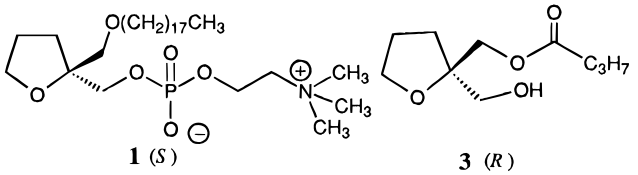
Asymmetrization of Tetrahydrofuran-2,2-dimethanol Using *l*-Menthone as a Chiral Template

Kapa Prasad,* Russell L. Underwood, and Oljan Repic

Chemical Research and Development, Technical R&D, Sandoz Research Institute, Sandoz Pharmaceuticals Corporation, 59 Route 10, East Hanover, New Jersey 07936

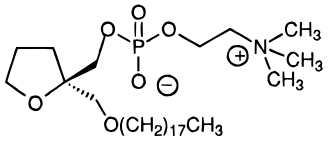
Received August 14, 1995

The synthesis of enantiomeric phospholipids **1** and **2** starting from chiral synthon **3** which was derived from porcine pancreas lipase mediated enantiotopos-differentiating hydrolysis of the corresponding dibutyrate was reported recently by us.[1] These phospholipids are of interest as potential antitumor[2] and multiple sclerosis[3] agents, respectively. In the present report we describe a nonenzymatic route to these enantiomers starting from the prochiral tetrahydrofuran-2,2-dimethanol (**4**) and *l*-menthone (**5**), utilizing the enantiodifferentiating functionalization methodology developed by Oku and coworkers.[4]



1 (*S*)

3 (*R*)

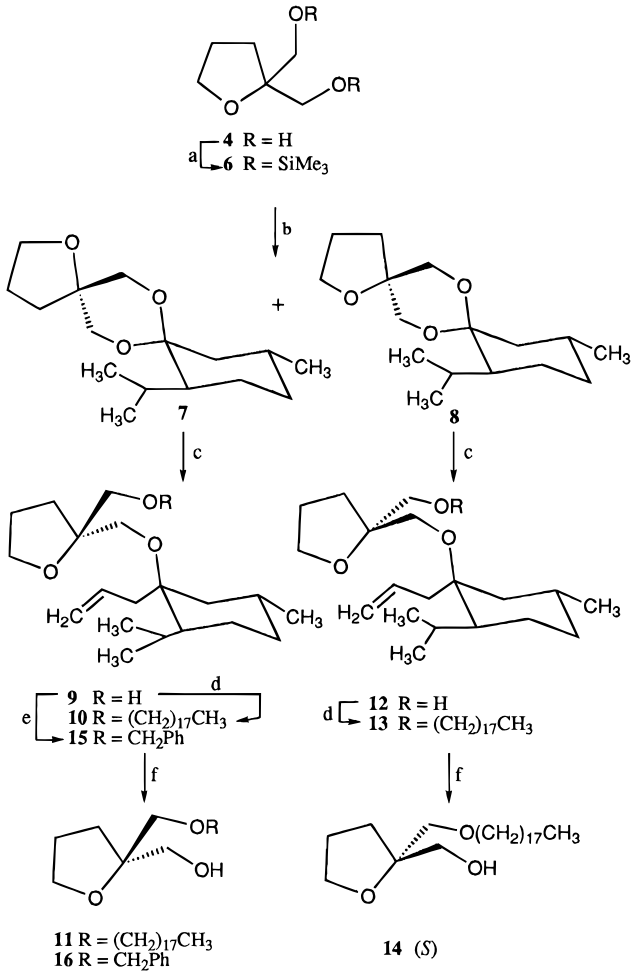


2 (*R*)

5

Tetrahydrofuran-2,2-dimethanol (**4**) was converted to **6** by treatment with hexamethyldisilazane/trimethylsilyl trifluoromethanesulfonate (TMSOTf) in THF at 0 °C. The reaction of **6** with *l*-menthone (**5**) in the presence of TMSOTf at −40 °C in CH_2Cl_2 yielded spiroketals **7** and **8** in 89% yield and a ratio of 7:2, respectively. The ratio of **7** to **8** could be further improved by conducting the ketalization step at −78 °C to give a 6:1 mixture, but at the expense of the chemical yield (42%). At −92 °C, the reaction was found to be too slow to follow. As the spiroketals are readily separable, we effected the ketalization at −40 °C preferring the high chemical yield and isolated the pure **7** and **8** by flash chromatography on silica gel in 69 and 20% yields, respectively.

