A Convergent Synthesis of Bis-2-oxo Amide Triacylglycerol Analogues as Potent Lipase Inhibitors Using Acyl Cyanophosphorane Methodology

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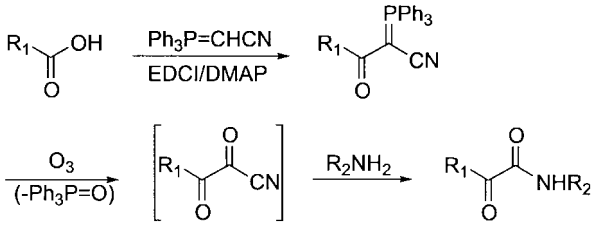
A number of bis-2-oxo amide triacylglycerol analogues, a recently reported potent human gastric lipase inhibitor and its new analogues, have been prepared starting from 1,3-dibromo-2-propanol utilizing acyl cyanophosphorane methodology as a key step in a convergent manner. The key coupling reaction has been accomplished at -78 °C between 1,3-diamino-2-propanol derivative and the labile diketo nitriles, derived from acyl cyanotriphenylphosphoranes upon oxidizing with O_3, under mild condition in moderate yields.

Keywords : Lipase inhibitors, Bis-2-oxo amide triacylglycerol, α-Keto amide, Cyano triphenylphosphorane.

Introduction

Lipase (*gastric and pancreatic*) inhibition has been the subject of considerable research interest in recent years not only because it may provide important information regarding the mechanism of enzyme action,[1] but also because it could ultimately lead to the development of new anti-obesity drugs.[2] Several types of lipase inhibitors have been reported so far,[3] and one of the key structural features of many inhibitors is the presence of electrophilic carbonyl residues such as trifluoromethyl ketones,[3a] tricarbonyls,[3b] α-keto esters,[3c] and most recently α-keto amides[3d,e] at the reactive centers in the molecules. Among these electron-deficient carbonyl residues, α-keto amide[4] is of special interest since it is the most frequently encountered electrophilic ketone pharmacophore found in many potent inhibitors of proteolytic enzymes e.g., serine protease, and chymase.[5] The conventional synthetic routes for α-keto amide residues are the oxidation of α-hydroxy amides using various oxidizing reagents,[6a] and the amidation of α-keto esters with amine nucleophiles.[6b] These two routes, however, lack generality and suffer from lengthy procedures. Several other approaches[6c,d,e] reported in the literature were also suffered from limited scopes. In order to circumvent these problems, Wasserman and co-workers have recently developed a *de novo* synthetic approach,[7] in which the acyl cyanophosphoranes are oxidized with O_3[7] or dimethyldioxirane[8] to furnish the labile α,β-diketo nitrile which then undergoes amidation to form an α-keto amide in a convergent manner (Eq. 1).



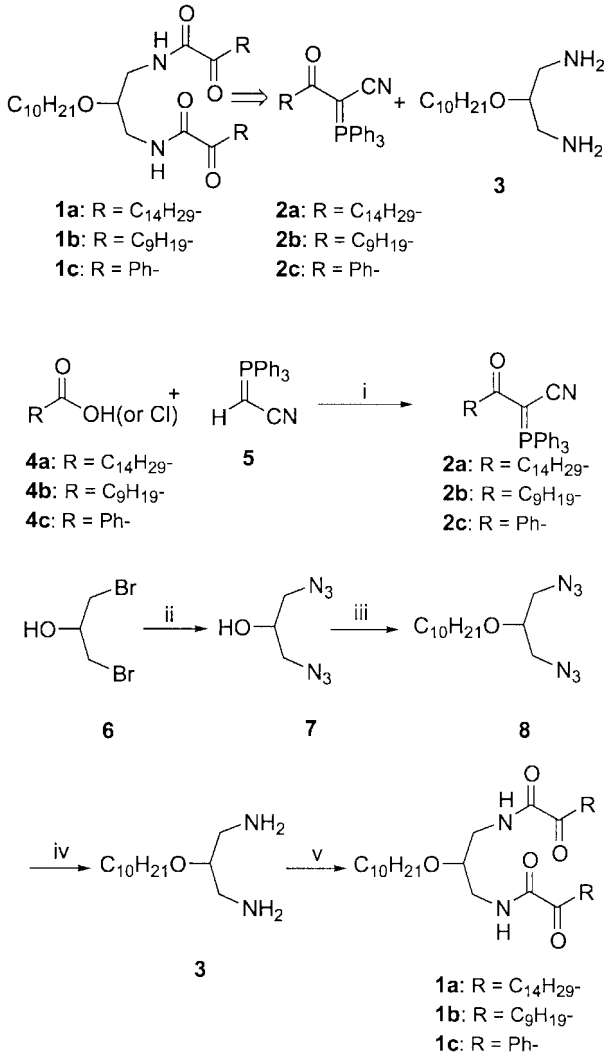
(1)

