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ANTITUMOR ETHER LIPIDS: AN IMPROVED SYNTHESIS OF ILMOFOSINE AND AN ENANTIOSELECTIVE SYNTHESIS OF AN ILMOFOSINE ANALOG

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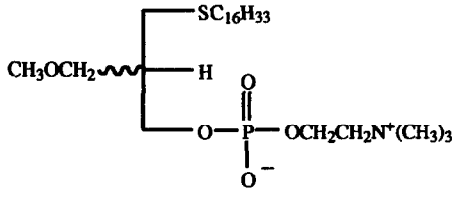
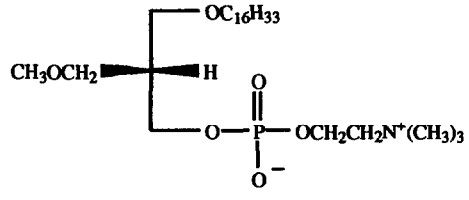
Abstract: Efficient routes to racemic Ilmofosine (**1**) and to the enantiomers of its oxygen analog, 2'-(trimethylammonio)ethyl 3-hexadecyloxy-2-methoxymethylpropanephosphate (**2**), are described starting from ethyl α-(hydroxymethyl)acrylate (**3**) or 2-methylene-1,3-propanediol (**6**).

2'-(Trimethylammonio)ethyl 3-hexadecylthio-2-methoxymethylpropanephosphate (BM 41.440: Ilmofosine, **1**)[1a] is one of the most potent antineoplastic ether-linked phosphocholines reported so far.[1b] This compound recently has been tested in clinical phase II trails in refractory cancer patients,[2] and has stimulated interest in analogs of Ilmofosine.[3] *rac*-Ilmofosine (**1**) was synthesized by Bosies *et al.*[1a] in an eight-step reaction sequence starting from diethyl bis(hydroxymethyl) malonate in 21% overall yield. Here we report an efficient synthesis of *rac*-**1**, and the first synthesis of the chiral oxygen analog of **1**, 2'-(trimethyl-ammonio)ethyl 3-hexadecyloxy-2-methoxymethylpropanephosphate (**2**).[4] In an extension of our studies of the influence of stereochemistry at the C-2 position of antitumor ether glycerolipids on biological activity,[5] we sought to prepare and test optically active oxygen analogs of **1**.



rac-**1** (Ilmofosine, BM 41.440)

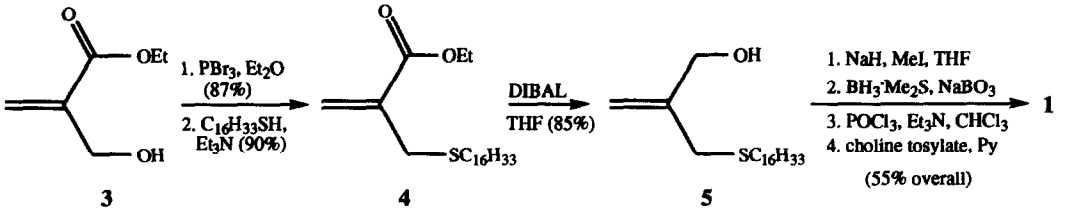


(*R*)-**2**

Our synthesis of Ilmofosine started from ethyl α-(hydroxymethyl)acrylate (**3**)[6] (Scheme 1). Treatment of acrylate **3** with phosphorus tribromide in ethyl ether provided α-(bromomethyl)acrylate. Alkylation of ethyl α-(bromomethyl)acrylate with hexadecylmercaptan in the presence of triethylamine afforded ethyl α-(hexadecylthiomethyl)acrylate (**4**) in 90% yield.[7] Reduction of acrylate **4** with diisobutylaluminum hydride (DIBAL) gave 3-hexadecylthio-2-methylene-1-propanol (**5**) in 85% yield. Alkylthiopropenol **5** was converted into **1** in a three-step sequence (55% overall yield): (1) alkylation of alkylthiopropenol **5** with sodium hydride and methyl iodide, (2) hydroboration with borane-dimethyl sulfide, followed by oxidative workup with sodium perborate,[8] and (3) phosphorylation with phosphorus oxychloride and coupling with choline tosylate in alcohol-free chloroform at -20 °C. Our synthesis of Ilmofosine is shorter than the Bosies *et al.*[1a] method, requiring only six steps to give

the desired product in 37% overall yield. Moreover, application of a chiral organoborane instead of $BH_3 \cdot Me_2S$ would allow preparation of chiral **1** via the asymmetric hydroboration method shown below for the synthesis of (*R*)-**2**.