With the pure spiroketals in hand, we attempted the enantiodifferentiating cleavage of **7** using literature conditions.[4] Addition of $TiCl_4$ to a solution of **7** and allyltrimethylsilane in CH_2Cl_2 at −85 °C resulted in the isolation of a mixture of two diastereoisomers in the ratio of 85:15 based on ^{13}C NMR. This ratio was further confirmed by independent measurement of optical purity (70% ee) of product **11** obtained in two steps from this diastereomeric mixture. As the ring cleavage of these spiroketals was established[4] as being highly stereoselective, occurring with the cleavage of the equatorial carbon−oxygen bond and retentive introduction of the nucleophile, we presume the loss in diastereoselectivity to be due to competing isomerization of spiroketal **7** to **8** under the reaction conditions. By modifying the reaction conditions, i.e., adding a precooled (−72 °C) solution of **7** in CH_2Cl_2 to a premixed solution of $TiCl_4$ and allyltrimethylsilane in CH_2Cl_2 at −90 °C, the selectivity in the ketal cleavage was improved to 94% de. As the absolute stereochemistry of product **11** had been independently determined by us earlier[1] and coupled with the known preference for the equatorial C−O bond cleavage in spiroketals of this type, the major spiroketal was assigned structure **7** and the cleavage product, **9**. Accordingly, the minor spiroketal and the cleavage product were assigned structures **8** and **12**, respectively.



a. Hexamethyldisilazane, TMSOTf; b. CH_2Cl_2, **5**,TMSOTf; c. allyltrimethylsilane, CH_2Cl_2, $TiCl_4$; d. THF, NaH, octadecyl bromide, TBAB; e. THF, NaH, benzyl bromide, TBAB; f. TFA, CH_2Cl_2

With the enantiodifferentiated products **9** and **12** obtained in high optical purity, the remaining objective was their conversion to **11** and **14**. This was achieved by alkylating with octadecyl bromide and removing the chiral auxiliary with trifluoroacetic acid. Alternatively, alcohols **9** and **12** could be converted to **11** and **14** by using a protection/deprotection strategy. This is illustrated with **9** which was converted into the benzyl ether **15**, followed by trifluoroacetic acid treatment to give **16** in high yield. The conversion of **16** to **14** was reported earlier by us.[1]

In conclusion, enantiodifferentiating functionalization of prochiral tetrahydrofuran-2,2-dimethanol was successfully achieved using *l*-menthone as the chiral template, and the chiral intermediates obtained were converted to

(1) Prasad, K.; Estermann, H.; Underwood, R.; Chen, C.-P.; Kucerovy, A.; Repic, O. *J. Org. Chem.* in press.
(2) Houlihan, W. J.; Lee, M. L.; Munder, P. G.; Nemecek, G. M.; Handley, D. H.; Winslow, C. M.; Happy, J.; Jaeggi, C. *Lipids* **1987**, *22*, 884.
(3) Chabannes, D.; Ryffel, B.; Bore, J.-F. *J. Autoimmunity* **1992**, *5*, 199.
(4) Harada, T.; Oku, A. *Synlett* **1994**, 95.

0022-3263/96/1961-0384$12.00/0

11 and **14**, which are precursors of phospholipids **1** and **2**, with high enantiomeric purity.

