note on methodology

An efficient asymmetric synthesis of diacylglycerols

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Abstract A convenient preparation of 1,2-diacyl-*sn*-glycerol or 2,3-diacyl-*sn*-glycerol is described starting from allyl bromide. The latter was converted to allyl 4-methoxyphenyl ether, which is dihydroxylated using AD-mix as a catalyst to yield 3-*O*-(4'-methoxyphenyl)-*sn*-glycerol or 1-*O*-(4'-methoxyphenyl)-*sn*-glycerol in high yield and high optical purity. After diacylation, ceric ammonium nitrate was used to remove the 4-methoxyphenyl group under mild conditions that avoid acyl migration to 1,3-dipalmitoylglycerol. Thus chiral 1,2-diacylglycerol can be prepared from allyl bromide in just four steps in 78% overall yield and high enantiomeric excess. This scheme represents an inexpensive method for the large-scale preparation of chiral 1,2-diacyl-*sn*-glycerol and 2,3-diacyl-*sn*-glycerol.—**Vilchèze, C., and R. Bittman.** An efficient asymmetric synthesis of diacylglycerols. *J. Lipid Res.* 1994. **35:** 734–738.

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Synthetic approaches to optically active glycerolipids have attracted a great deal of attention, largely because of interest in the structure and function of biological membranes. Many analogs of 1,2-diacyl-*sn*-glycerol have been prepared because diacylglycerol-requiring enzymes play a key role in phospholipid metabolism (1–4). The classical route from D-mannitol to diacylglycerols via cleavage of 1,2:5,6-di-*O*-isopropylidene-D-mannitol into glyceraldehyde derivatives is lengthy, requiring seven steps, and involves possible racemization of the intermediates on storage (see, for example, refs. 5–7, and references cited therein). Other approaches have used optically active precursors such as L-serine, L-arabinose, L-ascorbic acid, L-tartaric acid, (*S*)-malic acid, L-glyceric acid, glycidols, and derivatives of glycerol such as isopropylidene-*sn*-glycerol (7). We report here a new asymmetric synthesis of diacylglycerol that avoids the use of expensive reagents and also avoids a long synthetic route. This economical synthesis can be extended to yield other glycerolipids. Further elaboration of diacylglycerols into phospholipids by formation of phosphate ester linkages is accomplished by established methods (7); similarly, triacylglycerols may be obtained from diacylglycerol by formation of an additional fatty ester linkage.

MATERIALS AND METHODS

The solvents were dried by distillation as follows and then stored over 3 Å molecular sieves: tetrahydrofuran, from lithium aluminum hydride; dichloromethane, from phosphorus pentoxide or calcium hydride. Sodium hydride (NaH; 80% dispersion in mineral oil) was washed with dry hexane (dried by distillation from calcium hydride prior to use). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in deuterated chloroform ($CDCl_3$) at 200 MHz unless indicated otherwise. Chemical shifts are given in parts per million from tetramethylsilane as internal standard. Optical rotations were measured on a JASCO Model DIP-140 digital polarimeter using a 1-dm cell of 2-ml capacity. High performance liquid chromatography (HPLC) was carried out on a Perkin-Elmer Model 410 HPLC; the chiral column (Pirkle type IA) was purchased from J. T. Baker (Phillipsburg, NJ). Melting points are uncorrected. Silica gel GF thin-layer chromatography (TLC) plates of 0.25-mm thickness (Analtech, Newark, DE) were used to monitor reactions, with 10% sulfuric acid in ethanol and short-wavelength ultraviolet light to visualize the spots. E. Merck silica gel 60 (230–400 ASTM mesh) was used for flash chromatography. AD-mix-α and -β are new products available from Aldrich Chemical Co. (Milwaukee, WI) (catalog numbers 39,275-8 and 39,276-6, respectively). Palmitic acid, ceric ammonium nitrate (CAN), 4-dimethylaminopyridine (DMAP), dicyclohexylcarbodiimide (DCC), allyl bromide, 4-methoxyphenol, and (*R*)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetyl (MTPA) chloride were purchased from Aldrich. 1-*O*-Benzyl-*sn*-glycerol was obtained from Sigma Chemical Co. (St. Louis, MO).

