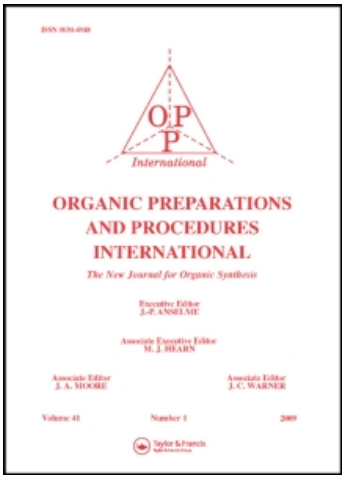


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

KILOGRAM-SCALE SYNTHESIS OF *bis*(6-HYDROXY-5,5-DIMETHYLHEXYL)ETHER (ESP24232), A NOVEL LIPID LOWERING AGENT

Jing Yang[a]; Ralf Mueller[a]; Emil Pop[a]; Jean-Louis H. Dasseux[b]; Daniela C. Oniciu[b]
[a] Alchem Laboratories Corporation, Alachua, FL [b] a Division of Pfizer Global Research and Development, Esperion Therapeutics, Ann Arbor, MI

To cite this Article Yang, Jing , Mueller, Ralf , Pop, Emil , Dasseux, Jean-Louis H. and Oniciu, Daniela C.(2004) 'KILOGRAM-SCALE SYNTHESIS OF *bis*(6-HYDROXY-5,5-DIMETHYLHEXYL)ETHER (ESP24232), A NOVEL LIPID LOWERING AGENT', Organic Preparations and Procedures International, 36: 6, 587 — 596
To link to this Article: DOI: 10.1080/00304940409355976
URL: http://dx.doi.org/10.1080/00304940409355976

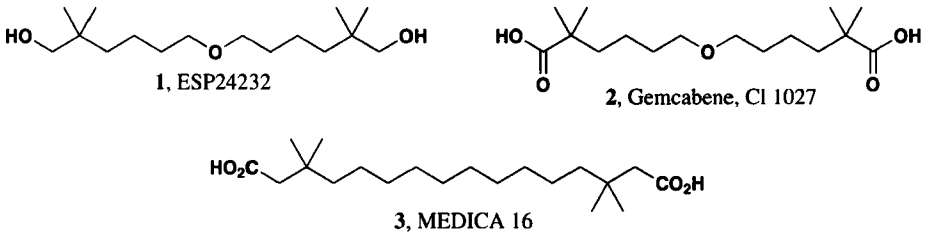
ORGANIC PREPARATIONS AND PROCEDURES INT., 36 (6), 587-596 (2004)

KILOGRAM-SCALE SYNTHESIS OF *bis*(6-HYDROXY-5,5-DIMETHYLHEXYL)ETHER (ESP24232), A NOVEL LIPID LOWERING AGENT

Jing Yang,[†] Ralf Mueller,[†] Emil Pop,[†] Jean-Louis H. Dasseux,[††] and Daniela C. Oniciu*,[††]

[†]*Alchem Laboratories Corporation, 13305 Rachael Boulevard, Alachua, FL 32615*
[††]*Esperion Therapeutics, a Division of Pfizer Global Research and Development*
3621 South State Street, 695 KMS Place, Ann Arbor, MI 48108
e-mail: Daniela.Oniciu@pfizer.com

As part of our continuous efforts to identify small molecules with lipid-lowering properties, we have synthesized and evaluated a variety of ether-diols with *gem* dimethyl- or *gem* methyl-/phenyl-substitution patterns.[1,2] Of these compounds, *bis*(6-hydroxy-5,5-dimethylhexyl)ether (**1**, ESP24232 *Fig. 1*) showed the most promise. Kilogram quantities of **1**



1, ESP24232

2, Gemcabene, CI 1027

3, MEDICA 16

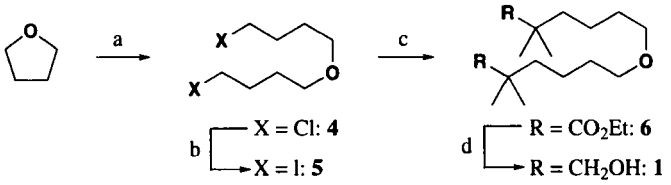
Chemical Structures of ESP24232 and of Related Lipid-lowering Molecules

Fig. 1

were thus required for further biological studies and potential clinical trials. Structures similar to **1**, such as the diacids **2**[3,4] and **3**,[5] are known and have also been tested with success for their cholesterol-lowering effects. In this work, the development of the synthesis of **1** from bench-scale to kilogram-scale is described. Special emphasis was placed on the avoidance of toxic and hazardous solvents and reagents, the reproducibility of the synthetic sequence, the removal and identification of the impurities in the final product and the potential for further scale-up.

