chemical ionization m/e (relative intensity) $(M + 1)^+$ 385 (6), 289 (3), 247 (10), 225 (10), 139 (100).

***d*-Menthyl 3,4-dibromocrotonate**: $[\alpha]_D$ +32.9° (*c* 1.32, EtOH).

***l*-Menthyl 4-Bromocrotonate (2).** Dibromide **5** was used without further purification. The crude product was dissolved in 50 mL of DME freshly distilled, and 30.5 g (0.20 mol) of DBU was added dropwise at 0 °C. When the addition was finished, the reaction was quenched with 3 N HCl (until acidic) and 70 mL of ethyl ether. The organic layer was washed with 20 mL of 3 N HCl. The combined aqueous layers were extracted with ethyl ether (3 × 80 mL). The combined organic layers were then washed with brine and dried with Na_2SO_4 and the solvent was evaporated. Ester **2** (36.5 g, 90% from menthyl 3-butenoate) was obtained after filtration through silica gel: R_f 0.4 (hex:Et_2O = 90:10); mp 35–36 °C; bp (Kugelrohr temp) 200 °C at 10^{-3} mm; $[\alpha]_D$ −60.2° (*c* 3.32, EtOH); IR (neat, NaCl) 2980, 2880, 1730, 1655 cm^{-1}; ^1H NMR ($CDCl_3$, TMS) δ 0.75 (d, 3 H, *J* = 7 Hz), 0.85–1.15 (m, 9 H), 1.35–1.6 (m, 2 H), 1.6–1.75 (br d, 2 H), 1.8–1.9 (m, 1 H), 1.95–2.1 (br d, 1 H), 4.0 (dd, 2 H, *J* = 8, 2 Hz), 4.75 (dt, 1 H), 6.05 (br d, 1 H, *J* = 16), 7.0 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 164.96 (C), 141.30 (CH), 125.05 (CH), 74.58 (CH), 47.00 (CH), 40.81 (CH_2), 34.18 (CH_2), 31.30 (CH), 29.07 (CH_2), 26.28 (CH), 23.48 (CH_2), 21.91 (CH_3), 20.62 (CH_3), 16.36 (CH_3). Anal. Calcd for $C_{14}H_{23}BrO_2$: C, 55.46; H, 7.59; Br, 26.37. Found: C, 55.00; H, 7.59; Br, 26.64.

***d*-Menthyl 4-bromocrotonate**: $[\alpha]_D$ +57.0° (*c* 0.50, EtOH).

***l*-Menthyl 2-Butenoate (4).** *l*-Menthol (25 g, 0.16 mol) was dissolved in 45 mL of freshly distilled Et_3N, and the mixture was mechanically stirred. Crotonly chloride (25.1 g, 0.24 mol) was added dropwise at 0 °C. A very thick white paste was formed. Freshly distilled THF (50 mL) was added to wash the walls of the flask, and then 30.5 g (0.20 mol) of DBU was added dropwise, at 0 °C. Workup of the reaction mixture prior to the addition of DBU resulted in quantitative isolation of deconjugated ester **3**. The mixture was allowed to warm up to room temperature and stirred for 3 h. The reaction mixture was diluted with ethyl ether and washed with 10% HCl (until acidic), and the combined aqueous layers were extracted with ethyl ether (3 × 80 mL). The combined organic layer was washed with 10% KOH, 10% HCl, and brine. It was then filtered through a plug of silica gel and dried with Na_2SO_4, and the solvent was evaporated to yield 35.1 g (98%) of crude ester **4** as a mixture of *E*:*Z* isomers (5:1): *E* R_f 0.54 (hex:Et_2O = 90:10), *Z* R_f in 0.67 (hex:EtO_2 = 90:10); bp (Kugelrohr temp) 150 °C at 10^{-3} mm; $[\alpha]_D$ −85.3° (*c* 1.73, EtOH) (of the 5:1 mixture); IR (neat, NaCl) 2930, 2880, 1710, 1660 cm^{-1}; *E* isomer ^1H NMR ($CDCl_3$, TMS) δ 0.75 (d, 3 H, *J* = 8 Hz), 0.9 (m, 6 H), 0.95–1.20 (m, 4 H), 1.35–1.60 (m, 2 H), 1.60–1.75 (br d, 2 H), 1.85 (dd, 3 H, *J* = 7, 2 Hz), 1.95–2.1 (br d, 1 H), 4.75 (dt, 1 H, *J* = 6 Hz, 12 Hz), 6.80 (dd, 1 H *J* = 2 Hz, 15 Hz), 6.95 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 165.87 (C), 143.74 (CH), 123.18 (CH_2), 73.60 (CH), 47.07 (CH), 40.91 (CH_2), 34.21 (CH_2), 31.29 (CH), 26.23 (CH), 23.50 (CH_2), 21.87 (CH_3), 20.59 (CH_3), 17.69 (CH_3) 16.30 (CH_3); mass spectrum, chemical ionization m/e (relative intensity) $(M + 1)^+$ 225 (3.7), 139 (100).