RESULTS

1-(4'-Methoxyphenyloxy)-prop-2-ene (Scheme 1, *1*)

To a solution of 100 mg (0.80 mmol) of 4-methoxyphenol in 2 ml of dry tetrahydrofuran were added 62 mg (2.60 mmol) of sodium hydride and 12 mg (0.04 mmol) of tetra-*n*-butylammonium bromide at 0°C under nitrogen. After the reaction mixture was stirred for 10 min at 0°C, a solution of 96 mg (0.80 mmol) of allyl bromide in 1 ml of dry tetrahydrofuran was added at 0°C. The reaction mixture was stirred at room temperature (rt) under nitrogen for 20 h and then the volatiles were removed under vacuum. The

Abbreviations: NMR, nuclear magnetic resonance; TLC, thin-layer chromatography; rt, room temperature; DMAP, 4-dimethylaminopyridine; DCC, dicyclohexylcarbodiimide; MTPA, (*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetyl; ee, enantiomeric excess; CAN, ceric ammonium nitrate; HPLC, high performance liquid chromatography.

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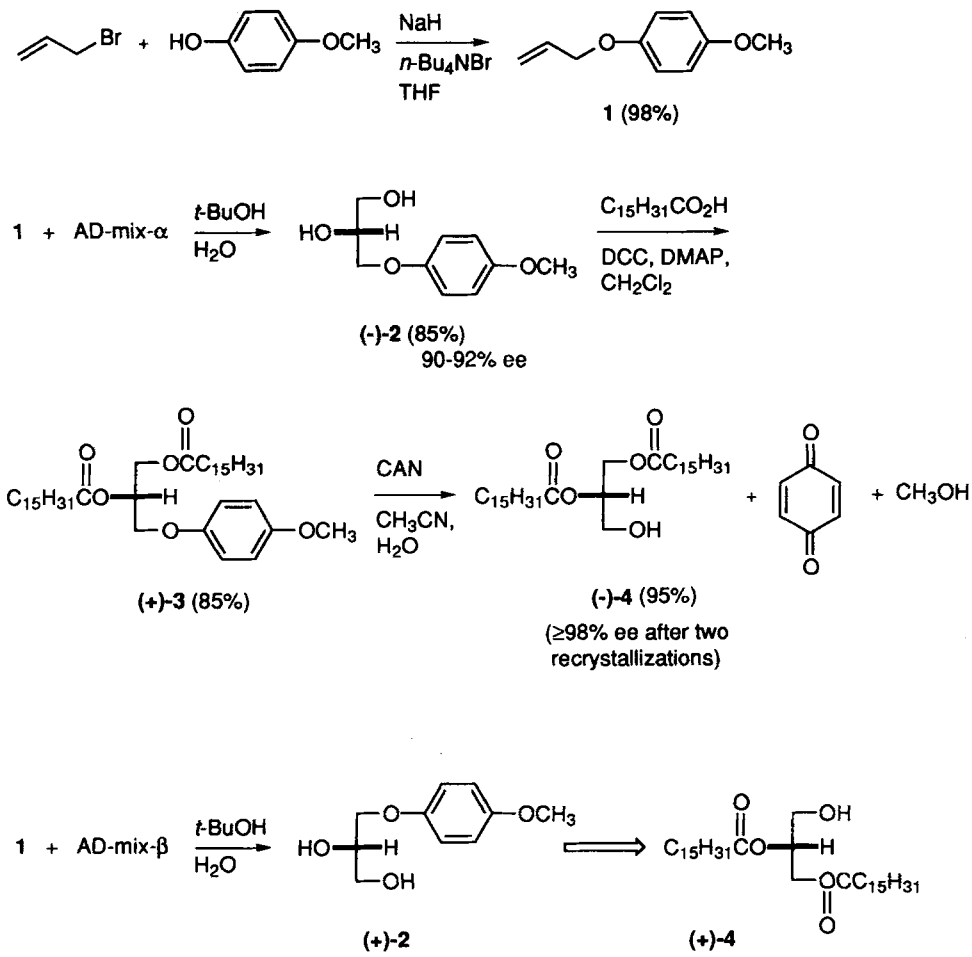