In preliminary attempts, the synthesis of **1** (*Scheme 1*)[1,2] began from the now commercially available[6] 4,4'-dichlorobutyl ether (**4**),[7] initially prepared by treatment of THF with phos-

phorus oxychloride and concentrated sulfuric acid. Substitution of chloride in **4** by iodide led to diiodobutyl ether **5**,[8] which was further reacted with lithio ethyl isobutyrate in THF/HMPA to generate **6**.[3] Subsequent reduction of the ester groups with lithium aluminum hydride provided **1**.

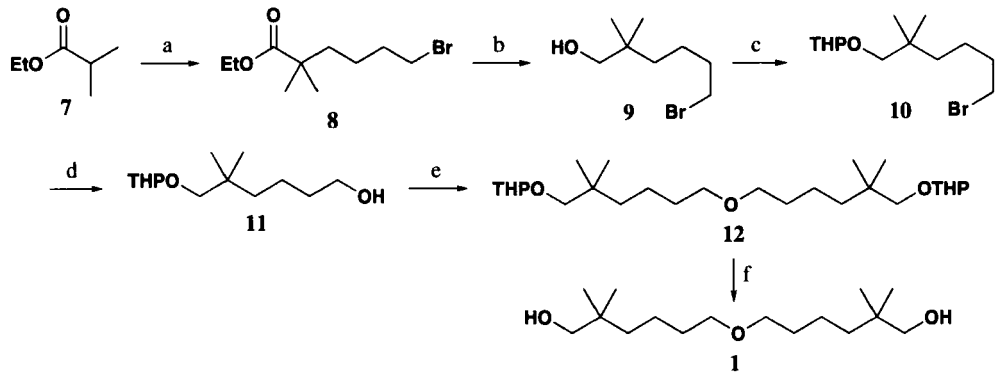


a) $POCl_3$, H_2SO_4, 56%; b) NaI, [acetone], 80%; c) ethyl isobutyrate, LDA, [THF/HMPA]; d) lithium aluminum hydride, [Et_2O], 85% over two steps.

Scheme 1

While this method included only four steps and proceeded in good overall yield (38%), it was abandoned because the impurity profile of the final product was not reproducible, and the required purity of > 98% determined by HPLC could not be obtained consistently. Different approaches to solve this problem were thus sought.

The Williamson reaction is the most commonly used method for the construction of the ether linkage.[9] Accordingly, the synthesis of **1** from two appropriately protected building blocks (**10** and **11**) was envisioned (*Scheme 2*).



Bench-scale method: a) LDA, 1,4-dibromobutane, [THF/HMPA], 70%; b) DIBAL-H, [benzene], 82%; c) 3,4-dihydro-2*H*-pyran, *p*TsOH, [CH_2Cl_2], 97%; d) K_2CO_3, [DMSO/water], 85%; e) NaH, **10**, [THF]; f) aqueous HCl, [MeOH], 42% over two steps.
Kilogram-scale method: a) LDA, 1,4-dibromobutane, [THF/DMPU], 64%; b) lithium borohydride/methanol, [CH_2Cl_2]; c) 3,4-dihydro-2*H*-pyran, *p*TsOH, [CH_2Cl_2]; d) K_2CO_3, [DMSO/water]; e) NaH, **10**, [THF]; f) aqueous HCl, [MeOH], 42% over two steps.

Synthesis of *bis*(6-Hydroxy-5,5-dimethylhexyl) ether (**1**)

Scheme 2

In the first bench-scale runs,[1,2] ethyl isobutyrate (**7**) was deprotonated with lithium diisopropylamide (LDA) solution in THF at –78°C and reacted with 1,4-dibromobutane in the presence of HMPA as co-solvent to give bromoester **8** in 70% yield after distillation.[10] Selective reduction of the ester group in **8** with diisobutylaluminum hydride (DIBAL-H, 1 M in hexanes)

in benzene solution at 50-60°C furnished bromo alcohol **9** (82%),[11] which was subsequently protected with 3,4-dihydro-2*H*-pyran in the presence of catalytic amounts of *p*-toluenesulfonic acid in dichloromethane to afford THP-ether **10** (97%).[11] Hydrolysis of **10** with K_2CO_3 in a refluxing mixture of DMSO and water[12] gave alcohol **11** (85%), concluding the synthesis of both building blocks required for the Williamson reaction. Initial attempts to condense **10** with **11** using various metal/solvent systems at room temperature or reflux with or without addition of crown ethers were unsuccessful. The conversion to protected ether **12** was finally achieved with sodium hydride (3 equiv) in THF. Deprotection of crude **12** with 1 M HCl in acetone for 3 days at room temperature provided **1**, which was purified by column chromatography (42% yield over both steps).