Experimental Section

The optical purity of alcohols **11**, **14**, and **16** was determined by ^{31}P NMR using a diazaphospholidine described in the literature.[5]

Tetrahydro-2,2-bis(((trimethylsilyl)oxy)methyl)furan (6). To a solution of 95.8 mL (0.454 mol) of hexamethyldisilazane in 100 mL of THF at 5 °C was added 0.44 mL (2.3 mmol) of TMSOTf followed by the addition of 30 g (0.227 mol) of **4** in 100 mL of THF. After stirring at 5 °C for 0.5 h, the reaction mixture was diluted with 100 mL of ether, washed with 50 mL of NH_4Cl solution, and concentrated under reduced pressure. The crude residue was distilled (130 °C/45 mbar), affording 51.48 g (82%) of **6**: ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.0, 68.4, 64.6, 29.5, 25.1, −0.7; MS (isobutane/DCI) *m/z* 277 $(MH)^+$. Anal. Calcd for $C_{12}H_{28}O_3Si_2$: C, 52.13; H, 10.21. Found: C, 51.83; H, 10.18.

Spiroketals 7 and 8. To a solution of 25 g (0.09 mol) of **6** in 50 mL of CH_2Cl_2 at −40 °C was added under nitrogen a solution of 15.34 g (0.099 mol) of **5** in 25 mL of CH_2Cl_2 followed by the addition of 3.5 mL (0.018 mol) of TMSOTf. Stirring was continued at −40 °C for 22 h, the reaction was quenched with 3.6 mL of pyridine and 100 mL of water, and the mixture was diluted with 100 mL of ether, washed with 50 mL of NH_4Cl solution, and concentrated under reduced pressure. The resulting layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was flash chromatographed on SiO_2 with hexane followed by hexane:EtOAc (97:3) to give 16.53 g of **7** and 4.92 g of **8** in a combined yield of 89%. Compound **7**: $[\alpha]^{25}_D = -38.4°$ (c = 1.06 in $CHCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 100.3, 75.9, 68.1, 66.8, 66.7, 50.6, 36.1, 34.8, 34.0, 29.0, 25.3, 24.1, 23.7, 22.1, 22.0, 18.5; MS (NH_3/DCI) *m/z* 269 $(MH)^+$. Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.66; H, 10.56. Compound **8**: $[\alpha]^{25}_D = -35.6°$ (c = 0.99 in $CHCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 99.9, 76.9, 67.6, 66.2, 65.8, 51.2, 36.3, 35.0, 31.0, 29.2, 25.3, 24.5, 23.7, 22.2, 22.1, 18.8; MS (NH_3/DCI) *m/z* 269 $(MH)^+$. Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.74; H, 10.63.

(*S*)-Tetrahydro-2-[[[1(e)-allyl-2(e)-isopropyl-5(e)-methylcyclohexanyl]oxy]methyl]-2-furanmethanol (9). To a solution of 89 mL (0.56 mol) of allyltrimethylsilane in 2.2 L of CH_2Cl_2 at −90 °C was added 61.5 mL (0.0615 mol) of 1 M solution of $TiCl_4$ in CH_2Cl_2, keeping the temperature below −90 °C. To the reaction mixture was added a precooled (−72 °C) solution of **7** (15 g, 0.056 mol) in 1.2 L of CH_2Cl_2 at such a rate that the temperature did not exceed −90 °C. After the addition, the mixture was stirred for 30 min at −90 °C, the reaction was quenched with 17 mL of pyridine, and the mixture was poured into a flask containing 1.5 L of EtOAc, 1.5 L of hexane, and 4 L of 10% aqueous KF solution. After stirring for 30 min, the mixture was filtered through Celite, the layers were separated, and the organic layer was dried, evaporated to dryness, and chromatographed on SiO_2 using EtOAc/hexane (1:4) to give 9.836 g (57%) of **9** as an oil: $[\alpha]^{25}_D = +3.7°$ (c = 1.42 in $CHCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.6, 117.5, 84.5, 79.2, 68.5, 66.4, 62.4, 47.9, 41.1, 40.5, 35.2, 30.4, 27.9, 26.1, 25.5, 23.5, 22.4, 20.6, 18.3; MS (NH_3/DCI) *m/z* 311 $(MH)^+$. Anal. Calcd for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04. Found: C, 73.33; H, 11.23.