Scheme 1. Asymmetric syntheses of 1,2-dipalmitoyl-*sn*-glycerol and 2,3-dipalmitoyl-*sn*-glycerol from allyl bromide.

residue was purified by flash chromatography (elution with hexane–ethyl acetate 98:2) to give 129 mg (98%) of compound ***1*** as a colorless liquid; R_f 0.38 ± 0.06 (elution with hexane–ethyl acetate 98:2); ^{1}H NMR ($CDCl_3$) δ 3.76 (3H, s, OCH_3), 4.48 (2H, dt, J = 1.4 Hz, J = 5.3 Hz, $C\underline{H}_2OC_6H_4OCH_3$), 5.27 (1H, dq, J = 1.4 Hz, J = 10.6 Hz, CH_2=), 5.37 (1H, dq, J = 1.4 Hz, J = 15.8 Hz, CH_2=), 6.05 (1H, tdd, J = 5.3 Hz, J = 10.6 Hz, J = 15.8 Hz, =CH), 6.84 (4H, m, C_6H_4).

(−)-3-*O*-(4'-Methoxyphenyl)-*sn*-glycerol (Scheme 1, (−)-*2*)

A biphasic solution of 1038 mg of AD-mix-α in 7.6 ml of *tert*-butyl alcohol–water 1:1 was cooled at 0°C, and added to 100 mg (0.61 mmol) of alkene ***1***. The reaction mixture was stirred for 24 h at 0°C, and 1120 mg of sodium sulfite was added at 0°C. After the mixture was stirred for 45 min at rt, 10 ml of chloroform was added, and the aqueous layer was extracted with chloroform (3 × 10 ml). The combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated, and purified by flash chromatography (elution with ethyl acetate–hexane 7:3) to give 104 mg (85%) of diol (−)-***2*** as a white solid; R_f 0.38 ± 0.06 (elution with ethyl acetate–hexane 7:3); mp 78°C [literature value (8) mp 78°C]; $[\alpha]^{26}_D$ −7.58° (c 4.0, MeOH) [literature value (8) $[\alpha]_D$ −8.25° (c 1.15, MeOH)]; ^{1}H NMR ($CDCl_3$) δ 2.45 (2H, br s, OH), 3.77–4.07 (8H, glycerol backbone and methoxy group), 6.84 (4H, s, C_6H_4).

(+)-1,2-Dipalmitoyl-3-*O*-(4'-methoxyphenyl)-*sn*-glycerol (Scheme 1, (+)-*3*)

To a solution of 72 mg (0.36 mmol) of (−)-diol ***2*** in 3.6 ml of dry dichloromethane were added under nitrogen 97 mg (0.79 mmol) of DMAP, 205 mg (0.79 mmol) of palmitic acid, and then 325 mg (1.58 mmol) of DCC. The reaction mixture was stirred at rt for 60 h, filtered, evaporated, and purified by column chromatography (elution with hexane–ethyl acetate 96:4) to give 208 mg (85%) of diester (+)-***3***; R_f 0.28 ± 0.03 (elution with hexane–ethyl acetate 95:5); mp 63.5–64°C; $[\alpha]^{27}_D$ + 11.3° (c 6.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (6H, t, J = 6.5 Hz,

ω-CH_3), 1.25 (48H, m, $(CH_2)_{24}$), 1.59 (4H, m, $(CH_2CH_2CO_2)_2$), 2.31 (2H, t, J = 7.3 Hz, CH_2CO_2), 2.33 (2H, t, J = 7.3 Hz, CH_2CO_2), 3.76 (3H, s, CH_3O), 4.06 (2H, d, J = 5.1 Hz, $CH_2OC_6H_4$), 4.28 (1H, dd, J = 6.1 Hz, J = 11.9 Hz, CH_2OCO), 4.43 (1H, dd, J = 3.9 Hz, J = 11.9 Hz, CH_2OCO), 5.36 (1H, m, CHOCO), 6.83 (4H, s, C_6H_4).