While the sequence above worked sufficiently well on small scale and provided the target compound in six steps in 20% overall yield, some of the steps were not feasible for scale-up to a 100-L glass reactor. Therefore, several alkylation attempts of **7** with 1,4-dibromobutane and LDA were conducted: the co-solvent HMPA (toxic and suspected carcinogen) was replaced with dimethylpropyleneurea (DMPU)[13] in THF at different concentrations (0-40% v/v); reaction temperatures were varied (–70 to –10°C) and different starting material concentrations and ratios were studied at different scales (concentration of **7** in THF from 0.025 M to 5.25 M; ratio **7**/1,4-dibromobutane/LDA = 100/130/100 or 105/140/100; scale from 7.5 mmol to 1.25 mol of **7**). The best results in these alkylation studies were obtained when **7** (1.05 equiv) was reacted with LDA (1 equiv) at –40°C, followed by addition of 1,4-dibromobutane (1.4 equiv) and DMPU (11% v/v), and warming to 20-25°C (65% yield, 99% pure by GC after distillation).[11,14] In the reduction of **8** to **9**, our main concern was to substitute benzene with a non-carcinogenic, preferably non-flammable solvent and to make the reaction more volume-efficient. Although 1.5 M solutions of DIBAL-H in toluene are available, this reagent supplies only 1 mol hydride/mol reagent. Reductions with lithium aluminum hydride or sodium borohydride on the other hand were not chemoselective and reproducible.[15] The same result was obtained when trimethyl borate was used as a catalyst.[16] We then evaluated the suitability of lithium borohydride[17] for the reduction of **8**. Since reactions performed in CH_2Cl_2 or THF at room temperature were too slow, the reduction in THF solution was carried out at reflux; however, significant amounts of side-products were produced, most likely due to substitution of the bromine. However, addition of methanol (1 equiv) to $LiBH_4$ (150 mol%) in diethyl ether at reflux temperature led to a rapid and selective reduction of **8** to **9**.[18] The highly flammable Et_2O could be safely replaced with CH_2Cl_2, furnishing **9** in high yield (95%) and purity (over 90%) without the need for further purification. The THP-protection to **10** with 3,4-dihydro-2*H*-pyran in the presence of *p*-toluenesulfonic acid gave good yields of product of acceptable purity in small scale experiments. Similarly, the ensuing hydrolysis of bromide **10** to alcohol **11** was performed with good yield and sufficient purity under the same conditions as described for preliminary small scale experiments (reaction with 2 equiv K_2CO_3 in a DMSO/water mixture at reflux). The last two steps of the synthesis were investigated further.

The excess of sodium hydride (introduced as a 60% w/w dispersion with mineral oil) used in the Williamson reaction was reduced from three to two equivalents without having an effect on the yield. A smaller excess, however, led to incomplete formation of **12**. Since mineral oil from the NaH dispersion contaminated the final product due to co-distillation, it was decided to use dry NaH (95%) in this reaction. The removal of the THP groups in **12** was accomplished with 1 M HCl in refluxing methanol instead of HCl in acetone at room temperature as originally performed. This change led to a shorter reaction time with fewer side-reactions. Finally, desired compound **1** was produced in 46% yield and 98% purity (GC) by reaction of **10** (1 equiv) and **11** (1 equiv) with NaH (2 equiv) in THF for 10 h at reflux and 17 h at 20-25°C, followed by deprotection with aqueous HCl in refluxing methanol (2 days) and purification by distillation. Although all intermediates in *Scheme 2* are liquids, only the first one (**8**) as well as the final product ESP24232 (**1**) required purification by distillation. The purities of all the other intermediates were suitable for their use in the synthesis and the yields obtained were satisfactory. Therefore, the procedure was considered adequate for transfer to larger scale.

Table 1 gives an overview of the scale-up study of three 1 kg batches of ESP24232 (**1**). The yields and purity results for the alkylation step to **8** varied little and were quite consistent: purities ranged from 95.7% to 98.7% (GC) and yields from 63.4% to 65%. Since distillation fractions with purities >95% (GC) were retained and combined, the slight deviations both in purity and yield of this experiment are explainable by different choices made during the distillation process. In one experiment, the amount of co-solvent DMPU was reduced by ca. 25% compared to the previous five runs without having a substantial influence on yield or purity.

Table 1. Overview of Scale-up Campaign of ESP24232 (**1**)