This approach has successfully been employed in the synthesis of several naturally occurring enzyme inhibitors such as poststatin,[9a] eurystatin A,[9b] bestatin,[9c] and several marine metabolites,[9d] and has recently been extended further for the synthesis of tricarbonyl units.[10] With this novel approach in mind, we envisioned that 2-oxo amide triacylglycerol analogues,[3e] recently reported human gastric lipase inhibitors, could efficiently be synthesized via Wassermans protocol in a convergent way.

Results and Discussion

Among several inhibitors reported,[3e] compound **1a**, the most effective lipase inhibitor in ether type compounds, and its new analogues **1b**, **1c** have been chosen as the representative compounds in our synthesis (Scheme 1).

In a retrosynthetic sense, the synthesis of compounds (**1a**, **b**, **c**) necessitates two compounds *i.e.*, acyl cyanophosphoranes (**2a**, **b**, **c**) and diamine derivative **3** as key intermediates as outlined in Scheme 1. The requisite acyl cyanophosphoranes **2** were readily prepared from the corresponding carboxylic acids **4** and (cyanomethylene)triphenylphosphorane (**5**)[11] according to the reported procedure[7, 9d] in good yields. The synthetic pathway to diamine counterpart **3** began with the commercially available 1,3-dibromo-2-propanol **6**, which was treated with NaN_3/DMF at 80 °C for 24 h to afford 1,3-diazido-2-propanol **7** in good yield.[12] In order to attach the *n*-decyl linkage to hydroxyl group of **7**,[13] the recently developed cesium-mediated protocol[13b] was adopted. Thus, treatment of 1,3-diazido-2-propanol **7** with $CsOH \cdot H_2O$ in the presence of 4-Å molecular sieve, and then with *n*-decyl bromide/ TBAI gave ether derivative **8** in high yield. Final conversion of diazide **8** into diamine **3** was accomplished quantitatively by hydrogenating over Pd/C (10%) in *ca.* 4-6 h under atmospheric pressure of hydrogen.[14] With two requisite compounds (**2**, **3**) in hand, the key coupling reaction was attempted as usual[7]: ozone-bubbling of the precooled (-78 °C) solution of **2a** (2.20 equiv) in CH_2Cl_2 for *ca.* 20 min in the presence of a small amount of activated 4-Å molecular sieve, then purging of the resulting solution (-78 °C) with argon for *ca.* 15 min afforded the diketo nitrile intermediate as a pale yellow solution. When this diketo nitrile solution



Scheme 1

(CH_2Cl_2, -78 °C) was reacted with diamine **3** by transferring diamine solution (DMSO/CH_2Cl_2, rt)[15] into the afore-mentioned diketo nitrile solution, the desired product **1a** was obtained in *ca.* 51% yield after purification by column chromatography. The coupling product **1a** was easily identified by ^{1}H-NMR, in which the amide protons (2H) appeared in highly down filed (*ca.* 7.4 ppm) as a broad multiplet owing to the adjacent α-oxo group, and the methylene protons (4H) next to the α, β-dicarbonyl residues appeared in *ca.* 2.9 ppm as a triplet. ^{13}C-nmr spectrum also indicated the presence of two carbonyl peaks at 160.67, 198.73 ppm corresponding to the amide carbon and α-oxo carbon, respectively. Other spectral data including ir clearly supported the formation of the desired product, and each peak matched exactly with reported values.[3e] It is noteworthy to mention that pentadecanoic acid was obtained in *ca.* 7-8% yield together with a couple of minor by-products.[16] The formation of this acid could be rationalized by the nucleophilic attack of H_2O molecule on the highly electrophilic α-oxo carbon atom of the labile α,β-diketo nitrile intermediate. With promising result in hand, we next tested decanoic acid derived-phosphorane ylide (**2b**) under the similar reaction condition to check the generality of our reaction. The tlc-pattern of the reaction mixture was similar with that of previous reaction, and the new coupling product (**1b**) was obtained in *ca.* 53% yield after flash column chromatography. In order to determine the scope of our reaction, phenyl substituted-cyanophosphorane ylide (**2c**) was also subjected to the same reaction condition to provide the target molecule **1c** in moderate yield (47%).

