# Solid-phase Synthesis of *sn*-1,2- and *sn*-2,3-Diacylglycerols via Ring-Opening of the Glycidyl-Bound Resin

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A general method developed for the parallel solid-phase synthesis of *sn*-1,2- and *sn*-2,3-diacyglycerol derivatives. The technique relies on the use of carboxylic acid-promoted epoxide ring-opening reactions of the glycidyl-bound resin **3**. The polymer-bound monoacylglycerol **5,** formed in this manner, is transformed to the respective polymer-bound diacylglycerols **7** and **9** by reaction of the free alcohol moiety with a second carboxylic acid under conditions that lead to retention or inversion of C-2 stereochemistry. The sequence is completed by $BCl_3$-promoted cleavage of **7** and **9** to form the *sn*-1,2- and *sn*-2,3-diacylglycerols, respectively.

## Introduction

Lipids play key roles as secondary messengers in cellular signal transduction and as hormones that regulate an enormous array of physiological processes.[1] For example, diacylglycerols (DAGs) are important intermediates in the biosynthesis of triacylglycerols and phospholipids and play a fundamental role in cellular signaling.[2] These substances are able to activate cellular mechanisms directly via protein activation or indirectly via the liberation of fatty acids which may be metabolized in agonist molecules.[3] Moreover, protein kinase C (PKC), which comprises a family of serine/threonine-specific isozymes that have a pivotal role in cellular signal transduction are activated by DAGs, generated either by phospholipase C (PLC) mediated hydrolysis of phosphatidylinositol-4,5-bisphosphate ($PIP_2$) or indirectly via phospholipase D and phosphatidic acid hydrolase. These glycerol derivatives, in which two hydroxyl groups are part of fatty acid esters, exist in three isomeric forms referred to as the *sn*-1,2-, *sn*-1,3-, and *sn*-2,3-DAGs (Figure 1). In mammals, the lingual lipase preferentially hydrolyzes the ester bond of the triacylglycerols at the *sn*-3 position to form *sn*-1,2- and *sn*-2,3-diacylglycerols. Naturally occurring DAGs have the S configuration at the C-2 position (as *sn*-1,2-diacylglycerol, see Figure 1). DAGs are widely used in the food, cosmetic, and pharmaceutical industries, and their application as intermediates for the synthesis of phospholipids, glycolipids, prodrugs, and structured lipids has great potential.[4] However, DAGs are not simple to prepare using a solution-phase synthetic method, although lipase-catalyzed regio- and stereoselective reactions serve as promising routes to the compounds.[5] Despite its ability to generate a wide variety of small organic molecule libraries,[6] solid−phase synthesis has not been applied extensively in the preparation of lipids, including DAGs.[7] As a part of our research on drug discovery,[8] we required the availability of a facile and rapid procedure for preparation of *sn*-1,2- and *sn*-2,3-DAGs. Below, the results of recent effort which have led to development of an efficient procedure for solid-phase synthesis of these substances.

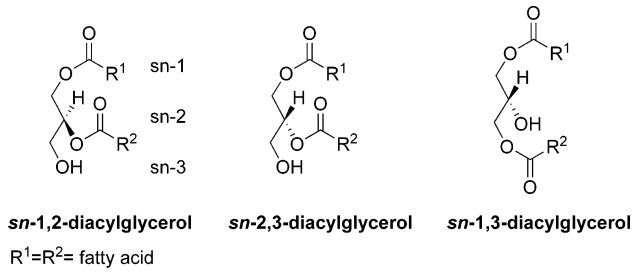


**Figure 1.** Isomers of DAGs substituted with fatty acids through ester bonds.

Herein, we would like to report our findings for an efficient procedure for the synthesis of *sn*-1,2- and *sn*-2,3-diacylglycerol derivatives on the solid phase. The solid-phase synthesis of *sn*-1,2- and *sn*-2,3-diacylglycerols in Scheme 1. The polymer-bound *sn*-1-monoacylglycerol resin **5** was generated by epoxide ring-opening reaction with carboxylic acid as key intermediates.