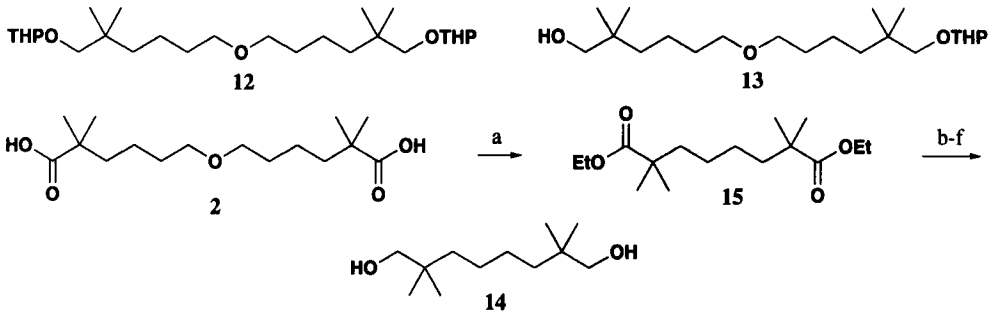
Conversion	No. of runs	Wt. SM (kg)	Wt. P (kg)	Purity (%)	Yield (%)
7 → **8**	6	2.6- 2.8	3.5 – 3.8	95.7-98.7[a]	63.4-65
8 → **9**	3	7.3-7.5	6.2-6.3	92.4-97.7[a]	101.9-106[c]
9 → **10**	3	5.1-6.3	7.9-9.9	93-94.9[a]	101.9-121.5[c]
10 → **11**	3	4.3-5.1	3.1-3.3	80.4-96.7[b]	89-99.9
11 → **12** → **1**	3	2.6-2.8	1.1-1.2	98.3-99.3[b]	40.5-43.2

a) Determined by GC-FID; b) determined by RP-HPLC; c) weight yield >100% caused by incompletely removed solvents from reaction or extraction; SM = starting material; P = product.

In the reduction step of **8** to bromo alcohol **9**, weight yields and purities varied by a greater margin (weight yields from 101.9% to 106%; purities from 92.4% to 97.7%). Since this compound is a viscous oil, the solvent (CH_2Cl_2) could not be completely removed[19] and calculated weight yields >100% were observed. However, as the reaction solvent in the next step was also CH_2Cl_2, additional solvent removal efforts seemed unnecessary. In one of the runs, the excess of $LiBH_4$ was reduced from 150 mol% to 134 mol%, but this change did not appear to affect the outcome. Complete removal of the solvent CH_2Cl_2 was not achieved in the synthesis of

10 either, because of the high viscosity of this oil.[19] In one of the three experiments, **10** was dried under high vacuum while stirring for 24 h in addition to the usual drying procedure,[19] but the reduced amount of residual CH_2Cl_2 had no apparent positive effect in the following steps. During the scale-up campaign, the most significant fluctuation in purities (80.4-96.7%) and yields (89-99.9%) was registered in the synthesis of alcohol **11**. More consistent results were again obtained in the final conversion of **11** via **12** to **1** (*Scheme 2, Table 1*). After the Williamson reaction, the crude intermediate **12** was directly deprotected with concd HCl in methanol to **1**, which was further purified by distillation (see Experimental Section for details). However, the product obtained in this manner still contained impurities **12** and **13** in the range of 5-7%. Therefore a second deprotection protocol employing the same conditions, concd HCl in refluxing methanol, was performed. After workup and additional fractional distillation *in vacuo*, kg-quantities of target compound **1** (ESP24232) having HPLC purities from 98.3 to 99.3% were obtained in yields ranging from 40.5 to 43.2% (over two steps). Moreover, the overall yield for the described six-step synthesis proved to be quite reproducible (19.4-20%).

Impurity profile of ESP24232 (1): The structures of the impurities **12**, **13**, and **14** present in the final product **1** in amounts ranging from 0.2 to 0.6% are displayed in *Scheme 3* (see Experimental Section for characteristic data). These impurities were isolated from fractions obtained during distillation of the final product.



a) LDA, 1,4-dibromobutane, [THF/DMPU]; b)-f) as in *Scheme 2*.

Impurities detected in the final product **1**

Scheme 3

Impurity **13** resulted from incomplete deprotection of intermediate **12**, while impurity **14**[20] was generated from diester by-product **15** formed in the first step of the sequence. Their presence in the final product has increased somewhat with the increase in batch size. The content of impurities **12** and **13** was reduced significantly by repetition of the deprotection process to **1** and by appropriate column characteristics and reflux ratio at the distillation stage (see Experimental Section).

In conclusion a laboratory synthesis for the potential cardiovascular agent *bis*(6-hydroxy-5,5-dimethylhexyl)ether (ESP24232, **1**) was scaled up to kilogram level. The main goal of the developmental work was to optimize the existing procedure for large-scale production. For

this purpose, toxic and hazardous conditions as well as parameters difficult to reproduce were eliminated as much as possible. The quantity of solvents was reduced for more efficient use of the capacity of the equipment and better waste management. Furthermore, side-reactions were reduced and the number and amount of impurities in the active pharmaceutical ingredient decreased accordingly. The structures of these impurities were determined and procedures for their synthesis were developed. In addition, analytical procedures for in-process monitoring and quality control methods for intermediates and final product were established. Most importantly, the developed manufacturing procedure proved to be reproducible in three parallel batches in terms of yield and quality of the final product.

