Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 3, pp. 837-842, 1996

0957-4166/96 $15.00 + 0.00

S0957-4166(96)00081-X

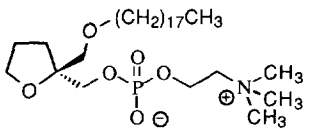
An Enantioselective Construction of a Tetrahydrofuran Synthon via an Epoxy Alcohol: Synthesis of *S*-Enantiomer of SRI 62-834

Kapa Prasad,* William J. Houlihan, Chung-Pin Chen, Russell L. Underwood, and Oljan Repic

Chemical Research and Development, Technical R&D,
Sandoz Research Institute, Sandoz Pharmaceuticals Corporation,
59 Route 10, East Hanover, NJ 07936, USA.

Abstract: A practical synthesis of tetrahydrofuran **7** is reported utilizing the Sharpless epoxidation as the key enantioselective step.

Phospholipid **1** (*S*-enantiomer of SRI 62-834), a potential antitumor agent, was first synthesized[1] by a route which used a porcine pancreatic lipase catalyzed desymmetrization of the prochiral dibutyrate ester of tetrahyrofuran-2,2-dimethanol as the key step. The second synthesis[2] of **1** involved an desymmetrization of the prochiral tetrahydrofuran-2,2-dimethanol with *l*-menthone, utilizing the enantiodifferentiating functionalization methodology developed by Oku and co-workers.[3] In this report, we describe another synthesis of **1** based on the retrosynthetic analysis shown in Scheme 1. This strategy incorporates the construction of the tetrahydrofuran[4] from an epoxy alcohol as the key step, summarized in Scheme 2.

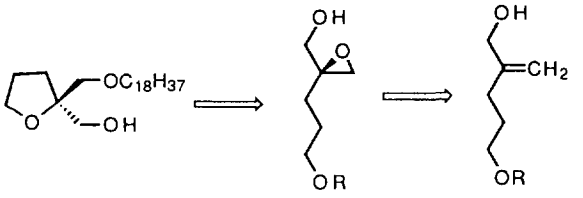


1

The first step of the synthesis required protection of 3-chloropropanol. We considered benzyl, tetrahydropyranyl and acetal groups for the hydroxyl protection, but from a large-scale perspective, we settled on the acetal protecting group because of the simplicity and ease of its introduction and removal. Intitially, the

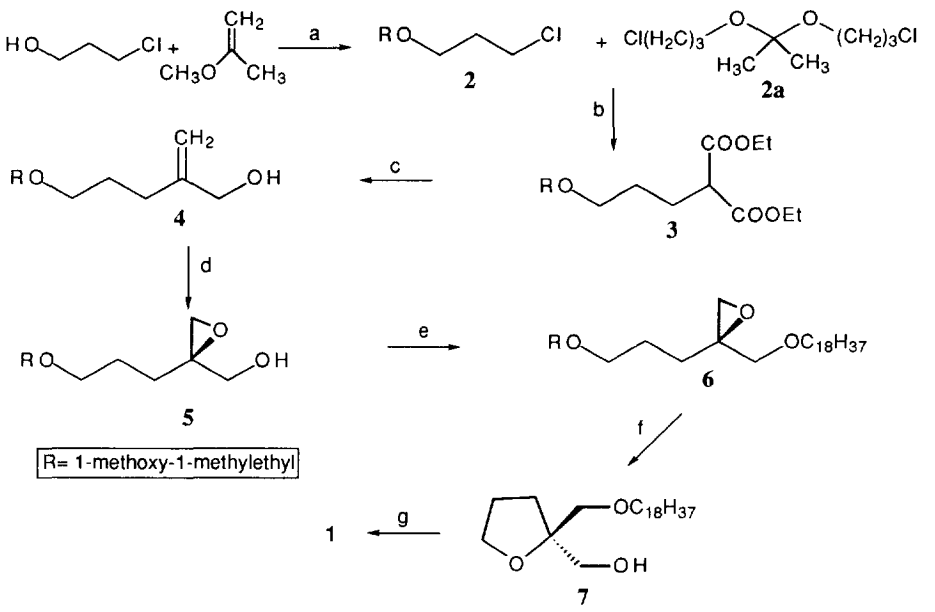
condensation of chloropropanol with 2-methoxypropene became problematic as HCl present in the starting material catalyzed polymerization. This was solved by neutralizing the acid impurity with $NaHCO_3$ just before use. The yield of the desired **2** and the ratio of the dimeric byproduct **2a** was found to be dependent upon the

Scheme 1



reaction temperature. The preferred reaction temperature was found to be between −60 to −65 °C. Under these conditions, the reaction was optimal with only approximately 2% of the dimer **2a** present.