(*S*)-Tetrahydro-2-((octadecyloxy)methyl-2-[[[1(e)-allyl-2(e)-isopropyl-5(e)-methylcyclohexanyl]oxy]methyl]furan (10). To a mixture of 1.498 g (37.4 mmol) of NaH (60% dispersion in mineral oil) and 1.058 g of tetrabutylammonium bromide in 30 mL of THF at 5 °C was added a solution of 6.839 g (22 mmol) of **9** in 30 mL of THF. The suspension was warmed to room temperature, and a solution of 9.759 g (28.6 mmol) of octadecyl bromide in 35 mL of THF was added. The mixture was refluxed for 30 h and cooled to 5 °C. The reaction was quenched with 12 mL of isopropyl alcohol, the mixture was washed with saturated ammonium chloride solution, dried, and evaporated to dryness, and the residue was chromatographed on SiO_2, eluting first with hexane and then with EtOAc/hexane (1:9) to give 6.89 g (56%) of **11** as an oil: $[\alpha]^{25}_D = +4.6°$ (c = 1.03 in $CHCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.8, 117.1, 84.1, 78.7, 73.7, 71.7, 68.3, 61.8, 47.8, 41.0, 40.4, 35.2, 31.8, 30.5, 29.6, 29.5, 29.5, 29.4, 29.2, 27.6, 26.1, 25.7, 25.4, 23.3, 22.5, 22.3, 20.4, 18.2, 13.9; MS (NH_3/DCI) *m/z* 580 ($M + N^+H_4$). Anal. Calcd for $C_{37}H_{70}O_3$: C, 78.94; H, 12.53. Found: C, 78.92; H, 12.69.

(*R*)-Tetrahydro-2-((octadecyloxy)methyl)-2-furanmethanol (11). To a solution of 6.597 g (11.7 mmol) of **10** in 235 mL of CH_2Cl_2 was added a precooled (5 °C) solution of 12 mL of trifluoroacetic acid. The solution was stirred at 5 °C for 1 h, and the reaction was quenched with 80 mL of 2 N NaOH solution. The layers were separated, and the organic layer was dried and evaporated to dryness. Flash chromatography of the residue on SiO_2 using hexane/EtOAc (6:1) followed by hexane/EtOAc (4:1) gave 4.229 g (94%) of **11:** ee before recrystallization = 97%, ee after recrystallization in heptane and seeding with pure crystals > 99%; $[\alpha]^{25}_{365} = +4.38°$ (c = 1 in MeOH); identical in all respects with the compound reported by us earlier.[1]

(*R*)-Tetrahydro-2-[[[1(e)-allyl-2(e)-isopropyl-5(e)-methylcyclohexanyl]oxy]methyl]-2-furanmethanol (12). Starting with 5.314 g (0.0198 mol) of **8**, 31.5 mL of allyltrimethylsilane, and 21.8 mL of 1 M solution of $TiCl_4$ in CH_2Cl_2 and using the procedure described for **9**, there was obtained 5.96 g (96.9%) of **12** as an oil: $[\alpha]^{25}_D = -13.2°$ (c = 1.23 in $CHCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.4, 117.4, 84.2, 79.1, 68.3, 66.5, 63.0, 47.8, 41.0, 40.4, 35.0, 30.6, 27.5, 26.0, 25.4, 23.3, 22.2, 20.3, 18.1; MS (NH_3/DCI) *m/z* 311 $(MH)^+$. Anal. Calcd for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04. Found: C, 73.35; H, 11.20.