EXPERIMENTAL SECTION

Chemical reagents were purchased from Sigma-Aldrich or Lancaster and were used without further purification. ACS grade solvents from Fisher Scientific or Mallinckrodt were routinely used for chromatographic purifications and extractions. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz and ambient temperature on Varian NMR spectrometers. Chemical shifts for proton NMR are given in parts per million downfield from an internal tetramethylsilane standard and ^{13}C chemical shifts are calibrated on the $CDCl_3$ resonance at 77.23 ppm, unless otherwise specified. Coupling constants (*J*) are given in Hz. The purity of target compounds was analyzed by HPLC using Shimadzu HPLC systems combined with UV and/or RI detection.

Ethyl 6-bromo-2,2-dimethylhexanoate (8).- In a 100 L glass reactor, a solution of ethyl isobutyrate (**7**, 3230 mL, 24.2 mol) and THF (5.3 L) was cooled to –38°C with stirring and Ar atmosphere. A solution of lithium diisopropylamide (2 M in THF/heptane, 11.5 L, 23 mol) was added dropwise over 135 min, while maintaining the temperature between –45 and –35°C. After 1 h, 1,4-dibromobutane (4020 mL, 33.7 mol) was added dropwise over 20 min, followed directly by addition of DMPU (420 mL, 3.5 mol) over 2 h, adjusting the addition rates in such a way as to keep the internal reactor temperature between –45 and –35°C. The reaction mixture was stirred for 1 h with cooling and then allowed to slowly warm to room temperature over the next 15 h. The mixture was hydrolyzed with saturated NH_4Cl solution (8.5 L) and water (5 L) and the layers were separated. The aqueous phase was extracted with ethyl acetate (2.2 L). The organic solutions were combined and washed with saturated NaCl solution (7.5 L), aqueous 1 N HCl solution (3.8 L), saturated $NaHCO_3$ solution (7.5 L), and saturated NaCl solution (2.5 L). The organic layer was dried over anhydrous $MgSO_4$ (550 g) and concentrated under reduced pressure. The residue (8178 g) was distilled in vacuum (bp 72-75°C/0.4-0.6 mmHg; *lit.*[11] 86°C/0.2 mmHg) to give **8** (3700 g, 97.5% pure by GC, 64.1% yield) as an oil. ^{1}H NMR ($CDCl_3$): δ 4.13 (q, 2 H, *J* = 7.1 Hz), 3.40 (t, 2 H, *J* = 6.8 Hz), 1.85 (m, 2 H), 1.60-1.45 (m, 2 H), 1.40-1.30 (m, 2 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.20 (s, 6 H). ^{13}C NMR ($CDCl_3$): δ 177.3, 60, 41.8, 39.4, 33.2, 32.9, 24.9, 23.3, 14. GC: 97.5% pure.

Anal. Calcd for $C_{10}H_{19}BrO_2$: C, 47.82; H, 7.62. Found: C, 48.12; H, 7.63

6-Bromo-2,2-dimethylhexanol (9).- A 100 L glass reactor was charged with dichloromethane (44 L) and lithium borohydride (95%, 984 g, 42.9 mol) under Ar atmosphere at room temperature. Methanol (1377 g, 43 mol) was added dropwise over 4 h 50 min with stirring, at a rate that maintained the temperature in the vessel below 28-32°C. A solution of **8** (98.1%, 7318 g, 28.6 mol) in dichloromethane (2.2 L) was added over 3 h 25 min at a rate that maintained a gentle reflux. The mixture was heated to reflux for 15 h, cooled to 0°C, and carefully hydrolyzed by addition of crushed ice (8 kg). Cold, saturated NH_4Cl solution (8.8 L) was added slowly and the mixture was stirred until the effervescence ceased. Water (16 L) was added, the layers were separated, and the aqueous layer was extracted with dichloromethane (2 x 6.6 L). The organic layers were combined and washed with saturated NH_4Cl solution (2 x 6.6 L) and saturated NaCl solution (6.6 L). The solution was dried over anhydrous $MgSO_4$ (1.1 kg) and concentrated under reduced pressure, affording **9**[11] (6338 g, 92.4% pure by GC, 106% weight yield) as an oil, which was used without further purification for the next step. ^1H NMR ($CDCl_3$): δ 3.43 (t, 2 H, J = 6.8 Hz), 3.33 (s, 2 H), 1.85 (m, 2 H), 1.61 (br, 1 H), 1.48-1.30 (m, 2 H), 1.28-1.22 (m, 2 H), 0.88 (s, 6 H). ^{13}C NMR ($CDCl_3$): δ 71.8, 37.7, 35.1, 34.1, 33.6, 23.9, 22.6.