Scheme 2



(a) 2-Methoxypropene, PPTS; (b) diethyl malonate, NaOEt, EtOH; (c) toluene, NaH, Red-Al®; (d) diethyl D-tartrate, titanium(IV) isopropoxide, t-butyl hydroperoxide; (e) THF, NaH, 1-bromooctadecane, tetrabutylammonium bromide; (f) MeOH, PPTS; (g) $POCl_3$, Et_3N, CH_2Cl_2; DMAP, pyridine, choline tosylate

With **2** in hand, the next task was the formation of the diethyl ester **3**. This reaction involved sodium iodide catalyzed coupling of the chloro compound **2** with diethyl malonate in presence of sodium ethoxide. The purity and yield of the resulting **3** was found to be dependent upon the stoichiometry of sodium iodide used; the optimum amount was approximately 15-20 mol percent. Formation of the allylic alcohol **4** was based on the work of Marshall.[5] The reaction occurs in two parts, the first being the formation of the enolate, followed by the reduction to the allylic alcohol. Considering the complexity involved in converting the diethyl ester to an allylic alcohol, a yield of 40% was considered satisfactory. A side product from the reduction was found to be the corresponding saturated compound.

The key step for introducing asymmetry in this synthesis is the Sharpless asymmetric epoxidation.[6] Using standard epoxidation conditions (diethyl D-tartrate/titanium(IV) isopropoxide and *t*-butyl hydroperoxide), one obtains a 80-85% yield of the desired epoxide with an enantiomeric excess of 93%. The alkylation of the epoxy alcohol **5** with 1-bromooctadecane under phase transfer conditions gave the octadecyl ether **6** in 55% yield. The next step involved a two-step, one-pot conversion of the octadecyl ether **6** to the cyclized product **7**. This was achieved by using pyridinium *p*-toluenesulfonate/methanol.

Although we purified each intermediate for characterization purposes, it was advantageous to postpone the purification as this was easily accomplished at this stage by chromatography on silica gel. After chromatography, the optical purity of **7** was enriched to >99% by crystallization from hexane using enantiopure seed crystals, as described in our earlier communication.[1] In addition, the absolute stereochemistry of **7** was established in that report. As **7** has already been used in making **1**, this constitutes yet another but probably the most efficient synthesis of the desired phospholipid.

EXPERIMENTAL SECTION

The enantiomeric purity of alcohols **5** and **7** was determined by ^{31}P NMR using a diazaphospholidine described in the literature.[7] Commercially available compounds from Aldrich were used in this work .

1-Chloro-3-(1-methoxy-1-methylethoxy)-propane (2). To a precooled solution (-60 to -65 ^{o}C) of 2-methoxypropene (288.4 g, 4 mol) and pyridinium p-toluenesulfonate (0.502 g) under nitrogen was added slowly over a period of 1 h 3-chloro-1-propanol (189.0 g, 2 mol, freshly treated with $NaHCO_3$).

The reaction mixture was stirred at −60 to −65 °C (internal temperature) for approximately 1 h and warmed to 0 °C. To the reactor was added a mixture of 0.025 L of saturated aq. sodium bicarbonate solution and 0.425 L of saturated aq. sodium chloride solution. The organic layer was separated and concentrated *in vacuo* (40 mm) at 40 °C to give a clear light oil. The light oil was dried at rt under high vacuum (1-2 mm) for 3 h to give 331 g (97%) of **2:** ^{1}H NMR ($CDCl_3$) δ 1.34 (6H, s), 2.00 (2H, m), 3.12 (3H, s), 3.53 (2H, t, J = 6), 3.65 (2H, t, J = 6.4); IR (neat) 2994, 1186, 1214, 1078, 1054 cm^{-1}; MS (DCI/NH_3) *m/z* 135/137 (MH^+-OCH_3).