***d*-Menthyl 2-butenoate**: $[\alpha]_D$ +79.4° (*c* 0.77, EtOH).

***l*-Menthyl 2,3-Dibromocrotonate (6).** *l*-Menthyl 2-butenoate (**4**) (34.5g, 0.15 mol) was dissolved in 50 mL of CCl_4 and mechanically stirred. Bromine (39 g, 0.25 mol) was added dropwise at 0 °C. After the addition was complete the solvent was evaporated to afford ester **6**, which was used immediately without further purification: R_f 0.67 (hex:Et_2O = 90:10); bp (Kugelrohr temp) 200 °C at 10^{-3} mm; $[\alpha]_D$ −32.1° (*c* 6.73, EtOH); IR (neat, NaCl) 2960, 2880, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, TMS) δ 0.75 (dd, 3 H, *J* = 8, 2.5 Hz), 0.90–1.00 (m, 7 H), 1.00–1.15 (m, 2 H), 1.4–1.6 (m, 2 H), 1.6–1.8 (br d, 2 H) 1.9 (d, 3 H, *J* = 6 Hz), 2.0–2.1 (m, 2 H), 4.3–4.6 (m, 2 H), 4.7–4.8 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 167.18 (C), 76.40 (CH), 50.03 (CH), 46.92 (CH), 45.59 (CH), 39.81 (CH_2), 34.11 (CH_2), 31.29 (CH), 25.96 (CH), 23.83 (CH_3) 23.24 (CH_2) 21.91 (CH_3), 20.64 (CH_3), 16.05 (CH_3); mass spectrum, chemical ionization m/e (relative intensity) $(M + 1)^+$ 385 (5.7), 225 (12), 139 (100).

***d*-Menthyl 2,3-dibromocrotonate**: $[\alpha]_D$ +32.0° (*c* 0.59, EtOH).

***l*-Menthyl 2-Bromocrotonate (1).** Dibromide **6**, which was used immediately without further purification was dissolved in 100 mL of DME and 30.5 g (0.20 mol) of DBU was added dropwise at 0 °C with mechanical stirring. After addition was completed, the reaction was quenched with 3 N HCl (until acidic) and 100 mL of ethyl ether. The organic layer was washed with 20 mL of 3 N HCl. The combined aqueous layers were extracted with ethyl ether (2 × 80 mL). The combined organic layers were washed with brine and dried with Na_2SO_4 and the solvent was evaporated. After filtration through a bed of silica gel, 41.0 g (88% from menthyl 2-butenoate) of ester **1** was obtained as a 50:50 *Z*:*E* mixture: *E* R_f 0.43 (hex:Et_2O = 95:5), *Z* R_f 0.34 (hex:Et_2O = 95:5); bp (of the 1:1 mixture) (Kugelrohr temp) 200 °C at 10^{-3} mm; $[\alpha]_D$ −74.3° (*c* 5.57, EtOH); IR (neat, NaCl) 2900, 2850, 1710, 1630 cm^{-1}; *E* isomer ^1H NMR ($CDCl_3$, TMS) δ 0.75 (d, 3 H, *J* = 7 Hz), 0.85–1.0 (m, 7 H), 1.0–1.2 (m, 2 H) 1.4–1.6 (m, 2 H), 1.65–1.75 (br d, 2 H), 205 (d, 3 H, 8 Hz), 2.0 (m, 2 H) 4.75 (dt, 1 H), 6.7 (q, 1 H, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$) 162.40 (C), 140.46 (CH), 112.33 (C), 76.23 (CH), 46.95 (CH) 40.63 (CH_2), 34.11 (CH_2), 31.35 (CH), 26.14 (CH), 23.35 (CH_2), 21.89 (CH_3), 20.65 (CH_3), 17.69 (CH_3), 16.15 (CH_3); *Z* isomer ^1H NMR ($CDCl_3$, TMS) δ 0.75 (d, 3 H, *J* = 7 Hz), 0.85–1.0 (m, 7 H), 1.0–1.2 (m, 2 H), 1.4–1.6 (m, 2 H), 1.95 (d, 3 H, *J* = 6 Hz), 2.0 (m, 2 H), 4.75 (dt, 1 H), 7.35 (q, 1 H, *J* = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 161.72 (C), 142.17 (CH), 118.26 (C), 76.39 (CH), 46.95 (CH), 40.63 (CH_2), 34.11 (CH_2), 31.35 (CH), 26.29 (CH), 23.45 (CH_2), 21.89 (CH_3), 20.65 (CH_3), 17.21 (CH_3), 16.35 (CH_3).