## Results and Discussion

The 2-chlorotrityl chloride resin **1** was selected as the polymer support since its benzylic chloride group is an ideal handle for formation of an ether bond to the alcohol moiety of glycidol. Accordingly, (*S*)-glycidol was treated with the 2-chlorotrityl chloride resin **1** in the presence of triethylamine (TEA) in dichloromethane (DCM) for 48 h at room temperature to give the glycidyl-bound resin **3.**[9] To determine the optimal procedures needed to prepare the *sn*-1,2- and *sn*-2,3-diacyglycerol target, we first investigated various

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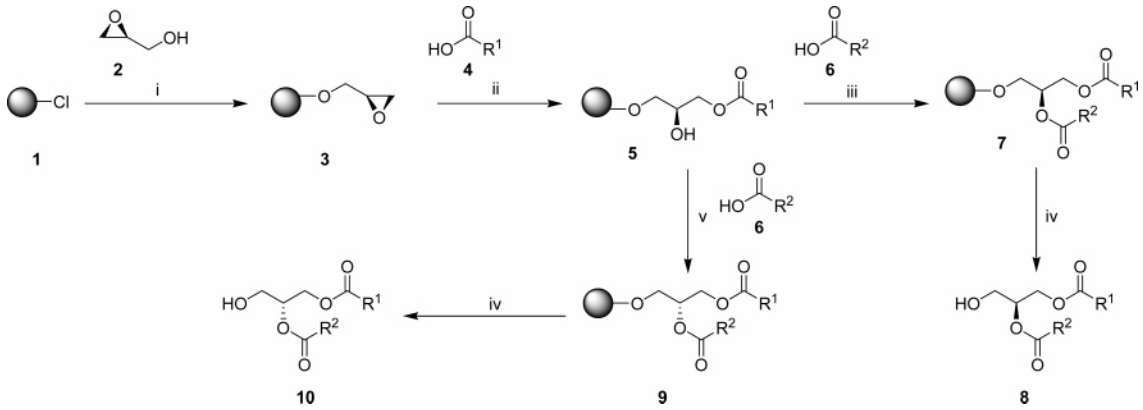
**Scheme 1**[a]




[a] Reagent and conditions: (i) TEA, DCM, room temp, 48 h; (ii) TBAB, DMF, 90 °C, 16 h; (iii) DIC, DMAP, DMF, room temp, 12 h; (iv) 1.0 M $BCl_3$ in DCM, DCM, −20 °C, 1 h; (v) DIAD, $PPh_3$, THF/DCM (1:1), room temp, 12 h.

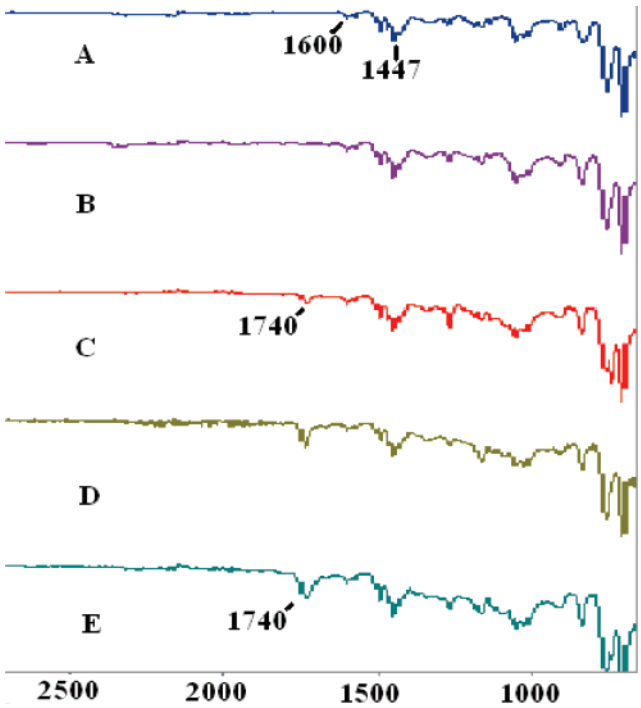



**Figure 2.** ATR-FTIR spectra on a single bead of resin **1** (A), **3** (B), **5** (C), **7** (D), and **9** (E). (wave number ($cm^{-1}$)).