(−)-1,2-Dipalmitoyl-*sn*-glycerol (Scheme 1, (−)-*4*)

Ceric ammonium nitrate (368 mg, 0.67 mmol) was added to a suspension of 189 mg (0.28 mmol) of diester (+)-*3* in 3.53 ml of acetonitrile–water 4:1 at 0°C. The mixture was stirred overnight at rt. Ethyl acetate (50 ml) and brine (50 ml) were added and the organic layer was washed with a saturated sodium hydrogen carbonate solution (3 × 50 ml), dried over anhydrous sodium sulfate, filtered, concentrated, and purified on a small silica-gel column (15 × 200 mm, elution with hexane–ethyl acetate 85:15) to give 151 mg (95%) of (−)-*4* R_f 0.37 ± 0.03 (elution with hexane–ethyl acetate 8:2); mp 66–67°C [literature value (9) mp 67–67.5°C; literature value (10) mp 66–68°C; literature value (11, 12) mp 68–69°C]; $[\alpha]^{27}_D$ −2.50° without recrystallization (*c* 5.2, $CHCl_3$); $[\alpha]^{27}_D$ −2.69° recrystallized twice from pentane–ethyl acetate (*c* 3.9, $CHCl_3$) [literature value (11) $[\alpha]_D$ −2.9° (*c* 8.0, $CHCl_3$); literature value (9) $[\alpha]_D$ −2.3° (*c* 8.0, $CHCl_3$); literature value (10) $[\alpha]^{22}_D$ −2.21° (*c* 9.9, $CHCl_3$); literature value (12) $[\alpha]_D$ −2.75° (*c* 7.62, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 0.88 (6H, t, J = 6.4 Hz, ω-CH_3), 1.26 (48H, m, $(CH_2)_{24}$), 1.61 (4H, m, $(CH_2CH_2CO_2)_2$), 2.08 (1H, t, J = 6.5 Hz, OH), 2.32 (2H, t, J = 7.3 Hz, CH_2CO_2), 2.34 (2H, t, J = 7.3 Hz, CH_2CO_2), 3.73 (2H, dd, J = 5.4 Hz, J = 6.5 Hz, CH_2OH), 4.23 (1H, dd, J = 5.6 Hz, J = 11.9 Hz, CH_2OCO), 4.33 (1H, dd, J = 4.5 Hz, J = 11.9 Hz, CH_2OCO), 5.08 (1H, m, CHOCO).

Evaluation of optical purity of *4*

The MTPA esters of twice-recrystallized (−)-*4* and *rac*-*4* were prepared by allowing 3 mg (0.005 mmol) of *4* to react with 5 mg (0.02 mmol) of (*R*)-(−)-MTPA chloride in 0.5 ml of dry dichloromethane in the presence of 3 mg (0.024 mmol) of DMAP. After the mixture had stirred overnight at rt, the crude MTPA ester was obtained by elution (with dichloromethane) through a Pasteur pipette containing silica gel. Thus, the excess of DMAP and polar compounds were removed, but care was taken to avoid any separation of diastereomers.

^{1}H NMR (400 MHz; $CDCl_3$) of the MTPA ester of *rac*-*4*: $-CH_2$OMTPA appeared as four doublets of doublets in the region of δ 4.2–4.4.

^{1}H NMR (400 MHz; $CDCl_3$) of the MTPA ester of (−)-*4*: $-CH_2$OMTPA appeared as two doublets of doublets in the region of δ 4.2–4.4. The absence of the other doublets of doublets in the sample derived from (−)-*4* indicates that the enantiomeric excess (ee) of (−)-*4* is ≥ 98% (limits of detection).

(+)-1-*O*-(4'-Methoxyphenyl)-*sn*-glycerol [(+)-*2*]

This compound was prepared from *1* and AD-mix-β as outlined above for the enantiomer (−)-*2*.