3-(1-Methoxy-1-methylethoxy)propyl-1,3-propanedioic acid diethyl ester (3). A stirred solution of diethyl malonate (35.17 g, 0.22 mol), sodium ethoxide (14.89 g, 0.22 mol) in anhydrous EtOH (715 mL) was heated at 80 °C for 1 h and then treated with **2** (30.5 g, 0.18 mol) over 15 min followed by the addition of sodium iodide (4.11 g, 0.027 mol). After an additional 10 h at 80 °C, the mixture was allowed to come to room temperature and was then treated with water (60 mL). The mixture was extracted with heptane (2 times 150 mL), and the combined organic extracts were concentrated *in vacuo* (40 °C); the resultant oil was purified on silica gel chromatography using heptane/EtOAc (2:1) to give 46.5 g (89%) of **3** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.27 (6H, t, J = 6), 1.33 (6H, s), 1.50-1.64 (2H, m), 1.90-2.04 (2H, m), 3.19 (3H, s), 3.35-3.44 (2H, m), 3.66 (1H, t, J = 6), 4.20 (4H, m); ^{13}C NMR ($CDCl_3$) δ 14.0, 24.4, 25.8, 27.7, 48.4, 51.8, 59.9, 61.2, 99.8, 169.4; IR (neat) 1751, 1734 cm^{-1}; MS (DCI/NH_3) *m/z* 201 (M^+-$C_4H_9O_2$).

5-(1-Methoxy-1-methylethoxy)-2-methylene-1-pentanol (4). A stirred suspension of sodium hydride (60% in mineral oil; 13.8 g, 0.17 mol of NaH) in anhydrous toluene (85 mL) under N_2 was heated to 87 °C, treated with **3** (26.13 g, 0.09 mol) over 40 min and then heated to 110 °C for 3 h. The resultant suspension was cooled to 85 °C and then treated with sodium bis(2-methoxyethoxy)aluminum hydride in toluene (Red-Al®, 52 mL of 3.4 M, 0.18 mol) at such a rate that the temperature was maintained at 85 - 90 °C. After an additional 1 h at 90 °C, the mixture was cooled to 5 °C, treated dropwise with 1 M NaOH (60 mL), stirred for 18 h at room temperature and treated with heptane (50 mL). The aqueous layer was separated, extracted with heptane (2 times 50 mL), and the combined organic layers were washed with 1 M NaOH (50 mL) and a mixture of saturated $NaHCO_3$/NaCl solutions (5 mL and 45 mL). The organic layer was separated, concentrated *in vacuo*, and the resultant oil was distilled under high vacuum (0.1 mm, 85-92 °C) to give 6.78 g (40%) of **4** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.32 (6H, s), 1.65-1.80 (2H, m), 1.84 (1H, br), 2.18 (2H, t, J = 7), 3.19 (3H, s), 3.40 (2H, t, J = 6), 4.08 (2H, s), 4.90 (1H, s), 5.15 (1H, s); ^{13}C NMR ($CDCl_3$) δ

24.4, 28.1, 29.7, 48.4, 60.3, 65.9, 99.9, 109.5, 148.6; IR (KBr) 3434 cm^{-1}; MS (DCI/NH_3) *m/z* 173.8 (M^+-OCH_3+NH_3).