2-(6-Bromo-2,2-dimethylhexyloxy)tetrahydropyran (10).- In a 100 L glass reactor, a solution of **9** (92.4%, 5973 g, 26.4 mol) and *p*-toluenesulfonic acid monohydrate (98.5%, 30.1 g, 158.0 mmol) in dichloromethane (36 L) was cooled to 1°C under stirring and Ar atmosphere. 3,4-Dihydro-2*H*-pyran (97%, 2885 g, 33.3 mol) was added dropwise over 4 h at a rate that maintained the temperature below 5°C. The mixture was stirred for 18 h and divided into three equal portions. Each portion was filtered through aluminum oxide (Brockmann Type I, activated, neutral, 3 kg each), which was washed with dichloromethane (2 L each). The combined organic filtrates were concentrated under reduced pressure and dried *in vacuo* (1-2 mmHg) for 24 h, affording **10**[11] (94.9% by GC, 7891 g, 101.9% weight yield) as an oil, which was used without further purification for the next step. ^1H NMR ($CDCl_3$): δ 4.55 (t, 1 H, J = 3.3 Hz), 3.84 (m, 1 H), 3.50 (m, 1 H), 3.47 (d, 1 H, J = 9 Hz), 3.42 (t, 2 H, J = 6.7 Hz), 2.99 (d, 1 H, J = 9 Hz), 1.88 (m, 2 H), 1.75-1.23 (m, 10 H), 0.91 (s, 3 H), 0.90 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 99.4, 76.6, 62.2, 38.6, 34.4, 34.2, 33.9, 30.9, 25.8, 24.8, 24.7, 22.9, 19.7.

5,5-Dimethyl-6-(tetrahydropyran-2-yloxy)hexan-1-ol (11).- To a 100 L glass reactor charged with a solution of **10** (94.9%, 4309 g, 14 mol) in DMSO (12.9 L), was added a solution of potassium carbonate (99.5%, 3856 g, 27.9 mol) in water (25.8 L). The mixture was heated to a gentle reflux for 48 h, cooled to room temperature, and diluted with water (14 L). The mixture was neutralized by addition of aqueous 5 M HCl (5.6 L) and extracted with dichloromethane (4 x 4.65 L). The combined organic solutions were washed with saturated NH_4Cl solution (3 x 4.65 L), dried over anhydrous $MgSO_4$ (465 g), and concentrated under reduced pressure to give **11** (88.2% by GC, 3222 g, 99.9% yield) as an oil, which was used without further purification for the next step. ^1H NMR ($CDCl_3$): δ 4.54 (t, 1 H, J = 3.9 Hz), 3.84 (m, 1 H), 3.62 (t, 2 H, J = 6.4 Hz), 3.50 (m, 1 H), 3.48 (d, 1 H, J = 9.1 Hz), 3 (d, 1 H, J = 9.1 Hz), 2.14 (s br, 1 H), 1.90-1.44

(m, 8 H), 1.40-1.22 (m, 4 H), 0.89 (s, 6 H). ^{13}C NMR ($CDCl_3$): δ 99.4, 76.5, 62.8, 62.2, 39, 34.3, 33.7, 30.8, 25.7, 24.7, 24.6, 20.1, 19.7.

Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38. Found: C, 67.65; H, 11.41

***bis*(6-Hydroxy-5,5-dimethylhexyl)ether (1) (ESP24232).**- A 100 L glass reactor was charged with anhydrous THF (25.7 L) under Ar atmosphere. After careful addition of sodium hydride (95%, 504 g, 19.95 mol), **11** (81.9%, 2801 g, 9.9 mol) was added under stirring over 1 h. The mixture was heated to reflux for 24 h and then cooled to room temperature. Bromide **10** (94.9%, 3056 g, 9.9 mol) was added over 20 min and the mixture was heated to reflux for 28 h. After cooling to room temperature, the mixture was hydrolyzed by addition of crushed ice (3 kg) and cold, saturated NH_4Cl solution (10 L). The mixture was extracted with ethyl acetate (9.9 L, then 2 x 3.3 L). The combined organic layers were washed with saturated NH_4Cl solution (3 x 6 L) and concentrated *in vacuo*. The residue (**12**, 5254 g) was dissolved in methanol (18.7 L) containing concentrated, aqueous HCl (1.87 L) and heated to reflux for 6 h. The mixture was cooled to room temperature and crushed ice (4.4 kg) was added. The pH of the solution was adjusted to 6.5 by addition of saturated $NaHCO_3$ solution (22 L). The phases were separated and the aqueous layer was extracted with ethyl acetate (12 L, then 2 x 6 L). The combined organic phases were washed with saturated NH_4Cl solution (4.7 L) and saturated NaCl solution (4.7 L), dried over anhydrous Na_2SO_4 (600 g), and concentrated *in vacuo* to give crude **1** (47.4% pure by GC, 3575 g). The crude material was divided into two portions (2084 g and 1491 g), which were distilled separately *in vacuo* (Vigreux column, 30 cm x 24 mm, vacuum-jacketed, heated to ca. 40°C; reflux ratio adjusted to ca. 8/1). The fractions distilling at 158-163°C/0.03-0.05 Torr and 151-167°C/0.1-0.3 Torr, respectively, were combined, affording **1** of higher purity (95.4% pure by GC, 1586 g). This material was dissolved in methanol (1 L) containing concentrated, aqueous HCl (100 mL) and heated to reflux for 3 h. The mixture was cooled to room temperature and crushed ice (1 kg) was added. The pH was adjusted to 7 by addition of saturated $NaHCO_3$ solution (600 mL). The mixture was extracted with ethyl acetate (3 x 1 L). The combined organic layers were washed with saturated NH_4Cl solution (2 x 1 L) and saturated NaCl solution (1 L), dried over anhydrous Na_2SO_4 (200 g), and concentrated *in vacuo*. The residue (1595 g) was divided into two portions (1000 g and 595 g), which were distilled separately *in vacuo* (Vigreux column, 30 cm x 24 mm, vacuum-jacketed, heated to ca. 40°C; reflux ratio adjusted to ca. 8/1). The fractions distilling at 150-160°C/0.03-0.1 Torr and 150-152°C/0.07-0.1 Torr, respectively, were combined, affording **1** (1130 g, 98.3% pure by HPLC, 41.6% yield) as a colorless, viscous oil. ^1H NMR ($CDCl_3$): δ 3.42 (t, J = 6.8 Hz, 4 H), 3.20 (s, 4 H), 2.80 (br s, 2H), 1.48 (quint, J = 6.8 Hz, 4 H), 1.10-1.30 (m, 8 H), 0.76 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 71.1, 70.6, 38.1, 34.8, 30.2, 23.8, 20.3. HRMS (FAB, POS, nba): Calcd for $C_{16}H_{35}O_3$ (MH^+): 275.2586; found: 275.2568. HPLC (Alltima C_8, 5 μ, 250 mm x 4.6 mm, acetonitrile/water = 58/42, flow rate 1 mL/min, RI detection, retention time 7.08 min): 98.3 % pure.