Evaluation of optical purity of *2*

The bis-MTPA ester of both enantiomers of *2* were prepared as follows. To a solution of 3 mg (0.015 mmol) of diol *2* in 0.5 ml of dry dichloromethane were added 5 mg (0.04 mmol) of DMAP and 10 mg (0.04 mmol) of (*R*)-(−)-MTPA chloride. The solution was stirred overnight at rt, concentrated, and passed through a small silica-gel column in a Pasteur pipette (elution with dichloromethane) to afford the MTPA ester: ^{1}H NMR (300 MHz; $CDCl_3$) of bis-MTPA ester of (−)-*2*: δ 3.42 (3H, s, CH_3O), 3.48 (3H, s, CH_3O), 3.77 (3H, s, $CH_3OC_6H_4$), 3.98 (2H, d, J = 5.4 Hz, $CH_2OC_6H_4$), 4.52 (1H, dd, J = 5.8 Hz, J = 12.3 Hz, CH_2OMTPA), 4.86 (1H, dd, J = 3.1 Hz, J = 12.3 Hz, CH_2OMTPA), 5.62 (1H, m, CHOMTPA), 6.75 (4H, m, C_6H_4), 7.34 (5H, m, C_6H_4), 7.45 (5H, m, C_6H_4).

^{1}H NMR (300 MHz; $C\bar{D}Cl_3$) of bis-MTPA ester of (+)-*2*: δ 3.41 (3H, s, CH_3O), 3.50 (3H, s, CH_3O), 3.77 (3H, s, $CH_3OC_6H_4$), 4.07 (2H, d, J = 5.0 Hz, $CH_2OC_6H_4$), 4.54 (1H, dd, J = 4.8 Hz, J = 12.5 Hz, CH_2OMTPA), 4.74 (1H, dd, J = 3.6 Hz, J = 12.5 Hz, CH_2OMTPA), 5.66 (1H, m, CHOMTPA), 6.79 (4H, m, C_6H_4), 7.35 (10H, m, C_6H_4).

The optical purity of *2* was determined by comparison of the ^{1}H NMR spectra of the diastereomeric MTPA esters derived from (+)-*2* and (−)-*2*. Integration of the H_A doublet of the AB quartet of each diastereomeric CH_2OMTPA group, base-line separated in the region of δ 4.65–4.88 ppm, indicated a 96:4 ratio (92% ee). This value of ee was confirmed by chiral HPLC analysis (Pirkle type IA column, 4.6 × 250 mm). Base-line separation of the diastereomeric (*R*)-MTPA esters derived from (−)-*2* was achieved. The % area (and retention times) for the two peaks of the bis-MTPA ester of (−)-*2* were 31.22 (t_R 41.23 min) and 1.68 (t_R 42.37 min) (elution with hexane–*i*-PrOH 99.5:0.5 and a flow rate of 0.3 ml/min), which correspond to an area ratio of 95:5 (90% ee).

Preparation of (+)-2,3-dipalmitoyl-*sn*-glycerol [(+)-*4*] from 1-*O*-benzyl-*sn*-glycerol

1-*O*-Benzyl-*sn*-glycerol (74 mg, 0.41 mmol) was diacylated as described previously (Scheme 1, compound *2*→*3*) using 344 mg (1.34 mmol) of palmitic acid, 163 mg (1.34 mmol) of DMAP, and 555 mg (2.69 mol) of DCC in 7.4 ml of dichloromethane. The diester was purified by column chromatography (elution with hexane–ethyl acetate 97:3) to give 228 mg of 1-*O*-benzyl-2,3-dipalmitoyl-*sn*-glycerol as a white solid (85%) (R_f 0.56 ± 0.03 (elution with hexane–ethyl acetate 95:5)). A solution of 127 mg of

the diester in 32 ml of 96% ethanol was hydrogenolyzed overnight at rt and atmospheric pressure, using palladium on carbon (10%, 100 mg) as a catalyst. The suspension was filtered, evaporated, and the product was purified on a small silica-gel column (15 × 200 mm, elution with hexane–ethyl acetate 85:15) to give 104 mg (95%) of (+)-***4***; R_f 0.42 ± 0.05 (elution with hexane–ethyl acetate 8:2); mp 66–67°C; $[\alpha]^{27}_D$ + 2.75° (*c* 4.0, $CHCl_3$).