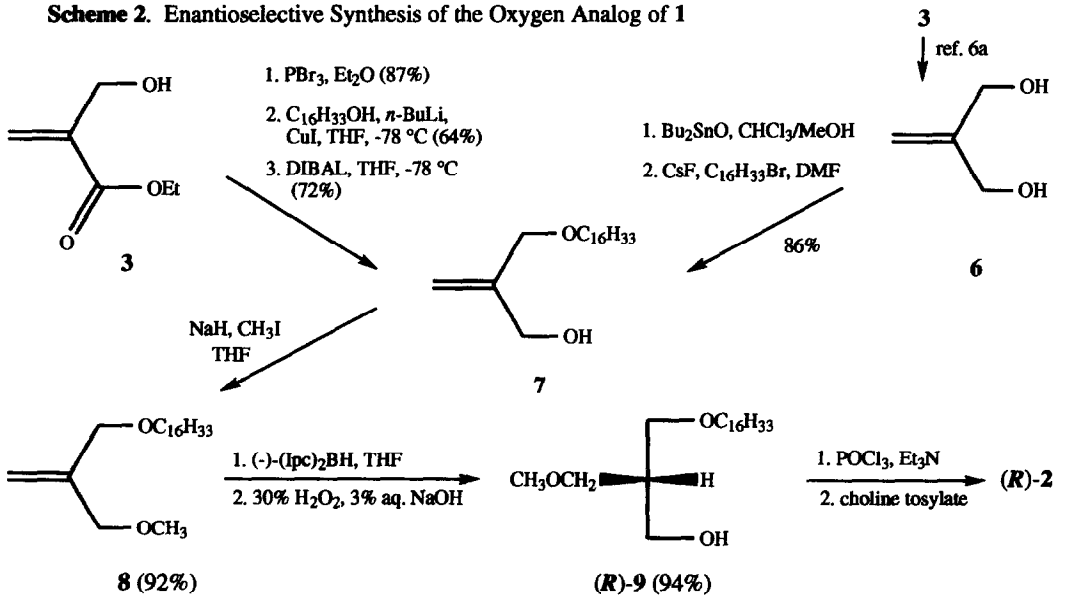
Scheme 1. Synthesis of Ilmofosine (1)



3 4 5

Two synthetic approaches to the oxygen analog of Ilmofosine (**2**) are described here (Scheme 2). The first method involved the one-pot selective monoalkylation of 2-methylene-1,3-propanediol (**6**)[6a] via a 1,3-cyclic stannoxane derivative[9] in chloroform/methanol followed by treatment with cesium fluoride and 1-bromohexadecane in DMF to give 2-hexadecyloxymethyl-2-propenol (**7**) in 86% yield.[10] The second method for the preparation of **7** involved nucleophilic attack by the copper(I) salt of a primary alcohol[11] (hexadecanol) on ethyl α-(bromo-methyl)acrylate in THF to yield ethyl 2-(hexadecyloxymethyl)acrylate in 64% yield. The latter compound was reduced with DIBAL in THF at -78 °C to give **7** in 72% yield.

Scheme 2. Enantioselective Synthesis of the Oxygen Analog of **1**



8 (92%) (*R*)-**9** (94%)

Methylation of **7** with methyl iodide and sodium hydride in THF gave 3-hexadecyloxy-2-methoxymethyl-1-propene (**8**) in 92% yield.[12] Asymmetric hydroboration of propene **8** with (-)-diisopino-

campheylborane [(-)-$(Ipc)_2BH$],[13] followed by the oxidation of the intermediate borane with hydrogen peroxide, yielded 3-hexadecyloxy-2-(*R*)-methoxymethyl-1-propanol [(***R***)-**9**] in 94% yield.[14] The enantiomeric excess (ee) of **9** was estimated to be 84% by chiral HPLC analysis[15] of the (*R*)-(+)-MTPA ester derivative of (***R***)-**9**. Asymmetric hydroboration of prochiral 1-alkenes with $(Ipc)_2BH$ normally provides poor enantiomeric excess,[16] but an excellent level of asymmetric induction has apparently been achieved here because of the large size difference[17] between the hexadecyloxy and methoxy groups of **8**. Finally, propanol (***R***)-**9** was treated with $POCl_3$ and excess choline tosylate in chloroform in the presence of triethylamine to give the target compound, (*R*)-2'-(trimethylammonio)ethyl 3-hexadecyloxy-2-methoxymethylpropanephosphate [(***R***)-**2**],[18] in 70% yield. The (*S*)-enantiomer of **2** was made by the hydroboration of propene **8** with (+)-$(Ipc)_2BH$.[19]