Anal. Calcd for $C_{16}H_{34}O_3$: C, 70.02; H, 12.49. Found: C, 69.73; H, 12.66

2-{6-[5,5-Dimethyl-6-(tetrahydropyran-2-yloxy)hexyloxy]-2,2-dimethylhexyloxy}tetrahydropyran (12) and 6-[5,5-Dimethyl-6-(tetrahydropyran-2-yloxy)hexyloxy]-2,2-dimethylhexan-1-ol (13).- Under N_2-atmosphere and at 0°C, to a solution of **1** (85.3 g, 0.31 mol) and *p*-toluenesulfonic acid monohydrate (0.35 g, 1.8 mmol) in CH_2Cl_2 (400 mL) was added dropwise 3,4-dihydro-2*H*-pyran (26.3 g, 0.31 mol) over 1.5 h. The reaction mixture was stirred at room temperature for 20 h and concentrated *in vacuo*. The residue was purified twice by column chromatography (silica; CH_2Cl_2/acetone = 95/5) to afford **12** (29 g, 21%) and **13** (35.7 g, 32%) as colorless oils. **12**: ^{1}H NMR ($CDCl_3$): δ 4.47 (t, 2 H, *J* = 3.3), 3.77 (m, 2 H), 3.44 (m, 2 H), 3.39 (d, 2 H, *J* = 9.1), 3.33 (t, 4 H, *J* = 6.6), 2.91 (d, 2 H, *J* = 9.1), 1.81-1.40 (m, 16 H), 1.30-1.19 (m, 8 H), 0.82 (s, 6 H), 0.81 (s, 6 H). ^{13}C NMR ($CDCl_3$ = 77 ppm): δ 99.03, 76.47, 70.87, 61.80, 39.14, 34.18, 30.62, 30.60, 25.53, 24.48, 24.41, 20.55, 19.37. HRMS (LSIMS, nba): Calcd for $C_{26}H_{49}O_5$ ($M-H^+$): 441.3567; found: 441.3610. HPLC: Alltima phenyl column, 250 x 4.6 mm, 5 μ; acetonitrile/water = 70/30, flow rate 1 mL/min; RI, retention time 7.40 min, 93.5% pure.

Anal. Calcd for $C_{26}H_{50}O_5$: C, 70.54; H, 11.38. Found: C, 70.80; H, 11.49

Compound **13**: ^{1}H NMR ($CDCl_3$): δ 4.53 (t, 1 H, *J* = 3.3), 3.88-3.78 (m, 1 H), 3.52-3.44 (m, 1 H), 3.45 (d, 1 H, *J* = 9.1), 3.41 (t, 2 H, *J* = 6.5), 3.39 (t, 2 H, *J* = 6.5), 3.30 (s br, 2 H), 2.99 (d, 1 H, *J* = 9.1), 1.90-1.40 (m, 12 H), 1.40-1.20 (m, 7 H), 0.89 (s, 3 H), 0.88 (s, 3 H), 0.84 (s, 6 H). ^{13}C NMR ($CDCl_3$ = 77 ppm): δ 98.48, 76.02, 70.94, 70.48, 70.38, 61.25, 38.84, 38.11, 34.65, 33.83, 30.24, 30.19, 25.22, 24.21, 24.17, 23.61, 20.22, 20.16, 18.92. HPLC: Alltima phenyl column, 250 x 4.6 mm, 5 μ; acetonitrile/water = 70/30, flow rate 1 mL/min; RI, retention time 5.05 min, 93.6% pure.