DISCUSSION

The new stereospecific synthesis of diacylglycerol reported here consists of four steps. First, allyl bromide is converted to allyl aryl ether ***1*** in 98% yield. Second, compound ***1*** is subjected to an asymmetric dihydroxylation reaction, giving the diol 3-*O*-(4'-methoxyphenyl)-*sn*-glycerol [(−)-***2***] in 85% yield and 90–92% ee (Scheme 1). For this dihydroxylation reaction commercially available AD-mix-α was used. The enantiomer of the diol ***2*** was obtained by using AD-mix-β. AD-mix-α and AD-mix-β contain potassium osmate and a chiral phthalazine ligand, and have been found to catalyze the dihydroxylation of many olefins in a process that minimizes the exposure to volatile osmium species (13–16).

The third step is a standard diacylation reaction in dichloromethane using an excess of palmitic acid in the presence of DCC and DMAP. Finally, the aryl ether group of the diester ***3*** is removed using CAN in aqueous solution under conditions that avoid acyl rearrangement (17). Diacyl-*sn*-glycerol ***4*** is easily separated from 1,4-benzoquinone on a short column of silica gel, using elution with hexane–ethyl acetate to avoid significant acyl migration. The enantiomeric excess of ***4*** is enhanced to ≥ 98% by two recrystallizations from pentane–ethyl acetate. Thus the method we describe offers the advantage, compared to previous methods, of being short and economical, as well as being stereospecific.

Other conditions for the CAN-mediated removal of the 4-methoxyphenyl group from diester ***3*** were examined. Ceric ammonium nitrate absorbed to silica gel or to alumina gave appreciable amounts of the undesired 1,3-dipalmitoylglycerol. In addition, the conversion of diester ***3*** to diacylglycerol ***4*** was much slower. Thus, we used CAN in 20% aqueous acetonitrile, obtaining the diacylglycerol ***4*** in 95% yield.

We also examined the possibility that 1,2-diacyl-*sn*-glycerol could undergo a 1→3 acyl migration process during the deprotection reaction, i.e., when diester ***3*** is treated with CAN. The compound resulting from such a 1→3 acyl migration would be 2,3-diacyl-*sn*-glycerol. Therefore, we synthesized 2,3-dipalmitoyl-*sn*-glycerol from 1-*O*-benzyl-*sn*-glycerol followed by diacylation and catalytic hydrogenolysis, and then we measured the optical activity. As shown in the Results section, the specific rotations of 2,3-dipalmitoyl-*sn*-glycerol and 1,2-dipalmitoyl-*sn*-glycerol (prepared using CAN in aqueous acetonitrile) are +2.75° and −2.69°, respectively. This observation indicates that 1→3 acyl migration does not take place when the aryl ether group of ***3*** is removed in the form of 1,4-benzoquinone by using CAN in acetonitrile–water 4:1 at rt.

The ee of diols (−)-***2*** and (+)-***2*** obtained by use of AD-mix-α and -β was determined by both HPLC analysis and ^{1}H NMR spectral analysis of the derived bis-(*R*)-MTPA esters, as described previously (18). We found high enantioselectivity (90% by HPLC analysis, 92% by NMR analysis).

We also examined the effect of different aryl groups in the asymmetric dihydroxylation reaction of allyl aryl ethers. Allyl benzyl ether gave a high yield of diol (90%) on asymmetric dihydroxylation, but the enantiomeric excess of the diol was only 50%. Allyl triphenylmethyl ether also underwent asymmetric dihydroxylation with low enantioselectivity (44% ee) and low yield (67%). Thus the 4-methoxyphenyl ether group was used in order to obtain high optical purity on dihydroxylation of ***1***.

In conclusion, the method described gives diacylglycerol in high yield (78%) and high chiral purity (90–92% ee) in only four steps. Although the present work shows the preparation of a saturated diacylglycerol (***4***), it may also be possible to prepare alkyl-linked and unsaturated acyl-linked glycerol derivatives by the route outlined here.

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