***d*-Menthyl 2-bromocrotonate**: 60:40 *Z*/*E* mixture $[\alpha]_D$ +72.9° (*c* 1.23, EtOH).

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An Effective Process for the Isolation of Docosahexaenoic Acid in Quantity from Cod Liver Oil

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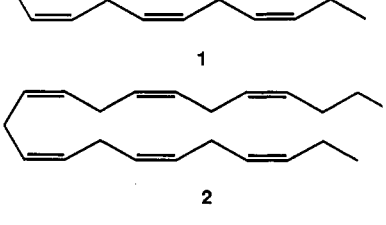
Received May 20, 1987

The marine-derived polyunsaturated fatty acids eicosapentaenoic acid (**1**) (EPA) and docosahexaenoic acid (**2**) (DHA) are currently of unusual interest because of several lines of evidence that point to beneficial effects of dietary fish lipid on cardiovascular health.[1-3] The mechanisms by which these cardioprotective effects arise are obscure and are likely to remain so until careful biochemical and biological studies on the role of the *individual* acids **1** and



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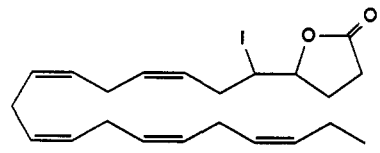
0022-3263/87/1952-4399$01.50/0

2 are carried out. This in turn requires the development of a practical method for the separation of 1 and 2 from fish lipid mixtures. The most widely used current method of separation involves tedious and costly chromatography of esters of 1 and 2 on silica gel impregnated with silver nitrate.[4] We report in detail a simple extractive isolation of DHA from cod liver oil that obviates the need for distillation or chromatography. The procedure is rapid and effective, and the scale is limited only by the capacity of available equipment. Troublesome emulsions are avoided by careful selection of extraction conditions. The process involves four steps, after which DHA is obtained in amounts equal to 10–15% of the initial weight of cod liver oil.

After saponification of the cod liver oil by warming with ethanolic potassium hydroxide, neutral compounds such as waxes, sterols, and unsaponified matter were removed by dilution with water and extraction, and the fatty acid mixture was obtained by acidification. The saturated and monounsaturated fatty acids were largely removed by precipitation of their lithium soaps from acetone.[5] Evaporation and acidification of the filtrate yielded a concentrated mixture of polyunsaturated fatty acids. The DHA content of the polyunsaturated fatty acids was determined by capillary column gas chromatography, and the mixture of acids was subjected to iodolactonization in aqueous tetrahydrofuran using 1.2 equiv of iodine and potassium iodide, based on the DHA present. The selective formation of the iodo γ-lactone 3 in the mixture, rather than the iodo δ-lactone 4, derived from EPA was expected



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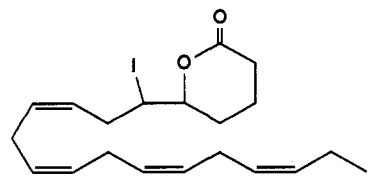