conditions (e.g., solvents, temperature, and catalysts) for the performance of the palmitic acid-induced ring-opening of the epoxide in the glycidyl-bound resin **3** to produce the monoacylated glycerol-bound resin **5** ($R^1 = C_{15}H_{31}$) (Tables 1 and 2).[10] The progress of these reactions was evaluated by monitoring of the appearance of ester band in single-bead attenuated total reflection Fourier transform infrared (ATR-FTIR) spectra at 1740 $cm^{-1}$ (Figure 2C). To probe the second acylation process, the polymer-bound monoacylglycerol **5a** was treated with valeric acid in the presence of diisopropyl-carbodiimde (DIC) and 4-dimethylaminopyridine (DMAP) to form the corresponding diacylglycerol **7a** ($R^1 = C_{15}H_{31}$, $R^2 = C_4H_9$, Table 2). The single-bead ATR-FTIR spectrum of **7a** (Figure 2D) showed a stronger ester band compared to monoacylglycerol resin **5a**. The *sn*-1,2-diacylglycerol target **8a** ($R^1 = C_{15}H_{31}$, $R^2 = C_4H_9$) was then liberated from the polymer-bound diacylglycerol **7a** by treatment with $BCl_3$ in DCM at −20 °C for 1 h.

**Table 1.** Results from an Investigation of Conditions to Promote Conversion of Glycidol Ether Resin **3** to Palmitate Ester-Containing Resin **5a**

| entry | catalyst[a] | solvent | temp (°C) | time (h) | yield[b,c] (%) |
|---|---|---|---|---|---|
| **1** | $BiCl_3$ | DMF | 90 | 16 | 11 |
| **2** | $Ti(O^iPr)_4$ | ether | 0 | 16 | 19 |
| **3** | *p*-TsOH | DMF | 90 | 16 | 8 |
| **4** | $BF_3OEt_2$ | $CH_3CN$ | 70 | 8 | |
| **5** | TBAI | $CH_3CN$ | 70 | 8 | |
| **6** | TBAB | $CH_3CN$ | 70 | 16 | 24 |
| **7** | TBAB | THF | 70 | 16 | 21 |
| **8** | TBAB | DMF | 90 | 16 | 29 |

[a] 0.2 equiv are used. [b] Four-step overall yields from 2-chlorotrityl chloride resin **1** (loading capacity of the resin **1** is 1.3 mmol $g^{-1}$). [c] Yield after column chromatography of crude product.

The results of investigations of the epoxide ring opening reactions of glycidyl-bound resin **3** are summarized in Table 1. The reaction of palmitic acid with resin **3** promoted by $BiCl_3$, $Ti(O^iPr)_4$, and *p*-TsOH led to formation of adduct **8a** in a low yield (entries 1, 2, and 3, Table 1). Also, the use of $BF_3OEt_2$ and tetrabutylammoniumiodide (TBAI) to induce this process is complicated by the respective cleavage of ether bond from glycidyl-bound resin **3** and the nucleophilic attact of iodide on the epoxide ring[10a] (entries 4 and 5, Table 1). Finally, terabutylammoniumbrimide (TBAB) causes ring-opening of epoxide to form the desired carboxyalkanol product **8a** in a 24% yield (entry 6, Table 1). We speculated that the low yield of this process might be a result of the low solubility of palmitic acid in $CH_3CN$. This led to an exploration of other solvents, such as THF and DMF, to carry out the reaction in the presence of TBAB as catalyst (entries 7 and 8, Table 1). The results show that the reaction in DMF yields the adduct **8a** in an optimized yield of 29% ($[\alpha]^{20}_D = -3.57$ ($c = 0.37$, $CHCl_3$)). The enantiomeric purity was determinated by the Mosher ester, and then the NMR signal of the $OCH_3$ group was found at $\delta$ 3.54/3.53 (ratio 1.00/0.10) for Mosher ester of **8a**).[11] With these conditions and the reaction sequence shown in Scheme 1, a variety of diacylglycerols **8** can be produced from the 2-chlorotrityl chloride resin **1** in the overall four-step synthesis (Table 2).[11] Spectroscopic and polarimeteric data accumulated on the products matched these reported in the literature. Compound **8k** was (s)-rich because of the comparison between the

