 32 H, aliphatic $\underline{H}$).

4-Hydroxy-N,N,N,-Trimethyl-7-(2-Oxopropyl)-3,5-Dioxa-9-Thia-4-Phosphopentacoxan-1-Aminium-4-Oxide, Hydroxide Inner Salt (**1a**). Bromide **10a** (1.1 g, 0.0021 mol) dissolved in chloroform (10 ml) was treated with a total of 15 ml of 33% trimethylamine in acetonitrile as described for **10b**. Silver carbonate (0.6 g, 0.0022 mol) was added and work-up, chromatography and precipitation of the product from chloroform with ether gave **10a** as a glass, 0.57 g (52%). Mass spectrum (FAB) m/z 538 (MH^+); ^1H NMR: δ 4.30 (brm, 4 H, $C\underline{H}_2OP$), 3.45 (brs, 11 H, $C\underline{H}_2NC\underline{H}_3$), 2.55 (m, 6 H, $C\underline{H}_2S$, $C\underline{H}_2CO$), 2.20 (s, 3 H, $C\underline{H}_3CO$), 1.25 (m, 36 H, aliphatic $\underline{H}$). Anal. calcd for $C_{27}H_{56}NO_5SP \cdot 1/2H_2O$: C, 59.30; H, 10.51; N, 2.56; S, 5.86; P, 5.66. Found: C, 58.99; H, 10.31; N, 2.27; S, 6.41; P, 5.75.

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FOOTNOTES AND REFERENCES

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8. Hydrogenation catalysts tried include palladium on carbon, ruthenium and Wilkinson's catalyst. Attempted hydride reagents include diborane, Vitride with and without Cu(I) additives, lithium aluminum hydride, sodium borohydride, triethylsilane in trifluoracetic acid and titanium trichloride. When **4** was reduced to an alcohol using diisobutylaluminum hydride, the expected alcohol formed but the thioenol ether linkage remained resistent to reduction.
9. J. B. Press, manuscript in preparation.