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on the basis of preliminary work[6] and from the known greater stability and faster rate of formation of γ-lactones over δ-lactones. However, considerable experimentation was required to find optimal reaction conditions. Extractive workup of the iodolactonization mixture thus gave 3 as the only neutral product. The iodo lactone 3 was then treated with iodotrimethylsilane, generated in situ from chlorotrimethylsilane and sodium iodide, to yield the desired acid.[7]

It is hoped that the detailed procedure recorded below will be useful to those in need of sizeable quantities of pure docosahexaenoic acid for biomedical and biochemical studies. Previous studies with pure DHA have revealed some unique and highly interesting properties, including strong inhibition of the enzyme prostaglandin H_2 synthase (K_i = 0.36 μM)[6] and lack of bioconversion to C_{22} leukotriene and prostaglandin analogues.[6]

Experimental Section

Solvents for extraction were of reagent quality and were used as received. Cod liver oil was obtained from the Marine Products Co., Boston, MA. Chlorotrimethylsilane and acetonitrile were distilled from calcium hydride before use. 2-Methyl-2-butene was passed through a column of basic alumina and stored over 3A molecular sieves. All solutions were dried over magnesium sulfate. Evaporations were carried out with a rotary evaporator at ca. 25 Torr. NMR spectra were obtained on a Jeol FX-270 spectrometer. Infrared spectra and ultraviolet spectra were recorded on Perkin-Elmer 683 and 559A spectrometers, respectively. Mass spectra were obtained with a Kratos-Erba MS-50 instrument. Gas chromatography was performed with a Hewlett-Packard 5890 gas chromatograph and 3392A integrator with a 6-m capillary column and flame ionization detection.

Saponification. To a mixture of 200 g of cod liver oil and 400 mL of 95% ethanol in a 4-L Erlenmeyer flask was added a hot solution of 50 g of potassium hydroxide in 400 mL of water with stirring under nitrogen. After it was stirred at 65 °C for 1.5 h, the resulting clear solution was diluted with 1600 mL of 95% ethanol followed by 1100 mL of water. The contents of the flask were divided equally among three 4-L separatory funnels, and each funnel was extracted with one 350-mL portion of 1,2-dichloroethane followed by six 160-mL portions. The dichloroethane was recovered by distillation, and the residues were discarded. The contents of each funnel were acidified with 180 mL of 1 M sulfuric acid and 670 mL of water. The solvent layer that formed was drawn off and retained. Each funnel was extracted with 1:1 ether–hexane (2 × 250 mL). The combined extracts were washed with water (2 × 300 mL) and brine (300 mL), dried, and evaporated to give 180 g of fatty acids.

Concentration. The fatty acids were dissolved in 750 mL of acetone and treated with 5 M lithium hydroxide until pH 9 was obtained. The volume of lithium hydroxide solution that was used was noted, and sufficient water was added to bring the total volume of added water to 220 mL. The mixture was diluted with 2750 mL of acetone and sealed under nitrogen, cooled to 0 °C for 12 h, and then filtered. The precipitate was washed with acetone, and the filtrate was acidified with 1 M hydrochloric acid and concentrated. The residue was extracted with dichloromethane (2 × 250 mL) and ether (250 mL). The combined extracts were washed with water (2 × 150 mL) and brine (150 mL), dried, and evaporated to give 50 g of polyunsaturated fatty acids. A 25-mg sample of the product was treated with excess ethereal diazomethane at 0 °C, and the resulting mixture of esters was analyzed by capillary GC to determine the percentage of DHA present.