**Table 2.** Four-Step Solid-Phase Synthesis of *sn*-1,2-Diacyglycerols **8**

| entry | $R^1$ (carboxylic acid) | $R^2$ (carboxylic acid) | (yield)[a,b] (%) |
|---|---|---|---|
| **8a** | palmitic acid[c] | valeric acid | 29 |
| **8b** | palmitic acid | vinyl acetic acid | 31 |
| **8c** | palmitic acid | cyclohexane carboxylic acid | 23 |
| **8d** | palmitic acid | decanoic acid[d] | 15 |
| **8e** | palmitic acid | oleic acid[e] | 20 |
| **8f** | palmitic acid | palmitic acid | 17 |
| **8 g** | palmitic acid | stearic acid[f] | 23 |
| **8h** | stearic acid | valeric acid | 25 |
| **8i** | stearic acid | stearic acid | 30 |
| **8j** | isovaleric acid | isobutylic acid | 21 |
| **8k** | isovaleric acid | isovaleric acid | 27 |
| **8l** | isovaleric acid | cyclohexane carboxylic acid | 24 |
| **8m** | isovaleric acid | palmitic acid | 14 |
| **8n** | isovaleric acid | stearic acid | 29 |
| **8o** | isobutylic acid | isobutylic acid | 33 |
| **8p** | isobutylic acid | valeric acid | 22 |
| **8q** | isobutylic acid | cyclohexane carboxylic acid | 35 |
| **8r** | isobutylic acid | decanoic acid | 26 |
| **8s** | isobutylic acid | palmitic acid | 28 |
| **8t** | isobutylic acid | stearic acid | 21 |

[a] Four-step overall yields from 2-chlorotrityl chloride resin **1** (loading capacity of the resin **1** is 1.3 mmol $g^{-1}$). [b] Yield after column chromatography of crude product. [c] Palmitic acid is $CH_3(CH_2)_{14}COOH$. [d] Decanoic acid is $CH_3(CH_2)_7COOH$. [e] Oleic acid is *trans*-$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$. [f] Stearic acid is $CH_3(CH_2)_{14}COOH$.

**Table 3.** Solid-Phase Synthesis of **10a**−**f**

| entry | $R^1$ (carboxylic acid) | $R^2$ (carboxylic acid) | yield[a,b] (%) |
|---|---|---|---|
| **10a** | palmitic acid | valeric acid | 21 |
| **10b** | palmitic acid | stearic acid | 31 |
| **10c** | isovaleric acid | cyclohexane carboxylic acid | 27 |
| **10d** | cyclohexane carboxylic acid | stearic acid | 22 |
| **10e** | cyclohexane carboxylic acid | valeric acid | 17 |
| **10f** | cyclohexane carboxylic acid | cyclohexane carboxylic acid | 15 |

[a] Four-step overall yields from 2-chlorotrityl chloride resin **1** (loading capacity of the resin **1** is 1.3 mmol $g^{-1}$). [b] Yield after column chromatography of crude product.

optical rotation of **8k** ($[\alpha]^{20}_D = -3.01$ ($c = 0.46$, $CHCl_3$)) and the reported value of the (s)-enantiomer ($[\alpha]^{20}_D = -3.92$ ($c = 3.34$, $CHCl_3$)).[6c]

The preparative potential of this solid-phase procedure was also explored in the context of *sn*-2,3-diacylglycerol synthesis. The Mitsunobu reaction[6b] of monoacylglycerol resins **5** was used to generate the diacylglycerol resin **9**, having inverted C-2 configurations. Accordingly, resin **5** was subjected to Mitsunobu reactions with carboxylic acid by using diisopropyl azodicarboxylate (DIAD) and triphenylphosphine.[12] The polymer-bound diacylglycerol **9,** formed in these process, display strong ester bands (Figure 2E) in their single-bead ATR-FTIR spectra. With this procedure, a variety of *sn*-2,3-diacylglycerols **10** are produced in good four-step overall yields (Table 3).

In conclusion, this effort has demonstrated that *sn*-1,2-diacylglycerol derivatives **8** and *sn*-2,3-diacyglycerol derivatives **10** can be efficiently generated using a novel solid-phase synthesis protocol. The polymer-bound *sn*-1-monoacylglycerol resin **5** served as key intermediate. This method can synthesize *sn*-1,2- and *sn*-2,3-diacyglycerol derivatives in good four-step overall yields with various carboxylic acids via a DIC coupling reaction and Mitsunobu esterfication, respectively.

## Experimental Section

**Materials and Methods.** The polystyrene Merrifield resin (1.3 mmol $g^{-1}$, 1% cross-linking, 100−200 mesh) was obtained from BeadTech Inc., Korea. Solvents were purchased from Merck and were anhydrous and HPLC grade. Reactions, filtrations, and washings were carried out on a MiniBlock (Bohdan). Solvent evaporation was performed on a GeneVac Atlas HT-4 centrifugal evaporator. Crude products were purified by parallel chromatography using a QuadFlash silica cartridge (Biotage catalog no. QK0-1107-1504L). All of the intermediate resins were monitored by ATR-FTIR (SensIR Technology). The structures of the final products were confirmed by $^1H$ NMR and $^{13}C$ NMR (Bruker AMX-500 FT NMR).