(*R*)-Tetrahydro-2-((octadecyloxy)methyl)-2-[[[1(e)-allyl-2(e)-isopropyl-5(e)-methylcyclohexanyl]oxy]methyl]furan (13). Starting with 0.500 g (1.61 mmol) of **12** and 0.713 g of octadecyl bromide, following the procedure as described for compound **10**, there was obtained 0.424 g (47%) of **13** as an oil: $[\alpha]^{25}_D$, no observed rotation in $CHCl_3$ at c = 1.1; ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.8, 117.3, 84.3, 78.8, 73.9, 72.0, 68.4, 61.9, 48.0, 41.2, 40.8, 35.3, 31.9, 31.1, 29.7, 29.7, 29.6, 29.61, 29.6, 29.3, 27.4, 26.2, 25.9, 25.6, 23.5, 22.7, 22.4, 20.5, 18.3, 14.1; MS (NH_3/DCI) *m/z* 580 ($M + N^+H_4$). Anal. Calcd for $C_{37}H_{70}O_3$: C, 78.94; H, 12.53. Found: C, 78.74; H, 12.74.

(*S*)-Tetrahydro-2-((octadecyloxy)methyl)-2-furanmethanol (14). Starting with 0.235 g (0.417 mmol) of **13** and utilizing the conditions described for compound **11**, there was obtained 0.127 g (79%) of **14**: ee before recrystallization = 97%, ee after recrystallization from heptane in the presence of pure seed crystals > 99%; mp 36 °C; $[\alpha]^{25}_{365} = -4.38°$ (c = 1 in MeOH); spectral data identical to the compound reported earlier by us.[1]

(*S*)-Tetrahydro-2-((benzyloxy)methyl)-2-[[[1(e)-allyl-2(e)-isopropyl-5(e)-methylcyclohexanyl]oxy]methyl]furan (15). To a mixture of 2.409 g (60 mmol) of NaH (60% dispersion in mineral oil) and 1.70 g (4.6 mmol) of tetrabutylammonium iodide in 55 mL of THF at 5 °C was added 11 g (35 mmol) of **9** in 55 mL of THF. The mixture was warmed to room temperature, followed by the addition of 5.0 mL (42.5 mmol) of benzyl bromide in 55 mL of THF, and then refluxed overnight. The reaction was quenched with 18 mL of 2-propanol, and 60 mL of aqueous ammonium chloride was added. The layers were separated, and the organic layer was washed with brine, dried with $MgSO_4$, and concentrated to dryness. The residue was flash chromatographed on SiO_2, eluting with hexane/EtOAc (95:5) to give 9.965 g (70%) of **15**: $[\alpha]^{25}_D = +5.2°$ (c = 0.78 in $CHCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 134.9, 128.19, 127.7, 127.3, 117.2, 84.3, 78.9, 73.5, 73.3, 68.5, 62.1, 47.9, 41.2, 40.6, 35.3, 30.63, 27.7, 25.9, 25.5, 23.5, 22.4, 20.5, 18.3; MS (NH_3/DCI) *m/z* 419 ($M + N^+H_4$). Anal. Calcd for $C_{26}H_{40}O_3$: C, 77.95; H, 10.06. Found: C, 77.98; H, 10.04.

(*R*)-Tetrahydro-2-((benzyloxy)methyl)-2-furanmethanol (16). To a solution of 9.605 g (24 mmol) of **15** in 480 mL of CH_2Cl_2 was added a precooled (5 °C) solution of 24 mL of trifluoroacetic acid. The solution was stirred at 5 °C for 1 h, and the reaction was quenched with 160 mL of 2 N NaOH solution. The layers were separated, and the organic layer was dried and evaporated to dryness. Flash chromatography of the residue on SiO_2 using hexane/EtOAc (3:1), followed by hexane/EtOAc (2:1), gave 4.868 g (91%) of **16**: $[\alpha]^{25}_D = +2.2°$ (c = 1.00 in $CHCl_3$); identical in all respects with the compound reported by us earlier.[1]

Acknowledgment. We thank Drs. M. Shapiro and E. Fu and their co-workers for spectroscopic measurements and valuable discussions.

Supporting Information Available: Spectroscopic data (^1H NMR and ^{13}C NMR) for all new compounds reported (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9515034

(5) Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 1224−1237.