Experimental Section

All reactions were carried out in oven-dried glassware under an argon atmosphere. Melting points were taken on a Electrothermal melting-point apparatus and are not corrected. IR-spectra were obtained on a JASCO FT-IR/410 using KBr or as CH_2Cl_2 solution. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were obtained in $CDCl_3$ or CD_3OD on Bruker Avance 400 or on Jeol spectrometer, and chemical shifts (δ) were reported in ppm downfield from tetramethylsilane. Mass spectra were obtained on a VG Autospec Ultima instrument in EI (70 eV) mode at the Research Supporting Team of KAIST. Flash column chromatography was carried out on silica gel (Merck, 230-400 mesh) and solvents were reported as V/V percent mixtures. CH_2Cl_2 was distilled from calcium hydride. (Cyanomethylene)triphenylphosphorane was prepared from (cyanomethylene)triphenylphosphonium chloride (Lancaster Synth. Inc.) according to the literature procedures.[9a] 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), bis-(trimethylsilyl)-acetamide (BSA), 4-dimethylaminopyridine (DMAP), 1,3-dibromo-2-propanol, $CsOH·H_2O$, tetrabutylammonium iodide (TBAI), dry DMF, dry DMSO, and Pd-C (10%) were purchased from Aldrich Chemical Co., and were used without purification. All other commercial reagents were purchased from commercial sources and used as received unless otherwise stated.

(Triphenylphosphoranylidene)pentadecanoylacetonitrile (2a): To a precooled (0 °C), stirred solution of pentadecanoic acid **4a** (1.53 g, 6.31 mmol) and (cyanomethylene)triphenylphosphorane **5** (1.90 g, 1.0 equiv) in 25 mL of dry CH_2Cl_2 were added EDCI (1.21 g, 1.0 equiv) and DMAP (cat). After being stirred at 0 °C for 1 h and at room temperature overnight under Ar, the reaction mixture was quenched with brine (30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (15 mL × 2). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated. The remaining residue was flash chromatographed on SiO_2 (Hexane/EtOAc, 2.5/1) to afford

2.80 g (85%) of **2a** as a white solid: R_f = 0.59 (Hexane/EtOAc, 1/1); mp 123-124 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H, *J* = 6.8 Hz, C*H*$_3$-), 1.25 (bs, 22H, $CH_3CH_2(CH_2)_{11}$-), 1.66 (m, 2H, CH_3CH_2-), 2.68 (t, 2H, *J* = 7.3 Hz, -C*H*$_2$C(=O)-), 7.50-7.63 (m, 15H, *aromatic*-H); ^{13}C-NMR ($CDCl_3$) δ 14.07, 22.65, 25.59, 29.32, 29.41, 29.49, 29.59, 29.63, 29.67, 31.89, 39.63 (d, *J* = 7.0 Hz), 48.27 (d, *J* = 126.0 Hz), 122.75 (d, *J* = 16.8 Hz), 123.08, 124.01, 129.04 (d, *J* = 12.6 Hz), 132.94 (d, *J* = 2.7 Hz), 133.57 (d, *J* = 10.2 Hz), 197.61 (d, *J* = 3.2 Hz); IR (KBr) 3066, 2922, 2949, 2173, 1581, 1435, 1176, 1105, 694 cm^{-1}; HRMS calcd for $C_{35}H_{44}NOP$ 525.3161, found 525.3153.