Iodo Lactone 3. A 3-L 3-neck flask fitted with a mechanical stirrer and nitrogen purge tube was charged with a solution of 50 g of polyunsaturated fatty acids (42% DHA, 65 mmol) in 827 mL of THF. A solution of 13 g (79 mmol) of potassium iodide and 39 g (390 mmol) of potassium bicarbonate in 413 mL of water was added with stirring. After 10 min, 20 g (79 mmol) of iodine was added, and the mixture was stirred at 23 °C for 48 h. The mixture was quenched with a solution of 312 g (3.1 mol) of potassium bicarbonate and 25 g (160 mmol) of potassium sulfite in 1100 mL of water and extracted twice with ethyl acetate (2 × 415 mL). The extracts were concentrated, and the residue was dissolved in 1880 mL of hexane. This was washed with 940 mL of 0.5 M potassium carbonate in 1:1 methanol–water. The methanolic potassium carbonate solution was promptly back-extracted with 940 mL of 1:1 ether–hexane. The combined ether–hexane solutions were washed with water (3 × 500 mL) and brine (500 mL), dried, and evaporated to yield 24.11 g (81%) of the iodo lactone 3: IR (NaCl) 1775 (γ-lactone C=O), 1645 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.59 (m, 1 H, 7-CH), 5.38 (m, 9 H, olefinic H), 4.26 (m, 1 H, 4-CH), 4.13 (m, 1 H, 5-CH), 2.81 (m, 8 H, 9-, 12-, 15-, and 18-CH_2), 2.70 (m, 2 H, 6-CH_2), 2.60 (m, 2 H, 2-CH_2), 2.45 (m, 2 H, 3-CH_2), 2.08 (m, 2 H, 21-CH_2), 0.97 (t, 3 H, 22-CH_3); MS (70 eV), *m/z* (relative intensity) 454, M^+ (88), 326 (100); high-resolution MS (70 eV, CI) for $C_{22}H_{31}IO_2H$, calcd 455.14488, found 455.14435.

Docosahexaenoic Acid 2. A solution of 24.11 g (53 mmol) of 3 in 100 mL of acetonitrile was dried over 4A molecular sieves

(4) For a typical separation scheme see: Teshima, S.; Tanazawa, A.; Tokiwa, S. *Nippon Suisan Gakkaishi* **1978**, *44*, 927.
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for 1 h and then added to a solution of sodium iodide (39.8 g, 265 mmol) and 2-methyl-2-butene (16.9 mL, 160 mmol) in 500 mL of acetonitrile in a 2-L 3-neck flask under nitrogen. Chlorotrimethylsilane (13.5 mL, 106 mmol) was added slowly by syringe. The mixture was stirred at 23 °C until the reaction was complete as determined by working up 20-μL aliquots and by TLC examination. The reaction was quenched by adding a solution of 13.4 g (106 mmol) of sodium sulfite and 12.5 g (42 mmol) of sodium citrate in 840 mL of water to the flask. The mixture was washed with 4:1 hexane–dichloromethane (3 × 250 mL), and the combined extracts were washed with water (5 × 250 mL) and brine (250 mL) and evaporated. The crude product was taken up in 640 mL of hexane, and the solution was extracted with 320 mL of 0.5 M potassium carbonate in 1:1 methanol–water. The alkaline solution was washed with 1:1 hexane–ether (2 × 160 mL) and then acidified under nitrogen with 90 mL of 4.5 M hydrobromic acid. The oily product was extracted with 2:1 hexane–ether (3 × 100 mL). The extracts were washed with water (2 × 75 mL) and brine (75 mL), dried, and evaporated to give 13.55 g (78%) of pure DHA (**2**): IR (NaCl) 1710 (C=O), 1645 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.38 (m, 12 H, olefinic H), 2.85 (m, 10 H, 6-, 9-, 12-, 15-, and 18-CH_2), 2.42 (m, 4 H, 2- and 3-CH_2), 2.08 (m, 2 H, 21-CH_2), 0.97 (t, 3 H, 22-CH_3); FAB MS, *m/z* (relative intensity) 329, MH^+ (1.9), 133 (12), 131 (18), 119 (27), 117 (33), 107 (24), 105 (47), 95 (31), 93 (56), 91 (98), 81 (38), 79 (97), 67 (100).

Methyl Docosahexaenoate. A 66-mg (200-μmol) sample of **2** was dissolved in 5 mL of distilled ether and the resultant mixture cooled to 0 °C. A slow stream of diazomethane in nitrogen (prepared by bubbling nitrogen through ethereal diazomethane) was passed into the sample in the dark until the esterification was complete. Evaporation gave 68 mg (100%) of methyl docosahexenoate: IR (NaCl) 1745 (C=O), 1645 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.38 (m, 12 H, olefinic H), 3.68 (s, 3 H, OCH_3), 2.85 (m, 10 H, 6-, 9-, 12-, 15-, and 18-CH_2), 2.38 (m, 4 H, 2- and 3-CH_2), 2.10 (m, 2 H, 21-CH_2), 0.97 (t, 3 H, 22-CH_3; MS (70 eV), *m/z* (relative intensity) 342 M^+ (80), 310 (27), 268 (12), 79 (100); high-resolution MS (70 eV) for $C_{23}H_{34}O_2$, calcd 342.25586, found 342.25566; GC (oven 190 °C) R_t 21.35 min, 95%. A sample of the methyl ester was hydrogenated with platinum in methanol; it was found to be identical with authentic methyl docosanoate by GC analysis.[8]

(8) This research was assisted financially by a grant from the National Institutes of Health.