Anal. Calcd for $C_{21}H_{42}O_4$: C, 70.34; H, 11.81. Found: C, 70.32; H, 11.91

2,2,7,7-Tetramethyloctane-1,8-diol (14), mp 120-122°C, (*lit.*[20] 122°C). ^{1}H NMR ($CDCl_3$): δ 3.33 (s, 4 H), 1.45 (br, 2 H), 1.22 (m, 8 H), 0.85 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 72.18, 38.86, 35.23, 24.95, 24.08.

Acknowledgment.- We thank Mrs. Ping Yang Han, Mrs. Zhen Di Zhao, and Mr. Raymond C. Malloy of Alchem Laboratories Corporation for their contributions to this work.

REFERENCES

1. J.-L. H. Dasseux and D. C. Oniciu, US Patent 6,410,802, March 31, 2000; *Chem. Abstr.*, **136**, 309931u (2002).

2. J.-L. H. Dasseux and D. C. Oniciu, US Patent 6,459,003, March 31, 2000; *Chem. Abstr.*, **133**, 291122g (2000).

3. C. L. Bisgaier, P. L. Creger, A. R. Saltiel and S. R. Tafuri, US Patent 5,756,544, February 25, 1997; *Chem. Abstr.*, **125**, 328104r (1996).

4. H. E. Bays, J. M. McKenney, C. A. Dujovne, H. G. Schrott, M. J. Zema, J. Nyberg and D. E. MacDougall, *Am. J. Cardiol.*, **92**, 538 (2003).

5. J. Bar-Tana, WO 9900116 A2, 1999; *Chem. Abstr.*, **130**, 105306k (1999).

6. This compound has since become commercially available from various major chemical suppliers.

7. K. Alexander and L. E. Schniepp, *J. Am. Chem. Soc.*, **70**, 1839 (1948).

8. E. P. Taylor and *J. Chem. Soc.*, 142 (**1952**).

9. H. Feuer and J. Hooz, *The Chemistry of the Ether Linkage*. Ed. S. Patai, *Interscience Publishers*, New York, p 445 (1967).

10. P. W. Manley, D. P. Tuffin, N. M. Allanson, P. E. Buckle, N. Lad, S. M. F. Lai, D. O. Lunt, R. A. Porter and P. J. Wade, *J. Med. Chem.*, **30**, 1812 (1987).

11. N. Ackerley, A. G. Brewster, G. R. Brown, D. S. Clarke, A. J. Foubister, S. J. Griffin, J. A. Hudson, M. J. Smithers and P. R. O. Whittamore, *J. Med. Chem.*, **38**, 1608 (1995).

12. G. R. Treves and P. A. Cruickshank, *Chem. Ind.*, 544 (1971).

13. T. Mukhopadhyay and D. Seebach, *Helv. Chim. Acta*, **65**, 385 (1982).

14. According to M. Kuwahara, Y. Kawano, M. Kajino, Y. Ashida and A. Miyake, [*Chem. Pharm. Bull.*, **45**, 1447 (1997)], reaction of ethyl isobutyrate with LDA and 1,4-dibromobutane in THF, first at –78°C and then at room temperature, afforded ethyl 6-bromo-2,2-dimethylhexanoate in 98% yield after distillation. It is assumed that a large excess of 1,4-dibromobutane was used in this reaction.

15. The chemoselectivity of reduction of similar bromo esters with $LiAlH_4$ depends on the conditions. In ether at room temperature, the bromo alcohol is the single product whereas in THF at reflux the reaction gives the alcohols exclusively. See: A. L. J. Beckwith and K. D. Raner, *J. Org. Chem.*, **57**, 4954 (1992).

16. H. C. Brown and S. Narasimhan, *J. Org. Chem.*, **49**, 3891 (1984).

17. H. C. Brown, S. Narasimhan and Y. M. Choi, *J. Org. Chem.*, **47**, 4702 (1982).

18. K. Soai and A. Ookawa, *J. Org. Chem.*, **51**, 4000 (1986).

19. Crude compounds **9** and **10** were dried in a rotary evaporator under high vacuum with the water bath heated to 45-50°C until a constant weight was obtained.

20. G. Cauquis, B. Haemmerlé, *Bull. Soc. Chim. Fr.*, 183 (**1970**).

(Received August 26, 2004; in final form November 10, 2004)