^{13}C) spectrometer using Me_4Si as internal standard and $CDCl_3$ as solvent. $^{13}C(^1H)$ NOED experiments were performed as described in the literature[7] as modified in the pulse-sequence diagram (*vide supra*). Mass spectrometry was performed on either an MAT 212 or MAT 311A spectrometer. "Chromatography" refers to the flash column chromatography technique[11] over EM silica gel 60 (0.040–0.063 mm).

Methyl (*Z*)-2-[3-Methoxy-2-[(methoxycarbonyl)amino]-3-oxo-1-propenyl]-6-methyl-4-pyridinecarboxylate (5). A solution of 15.5 g (108 mmol) of methyl 2,4-dioxopentanoate and 3.40 g (56.6 mmol) of urea in 200 mL of absolute MeOH was refluxed for 4 days. The dark solution was evaporated to dryness and the solid residue chromatographed by using 10% Et_2O/CH_2Cl_2 as eluent, affording 10.5 g (63.3%) of bright yellow solid. Recrystallization from 100 mL of MeOH gave 6.7 g (40% overall yield) of bright yellow crystals: mp 134.5–7.5 °C; UV (MeOH) λ_{max} 334 (ϵ 1.30 × 10^4), 274 (1.78 × 10^4), 219 nm (sh) (1.27 × 10^4); IR (KBr) 1730 (CO) and 1715 (CO), 3400 cm^{-1} (NH); EIMS 308 (M^+), 277, 249, 216, 205, 190 (base peak); ^{13}C NMR ($CDCl_3$) δ 24.14 (6-CH_3), 52.33, 52.43, 52.52 ($CH_3OC(O)$), 111.45 (C-7), 120.25 (C-5), 121.11 (C-3), 134.32 (C-8), 138.13 (C-4), 153.71 (C-9), 154.90 (C-2), 157.97 (C-6), 164.88 and 164.91 (3 carbons, $CH_3OC(O)$); ^1H NMR ($CDCl_3$) all singlets δ 11.32 (NH), 7.58 (pyridine 3-H, 5-H), 6.28 (vinyl 7-H), 3.95 and 3.89 (ester methyls), 3.78 (carbamate methyl), 2.65 (pyridine 6-Me). Anal. Calcd for $C_{14}H_{16}N_2O_6$, MW 308.29: C, 54.54; H, 5.23; N, 9.09. Found: C, 54.30, 54.06; H, 4.98, 5.20; N, 8.96, 9.17.

Crystals of **5** suitable for X-ray analysis were grown by vapor diffusion[12] of water vapor into a methanol solution of **5**.

Ethyl (*Z*)-3-[2-ethoxy-1-[(ethoxycarbonyl)amino]-2-oxoethylidene]-1,2,3,5,6,7-hexahydrodicyclopenta[*b*,*e*]pyridine-8-carboxylate (7a), R = Et, R^1,R^2 = CH_2CH_2, was prepared from **6a** and urea in absolute EtOH in an analogous manner to give a 72.6% yield of amber waxy solid with a characteristic orange fluorescence (long-wavelength UV) after chromatography using 5% Et_2O/CH_2Cl_2 as eluent: mp 63–73 °C; EIMS 402 (M^+); exact mass calcd for $C_{21}H_{26}N_2O_6$ 402.1791, found 402.1787; ^1H NMR ($CDCl_3$) δ 10.95 (br s, 1, NH), 4.6–4.0 (m, 6, (O)$COCH_2$), 3.4–2.8 (m, 6, CH_2), 2.6–1.6 (m, 4, CH_2), 1.5–1.1 (m, 9, (O)$COCH_2CH_3$).

Ethyl (*Z*)-4-[2-ethoxy-1-[(ethoxycarbonyl)amino]-2-oxoethylidene]-1,2,3,4,5,6,7,8-octahydro-9-acridinecarboxylate (7b), R = Et, R^1,R^2 = $CH_2CH_2CH_2$, was prepared from **6b**[9b] as above to give a 2.1% yield of an amber waxy low-melting solid: EIMS 430 (M^+); exact mass calcd for $C_{23}H_{30}N_2O_6$ 430.2104, found 430.2100; ^1H NMR δ 12.90 (br s, 1, NH), 4.6–4.0 (m, 6, (O)$COCH_2$), 3.1–2.2 (m, 8, CH_2), 2.2–1.6 (m, 6, CH_2), 1.6–1.2 (m, 9, (O)-$COCH_2CH_3$). The major product (18.2%) isolated from this reaction was a liquid dimer of **6b** of undetermined structure:[13] EIMS and CIMS 396 (M^+). Anal. Calcd for $C_{20}H_{28}O_8$: C, 60.59; H, 7.12; N, 0.00. Found: C, 60.10; H, 7.24; N, 0.00.