A Novel and Stereospecific Synthesis of (5*R*,6*S*)-6-(Aminomethyl)-2-(ethylthio)penemcarboxylic Acid[1]

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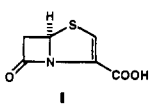
Penem-3-carboxylic acid (I) and its derivatives represent the first major series of totally synthetic β-lactam antibiotics. Structurally, these compounds occupy a position between penicillins and cephalosporins, being, in a sense, nor analogues of the latter.[2] Several penem derivatives bearing a 6(*R*),8(*R*)-hydroxyethyl substituent similar to that found in thienamycin[3] have demonstrated potent, broad-spectrum antibacterial activity.[4] In an effort to prepare structurally novel compounds that might combine the potent antibacterial activity of the 6(*R*)-hydroxyethyl derivatives with enhanced pharmacokinetics, we became interested in derivatives of the 6α-(aminomethyl)penemcarboxylic acid (II) in hopes that the zwitterionic character of these compounds might enhance their stability. While some (aminoalkyl)penems had been previously synthesized by displacement of activated hydroxyl groups from penems,[5] we sought a more direct entry into the system. Also, since only those penem derivatives with the 5*R* absolute configuration demonstrate antibacterial activity,[6] we wanted our synthesis to start with optically pure material and to proceed in such a way as to retain stereochemical integrity.



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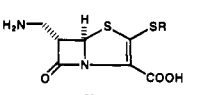

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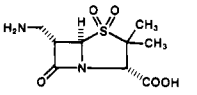
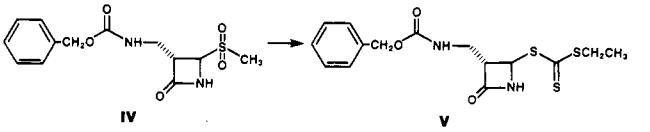


III

A series of 6α-(aminomethyl)penicillanic acid sulfones, including the 6α-aminomethyl derivative III, which display potent β-lactamase-inhibiting activity, has been recently reported from our laboratories.[7,8] This readily available starting material had the proper chirality at C-5 and appeared to provide an excellent entry into the 6α-(aminomethyl)penem series, provided that the penem ring could be constructed upon the β-lactam ring while maintaining stereochemical integrity.

The *p*-NO_2-CBZ-protected methyl ester of compound III (compound **1**, Scheme I) was subjected to DBN (or DBU) in CH_2Cl_2 for 3 h, essentially under the conditions of Stoodley et al.[9] The resulting sulfinic acid **2** could be isolated by extraction into aqueous sodium bicarbonate and purified by column chromatography, after which it could be alkylated in essentially quantitative yield to give the sulfone **3** by treatment of its tetra-*n*-butylammonium salt with methyl iodide. Although the DBN salt of **2** arising from the ring-opening reaction could be alkylated directly with methyl iodide to give the sulfone **3**, the two step procedure resulted in a higher, cleaner yield.[10] Dealkylation on nitrogen was achieved with $KMnO_4$ with $NaIO_4$ as reoxidant by the method of Yoshida et al.[11] to give the desired crystalline azetidinone **4** $[\alpha]^{22}_D$ −8.3° (*c* 1.0, acetone).

The azetidinone reacted readily with potassium ethyltrithiocarbonate under phase-transfer conditions to give the desired crystalline trithiocarbonate **5** in 31% yield. A similar reaction with the carbobenzyloxy analogue IV gave the corresponding crystalline trithiocarbonate V in 72% yield, supporting the fact that displacement of the sulfone moiety from the α-aminomethyl-substituted azetidinone can be a facile, high-yield process.



IV V

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