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**Supporting Information Available.** $^1H$ NMR spectral data and polarimetric data of compounds **8a**−**t** and **10a**−**f**, $^{13}C$ NMR spectral data and elemental analysis of compound **8a**, FAB-MS data of **8a** and **10a**, optical purity (enantiomeric excess) and $^1H$ NMR spectral data of the Mosher ester of **8a** and **10a**, and procedure for preparation of the Mosher ester of **8a**.

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(11) General procedure for the synthesis of **8a**. To a suspension of 2-chlorotrityl chloride resin **1** (5 g, 6.5 mmol, 1.3 mmol $g^{-1}$) in dry DCM (50 mL) was added TEA (5.6 ml, 40 mmol), followed by the slow addition of (*S*)-glycidol (2.7 ml, 40 mmol) in dry DCM at 0 °C. The suspension was shaken for 48 h at room temperature under an argon atmosphere. The glycidyl-bound resin **3** was filtered, washed with DMF (2 × 100 mL), DCM (2 × 100 mL), and MeOH (2 × 100 mL), and dried under high vacuum. The glycidyl bound resin **3** (2.0 g, 2.6 mmol) was suspended in dry DMF (30 mL), and TBAB (83 mg, 0.26 mmol) and palmitic acid (6.7 g, 26.0 mmol) were successively added. The mixture was shaken for 16 h at 90 °C. The polymer-bound monoacylglycerol resin **5a** was filtered, washed with DMF (2 × 100 mL), DCM (2 × 100 mL), and MeOH (2 × 100 mL), and dried under high vacuum. The polymer-bound monoacylglycerol resin **5a** (100 mg, 0.13 mmol) was swollen in DMF (4 mL) and DIC (0.1 mL, 0.65 mmol), followed by the addition of valeric acid (0.07 mL, 0.65 mmol). After the reaction was shaken for 12 h at room temperature, the polymer-bound diacylglycerol resin **7a** was filtered and washed with DMF (2 × 20 mL), DCM (2 × 20 mL), and MeOH (2 × 20 mL) and dried under high vacuum. The polymer-bound diacylglycerol resin **7a** (100 mg, 0.13 mmol) in DCM (4 mL) was added to boron trichloride (0.65 mL, 0.65 mmol, 1.0 M in DCM) at −20 °C for 1 hr, The reaction mixture was poured into a saturated $NaHCO_3$ solution, and the organic layer was concentrated. Purification by column chromatography gave the corresponding desired product, hexadecanoic acid 3-hydroxy-2-pentanoyloxy-propyl ester (**8a**). $[\alpha]^{20}_D$: −3.57 ($c$ = 0.37, $CHCl_3$). Enantiomeric excess (ee): 82%. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 5.08 (m, 1H), 4.31 (d, 1H, $J$ = 4.5 Hz), 4.25 (d, 1H, $J$ = 5.7 Hz), 3.73 (m, 2H), 2.36 (t, 2H, $J$ = 7.6 Hz), 2.32 (t, 2H, $J$ = 7.6 Hz), 1.62−1.60 (m, 4H), 1.29−1.25 (m, 26H), 0.92 (t, 3H, $J$ = 7.4 Hz), 0.88 (t, 3H, $J$ = 6.8 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 173.83, 173.45, 72.12, 62.00, 61.56, 45.78, 34.12, 34.01, 31.93, 29.70, 29.66, 29.62, 29.47, 29.37, 29.27, 29.13, 27.00, 24.90, 22.70, 22.20, 14.13, 13.71. Anal Calcd for $C_{24}H_{46}O_5$ (414.33): C, 69.52; H, 11.18. Found: C, 69.55; H, 11.15. FAB-MS ($m/z$ + $Na^+$): 437. The enantiomeric purity was determinated by the Mosher ester by esterfication of **8a** and **10a.** The NMR signal for the $OCH_3$ group is found at $\delta$ 3.54/3.53 (ratio 1.00/0.10) for the Mosher ester of **8a**.[5e] The Mosher ester of **8a** was prepared as described below. The Mosher ester was prepared by reaction of **8a** (25 mg, 0.06 mmol) with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (23 mg, 0.09 mmol) in a cooled (ice bath) solution in triethylamine. The mixture was stirred at ice bath temperature for 1 h and then at room temperature for 1 h. Ether was added, and the ether layer was washed with aqueous saturated $NaHCO_3$; the layers were separated, and the aqueous layer was washed twice with ether. The ether extracts were combined, dried ($Na_2SO_4$), filtered, and concentrated to give 35 mg (92%) of the desired ester, the Mosher ester of **8a**. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.50 (m, 2H), 7.41 (m, 3H), 5.31 (m, 1H), 4.59 (dd, 1H, $J$ = 11.9 Hz, $J$ = 3.8 Hz), 4.36 (dd, 1H, $J$ = 11.9 Hz, $J$ = 5.5 Hz), 4.26 (dd, 1H, $J$ = 11.9 Hz, $J$ = 4.7 Hz), 4.12 (dd, 1H, $J$ = 11.9 Hz, $J$ = 5.8 Hz), 3.54 and 3.53 (s, 3H), 2.31−2.26 (m, 4H), 1.60−1.54 (m, 4H), 1.32−1.25 (m, 26H), 0.91−0.87 (m, 6H).