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Registry No. **2**, 39847-91-1; **5**, 117098-05-2; **6a**, 85258-72-6; **6b**, 117098-06-3; **7a**, 117098-07-4; **7b**, 117098-08-5; urea, 57-13-6.

Supplementary Material Available: Experimental details of crystal **5**, PLUTO-type drawing of **5**, labeled ORTEP drawing of **5**, stereoview of the unit cell packing diagram, tables of atomic coordinates and isotropic thermal parameters, bond lengths, bond angles, anisotropic thermal parameters, and H-atom coordinates and isotropic thermal parameters (11 pages). Ordering information is given on any current masthead page.

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Convenient Method for the Recovery of Eicosapentaenoic Acid from Cod Liver Oil

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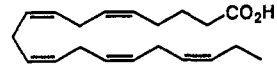
The marine-derived polyunsaturated fatty acids eicosapentaenoic acid (1) (EPA) and docosahexaenoic acid (2) (DHA) are currently of much interest due to the increasing evidence that points to a beneficial role of fish lipids in maintaining cardiovascular health.[1-3] We have recently reported a process for the extractive isolation of DHA from cod liver oil[4] that avoids the need for distillation or chromatography. We now describe in detail how EPA may be separated with similar ease from the residues remaining from the preparation of DHA.



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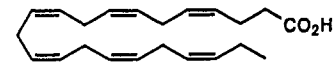

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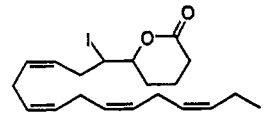

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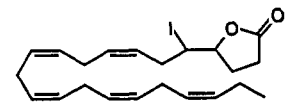

4

Following the selective conversion of DHA to iodo lactone 4,[4] extractive workup yielded an alkaline solution containing the unreacted fatty acids as a byproduct. Acidification and extraction gives a mixture of polyunsaturated fatty acids enriched in EPA. This mixture is subjected to iodolactonization in aqueous tetrahydrofuran using an excess of iodine and potassium iodide. Following extractive workup, a mixture of the iodo lactones **3** and **4**, derived from EPA and the residual DHA, is obtained. The ratio of **3** to **4** can be estimated from the ^1H NMR spectrum of the mixture by integration of the signals at 3.95 and 4.25 ppm, due to **3** and **4**, respectively. The mixture of **3** and **4** is then treated with iodotrimethylsilane, generated in situ from chlorotrimethylsilane and sodium iodide, using 1.4 equiv based on the amount of **3** present.[5] Selective cleavage of the iodo δ-lactone **3** in the presence of the iodo γ-lactone **4** occurs as a result of the greater stability of the γ-lactone system in **4**. As soon as most of the δ-lactone **3** has reacted (ca. 2 h at 22 °C), the reaction mixture is worked up to yield pure EPA. The procedure given below is well suited for the preparation of quantities of eicosapentaenoic acid.

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Experimental Section

Materials and methods used were as described previously.[4]

Recovery of Fatty Acids. The methanolic potassium carbonate extract remaining from the preparation of 4 was slowly acidified under nitrogen with 170 mL of 3 M sulfuric acid. The oil was extracted with 1:1 ether–hexane (3 × 250 mL). The combined ether–hexane solutions were washed with water (2 × 200 mL) and brine (200 mL), dried, and evaporated to give 30.7 g of polyunsaturated fatty acids.

Iodolactonization. The fatty acids were dissolved in 530 mL of THF in a 2-L flask. A solution of 25 g (0.25 mol) of potassium bicarbonate and 38 g (0.23 mol) of potassium iodide in 265 mL of water was added with stirring. After 15 min, iodine (118 g, 0.46 mol) was added. The flask was sealed under nitrogen and stirred in the dark at 4 °C for 48 h. The mixture was poured slowly into a solution of 194 g (1.94 mol) of potassium bicarbonate and 145 g (0.92 mol) of potassium sulfite in 700 mL of water. The mixture was extracted with ethyl acetate (2 × 270 mL), and the extracts were evaporated. The residue was dissolved in 1170 mL of hexane and extracted with 580 mL of 0.5 M potassium carbonate in 1:1 methanol–water. The alkaline solution was promptly back extracted with 580 mL of 1:1 hexane–ether. The combined hexane–ether solutions were washed with water (3 × 260 mL) and brine (260 mL) and evaporated. The residue was applied to a bed of silica gel (230–400 mesh, 7 cm × 7 cm) and filtered under pressure with 1600 mL of 1:1 dichloromethane–hexane. Evaporation gave 11.1 g of a mixture of 3 and 4.