In conclusion, the present work describes an improved synthesis of *rac*-Ilmofosine (**1**) and an enantioselective synthesis of its oxygen analog **2** starting from ethyl α-(hydroxymethyl)acrylate (**3**) or 2-methylene-1,3-propanediol (**6**). Initial in vitro tests of the effects of both (***R***)- and (***S***)-**2** on the growth of a breast cancer cell line (MCF-7) and a colon cancer cell line (T84) showed a potent inhibition of cell growth; the cytotoxicity of (***S***)-**2** against MCF-7 cells was higher than that of (***R***)-**2**.

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7. To a solution of hexadecylmercaptan (2.81 g of 92% purity, ca. 10 mmol) and triethylamine (1.41 g, 14 mmol) in 25 mL of THF was added ethyl α-(bromomethyl)acrylate (1.93 g, 10 mmol). After the reaction mixture was stirred for 24 h at rt, thiomethylacrylate **4** was extracted with hexane, and the product was purified by silica gel column chromatography (elution with petroleum ether), affording 3.33 g (90%) of **4**.
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10. Propanediol **6** (4.41 g, 50 mmol) and dibutyltin oxide (13.7 g, 55 mmol) were refluxed in chloroform/methanol (25 mL, 10:1 v/v) for 24 h to obtain a clear solution. The solvents were evaporated under reduced pressure to give the stannoxane derivative as a white solid. Cesium fluoride (14.5 g, 95 mmol) was added, and the mixture was dried under high vacuum overnight. To this reaction mixture DMF (25 mL) and 1-bromohexadecane (16.8 g, 55 mmol) were added, and the reaction mixture was stirred for 24 h at rt. After 24 h the reaction mixture was heated at 50 °C for 1 h. Silica gel chromatography (elution with hexane/EtOAc 4:1) afforded 3-hexadecyloxy-2-methylene-1-propanol (**7**) in 86% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.88 (t, 3H, J = 6.3 Hz), 1.25 (s, 26H), 1.58 (t, 2H, J = 7.1 Hz), 2.06 (t, 1H, J = 5.5 Hz), 3.43 (t, 2H, J = 6.5 Hz), 4.04 (s, 2H), 4.18 (d, 2H, J = 5.7 Hz), 5.14 (d, 2H, J = 9.3 Hz).
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12. Compound **8**: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.88 (t, 3H, J = 6.3 Hz), 1.25 (s, 26H), 1.56 (m, 2H), 3.33 (s, 3H), 3.41 (t, 2H, J = 6.4 Hz), 3.93 (s, 2H), 3.96 (s, 2H), 5.16 (s, 2H); MS: m/z 326 (M^+).
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14. Compound **9**: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.88 (t, 3H, J = 6.3 Hz), 1.25 (s, 26H), 1.55 (t, 3H, J = 7.8 Hz), 2.04-2.15 (m, 1H), 3.34 (s, 3H), 3.41-3.60 (m, 6H), 3.70 (d, 2H, J = 4.9 Hz); MS: m/z 344.
15. The %ee was determined by chiral HPLC (Pirkle type IA column, 4.6 x 250 mm, J.T. Baker) of the crude (*R*)-(+)-MTPA ester derived from (*R*)-**9** (R_t 39.62 and 41.21 min, elution with hexane/2-propanol 99:1, flow rate 0.3 mL/min).
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18. Compound **2**: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.88 (t, 3H, J = 6.3 Hz), 1.25 (s, 26H), 1.51 (br s, 2H), 2.10-2.23 (m, 1H), 3.22 (s, 9H), 3.32 (s, 3H), 3.44-3.61 (m, 4H), 3.61 (s, 2H), 3.88-3.93 (m, 4H), 4.31 (br, s, 2H); HRMS (FAB, MH^+) m/z Calcd for $C_{26}H_{57}O_6NP$: 510.39027. Found: 510.3903. The observed rotations of **2** and **9** were nearly zero in $CHCl_3$ and C_6H_6 (*c* 5.0).
19. The (*R*)-(+)-MTPA ester derived from (*S*)-**9** gave R_t 40.56 and 42.52 min under the same HPLC conditions as given in ref. 15.

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