***R*-2-[3-(1-Methoxy-1-methylethoxy)]propyloxiranemethanol (5).** A mixture of diethyl D-tartrate (29.4 g, 0.142 mol), powdered molecular sieves (4 Å, 30 g) and titanium(IV) isopropoxide (32.2 mL, 30.13 g, 0.106 mol) in anhydrous CH_2Cl_2 (1.2 L) under N_2 was stirred for 1 h at 0 °C, cooled to -20 °C and treated with *t*-butyl hydroperoxide in isooctane (5.5 M, 130 mL, 0.715 mol). The mixture was stirred for 1 h, treated with a solution of **4** (67 g, 0.356 mol) in CH_2Cl_2 (100 mL) over a 1 h period, stirred an additional 4.5 h at -20 °C, and then 5 N NaOH (300 mL) was added while maintaining the temperature at -20 °C. The suspension was stirred at room temperature for 16 h and filtered through Celite. The white paste remaining on the Celite was washed with CH_2Cl_2 (500 mL), and the combined organic layers were concentrated *in vacuo* to give **5** (35.4 g, 85%, ee 93%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.35 (6H, s), 1.50-2.04 (5H, m), 2.74 (1H, d, *J* = 6), 2.92 (1H, d, *J* = 6), 3.22 (3H, s), 3.43 (2H, t, *J* = 6.5), 3.60-3.90 (2H, m); ^{13}C NMR ($CDCl_3$) δ 24.5, 25.2, 28.9, 48.6, 50.0, 59.7, 60.4, 63.2, 99.9; IR (KBr) 3450 cm^{-1}; MS (DCI/NH_3) *m/z* 190 (M^+-OCH_3+NH_3), 173 (M^+-OCH_3). Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.97. Found: C, 58.80; H, 10.07.

***R*-2-[3-(1-Methoxy-1-methylethoxy)]propyl-2-[(octadecyloxy)methyl]oxirane (6).** A stirred solution of **5** (25.5 g, 0.125 mol) in anhydrous THF (250 mL) under N_2, cooled to 0 °C, was treated portionwise with sodium hydride (60% mineral oil, 10 g, 0.125 mol of NaH) and then stirred for an additional 0.5 h at 0 °C and 1 h at room temperature. The suspension was treated successively with 1-bromooctadecane (54.1 g, 0.163 mol) and tetrabutylammonium iodide (13.1 g, 0.0375 mol), heated at 45 °C for 4 h, cooled to 0 °C, treated dropwise with water (200 mL) and then extracted with two 250-mL portions of hexane. The combined organic layers were washed with brine (500 mL) and then concentrated *in vacuo* to an oil. The crude product was chromatographed on silica gel using hexane/ethyl acetate (2:1) to give 31.4 g (55%) of **6**. ^1H NMR ($CDCl_3$) δ 0.89 (3H, t, *J* = 6), 1.20-1.40 (30H, m), 1.33 (6H, s), 1.50-1.80 (6H, m), 2.64 (1H, d, *J* = 6), 2.66 (1H, d, *J* = 6), 3.20 (3H, s), 3.36-3.52 (6H, m), 3.56 (1H, d, *J* = 10); 1.35 (6H, s), 1.50-2.04 (5H, m), 2.74 (1H, d, *J* = 6), 2.92 (1H, d, *J* = 6), 3.22 (3H, s), 3.43 (2H, t, *J* = 6.5), 3.60-3.90 (2H, m); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 24.5, 25.0, 25.2, 26.1, 28.8, 29.4, 29.5, 29.7, 31.9, 48.3, 48.4, 50.2, 58.4, 60.5, 71.7, 72.7, 99.8; MS (DCI/NH_3) *m/z* 442 (M^+-OCH_3+NH_3), 425 (M^+-OCH_3). Anal. Calcd for $C_{28}H_{56}O_4$: C, 73.63; H, 12.36. Found: C, 73.26; H, 12.50.

***R*-2-Hydroxymethyl-2-octadecyloxymethyltetrahydrofuran (7).** A mixture of **6** (29.3 g, 0.0625 mol) and pyridinium p-toluenesulfonate (0.251 g, 0.001 mol) in 110 mL of methanol was stirred at room temperature for 18 h and concentrated in vacuo; the residue was chromatographed on SiO_2 using hexane/EtOAc (3:1), and the product was crystallized from hexane at −15 °C with the aid of optically pure seed crystals to give **7** (16.9 g, 55%, *ee* >99%) as a white solid: mp 36-37 °C; $[\alpha]_{378}$ +4.38 (c = 1.1 MeOH); identical in all respects with the compound reported by us earlier.[1]

Acknowledgment. We thank Professor K.B. Sharpless for useful discussions and Drs. M. Shapiro and E. Fu and their co-workers for spectroscopic measurements.

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(*Received in USA* 11 *January* 1996)