Eicosapentaenoic Acid (1). A solution of 11.1 g of 3 and 4 in 150 mL of acetonitrile was dried for 1 h over 4A molecular sieves and then added to a solution of 16.9 g (0.11 mol) of sodium iodide in 100 mL of acetonitrile in a 1-L three-neck flask fitted with a nitrogen purge and septum inlet. 2-Methyl-2-butene (4.77 mL, 45 mmol) was added, followed by chlorotrimethylsilane (3.80 mL, 30 mmol). The mixture was stirred at 22 °C for 2 h. TLC analysis (CH_2Cl_2) of the mixture revealed a steady decrease in the amount of 3 present in the mixture, with 4 remaining unaffected. The reaction was stopped by the addition of a solution of 3.8 g (30 mmol) of sodium sulfite and 3.5 g (12 mmol) of sodium citrate in 350 mL of water. The mixture was extracted with 4:1 hexane–dichloromethane (3 × 100 mL), and the combined extracts were washed with water (5 × 100 mL) and brine (100 mL) and concentrated. The crude product was taken up in 340 mL of hexane and extracted with 170 mL of 0.5 M potassium carbonate in 1:1 methanol–water. The alkaline solution was washed with 1:1 hexane–ether (2 × 70 mL) and then acidified under nitrogen with 50 mL of 4.5 M hydrobromic acid. The product was extracted with 2:1 hexane–ether (3 × 50 mL). The extracts were washed with water (3 × 30 mL) and brine (30 mL), dried, and evaporated to give 3.50 g of pure EPA (1): IR (NaCl) 1710 (C=O), 1645 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.38 (m, 10 H, olefinic H), 2.84 (m, 8 H, 7-, 10-, 13-, 16-CH_2), 2.37 (t, 2 H, 2-CH_2), 2.12 (m, 4 H, 4- and 19-CH_2), 1.71 (m, 2 H, 3-CH_2), 0.97 (t, 3 H, 20-CH_3); FAB MS, m/z (relative intensity) 303 (MH^+, 2.4).

Methyl Eicosapentaenoate. A 101-mg (330-μmol) sample of 1 was dissolved in 7 mL of distilled ether and cooled to 0 °C. A slow stream of diazomethane in nitrogen (prepared by bubbling nitrogen through ethereal diazomethane) was passed into the sample until the esterification was complete. Drying, filtration, and evaporation gave 97 mg (93%) of methyl eicosapentaenoate: IR (NaCl) 1745 (C=O), 1645 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.38 (m, 10 H, olefinic H), 3.67 (s, 3 H, OCH_3), 2.84 (m, 8 H, 7-, 10-, 13-, 16-CH_2), 2.32 (t, 2 H, 2-CH_2), 2.10 (m, 4 H, 4- and 19-CH_2), 1.70 (m, 2 H, 3-CH_2), 0.97 (t, 3 H, 20-CH_3); CI MS (70 eV), m/z (relative intensity) 317 (MH^+, 100), 285 (17); GC (OV-1) (oven 180 °C) t_R 6.27 min, 95%. A sample of the methyl ester was hydrogenated with platinum in methanol; it was found to be identical with authentic methyl eicosanoate by GC analysis.

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Registry No. 1, 10417-94-4; 2, 6217-54-5.

Communications

A Novel Lanthanide-Induced Rearrangement

Summary: Treatment of α-hydroxy ketone 4 with samarium diiodide led to tricyclic alcohol 6 in high yield. Two intermediates in this process, α-hydroxy ketone 7 and ketone 8, have been isolated and identified. This process combines a Lewis acid (Sm^{3+}) mediated ring expansion with reductive loss of a hydroxyl substituent and transannular ketyl cyclization. The stereoelectronic features that make these transformations favorable are discussed in detail.

Sir: There has recently been great interest in the development and use of lanthanide-based reagents in organic synthesis.[1] In addition to their now traditional use as NMR shift reagents,[2] lanthanides have been shown to serve as catalysts for Diels–Alder reactions,[3] to provide interesting selectivity in various reductions and oxidations,[4] and to present an alternative to Grignard reagents and alkali metal enolates in additions to carbonyl compounds.[5] Although a theme common to these applications is the Lewis acidity of the lanthanide reagents, relatively few examples of lanthanide-induced rearrangements have been documented.[6] We now report a novel samarium-induced rearrangement–reduction–reductive cyclization, which we

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