(12) General procedure for the synthesis of **10a**. The polymer-bound monoacylglycerol resin **5** (100 mg, 0.13 mmol) was swollen in THF/DCM (1:1, 4 mL), followed by the addition of diisopropyl azodicaroxylate (0.13 mL, 0.65 mmol), triphenylphosphine (170 mg, 0.65 mmol), and valeric acid (0.07 mL, 0.65 mmol). After the reaction was shaken for 12 h at room temperature, the polymer-bound diacylglycerol resin **9a** was filtered, washed with DMF (2 × 20 mL), DCM (2 × 20 mL), and MeOH (2 × 20 mL), and dried under high vacuum. To the polymer-bound diacylglycerol resin 9**a** (100 mg, 0.13 mmol) in DCM (4 mL) was added boron trichloride (0.65 mL, 0.65 mmol, 1.0 M in DCM) at −20 °C for 1 h. The reaction mixture was poured into a saturated $NaHCO_3$ solution, and the organic layer was concentrated. Purification by column chromatography gave the corresponding desired product, hexadecanoic acid 3-hydroxy-2-pentanoyloxy-propyl ester (**10a**). $[\alpha]_D$: +2.88 ($c$ = 0.33, $CHCl_3$). Enantiomeric excess (ee): 69%. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 5.08 (m, 1H), 4.31 (d, 1H, $J$ = 4.6 Hz), 4.25 (d, 1H, $J$ = 12.0 Hz, $J$ = 5.7 Hz), 3.73 (m, 2H), 2.36 (t, 2H, $J$ = 7.6 Hz), 2.32 (t, 2H, $J$ = 7.5 Hz), 1.62−1.60 (m, 4H), 1.28−1.25 (m, 26H), 0.92 (t, 3H, $J$ = 7.4 Hz), 0.88 (t, 3H, $J$ = 6.8 Hz). FAB-MS ($m/z$ + $Na^+$): 437. The NMR signal for the $OCH_3$ group is found at $\delta$ 3.54/3.53 (ratio 1.00/5.35) for the Mosher ester of **10a** $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.50 (m, 2H), 7.41 (m, 3H), 5.31 (m, 1H), 4.59 (dd, 1H, $J$ = 11.9 Hz, $J$ = 3.9 Hz), 4.37 (dd, 1H, $J$ = 11.9 Hz, $J$ = 5.8 Hz), 4.27 (dd, 1H, $J$ = 11.9 Hz, $J$ = 4.6 Hz), 4.08 (dd, 1H, $J$ = 11.9 Hz, $J$ = 5.6 Hz), 3.54 and 3.53 (s, 3H), 2.31−2.26 (m, 4H), 1.60−1.54 (m, 4H), 1.32−1.25 (m, 26H), 0.91−0.87 (m, 6H). Octadecanoic acid 1-hexadecanoyloxymethyl-2-hydroxy-ethyl ester (**10b**). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 5.08 (m, 1H), 4.31 (d, 1H, $J$ = 4.5 Hz), 4.25 (d, 1H, $J$ = 6.6 Hz), 3.74 (d, 2H, $J$ = 5.4 Hz), 2.35 (t, 2H, $J$ = 7.5 Hz), 2.32 (t, 2H, $J$ = 7.5 Hz), 1.62 (m, 4H), 1.30−1.25 (m, 52H), 0.88 (t, 6H, $J$ = 6.8 Hz). $[\alpha]_D$: +1.84 ($c$ = 0.31, $CHCl_3$).

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