(Triphenylphosphoranylidene)decanoylacetonitrile (2b): Compound **2b** was obtained following the same procedure as described for **2a** from decanoic acid **4b** in 81% yield: White solid; R_f = 0.46 (Hexane/EtOAc, 1/1); mp 116.0-117.0 °C; ^{1}H-NMR ($CDCl_3$) δ 0.85 (t, 3H, *J* = 6.8 Hz, C*H*$_3$-), 1.27 (bs, 12H, $CH_3CH_2(CH_2)_6$-), 1.64 (m, 2H, CH_3CH_2-), 2.66 (t, 2H, *J* = 7.5 Hz, -C*H*$_2$C(=O)-), 7.46-7.61 (m, 15H, *aromatic*-H); ^{13}C-NMR ($CDCl_3$) δ 14.09, 22.66, 25.58, 29.29, 29.41, 29.49, 29.54, 31.89, 39.63 (d, *J* = 7.0 Hz), 48.26 (d, *J* = 125.9 Hz), 122.80 (d, *J* = 16.9 Hz), 123.05, 123.98, 129.05 (d, *J* = 12.8 Hz), 132.95 (d, *J* = 2.8 Hz), 133.57 (d, *J* = 10.2 Hz), 197.60 (d, *J* = 3.8 Hz); IR (KBr) 3068, 2925, 2852, 2174, 1582, 1175, 1108, 693 cm^{-1}; HRMS calcd for $C_{30}H_{34}NOP$ 455.2378, found 455.2314.

(Triphenylphosphoranylidene)benzoylacetonitrile (2c): To a stirred, precooled (0 °C) solution of (cyanomethylene) triphenylphosphorane **5** (1.17 g, 3.87 mmol) and BSA (1.15 mL, 1.20 equiv) in 20 mL of dry CH_2Cl_2 was added benzoyl chloride **4c** (448.8 μL, 1.00 equiv) by syringe, and the resulting solution was stirred for 30 min at 0 °C, then for 12h at rt under Ar. The reaction was quenched by addition of dilute $NaHCO_3$ (20 mL), and two layers separated. The aqueous layer was extracted further with CH_2Cl_2 (10 mL × 3), and the combined organic layers were washed with saturated brine, dried over $MgSO_4$ and evaporated. Purification of the crude product by flash column chromatography on SiO_2 (Hexane/EtOAc, 1/1) afforded **2c** as a white solid: Yield: 83%; R_f = 0.57 (Hexane/EtOAc, 1/1); mp 204.0-206.0 °C (lit.[7] 205.0-207.0 °C); ^{1}H-NMR ($CDCl_3$) δ 7.37-7.72 (m, 18H, *aromatic*-H), 8.01 (bd, 2H, *aromatic*-H); IR (KBr) 3058, 2175, 1548, 1439, 1340, 1211, 1110, 709 cm^{-1}.

1,3-Diazido-2-propanol (7): A mixture of 1,3-dibromo-2-propanol **6** (3.43 g, 15.8 mmol) and NaN_3 (3.07 g, 3.0 equiv) in 20 mL of dry DMF was heated at 80 °C for 24 h under Ar. Upon cooling to room temperature the reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (15 mL × 3). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and filtered. The solvent was evaporated *in vacuo*, and the oily residue was purified by flash column chromatography on SiO_2 (Hexane/EtOAc, 3/1) to afford **7** (1.96 g, 88%) as a colorless oil: R_f = 0.36 (Hexane/EtOAc, 3/1); ^{1}H-NMR ($CDCl_3$) δ 2.41 (bs, 1H, *H*OCH-), 3.37-3.46 (m, 4H, 2 × -C*H*$_2$N$_3$), 3.94 (m, 1H, HOC*H*-); IR (CH_2Cl_2) 3414, 2107, 1445, 1280, 1096 cm^{-1}.

1,3-Diazido-2-decyloxypropane (8): A mixture of **7** (499.0 mg, 3.51 mmol), $CsOH\cdot H_2O$ (1.18 g, 2.0 equiv), and 4-Å molecular sieve (199.6 mg) in 10 mL of dry CH_3CN was vigorously stirred at room temperature for 20 min under Ar. To this were added 1-bromodecane (2.19 mL, 3.0 equiv) and TBAI (1.30 g, 1.0 equiv), and the resulting mixture was stirred at room temperature for 48 h under Ar. The mixture was filtered, and the filtrate was concentrated *in vacuo*. Flash column chromatography of the residue on SiO_2 (Hexane/EtOAc, 2/1) provided **8** (861.0 mg, 87%) as a colorless oil: R_f = 0.38 (Hexane/CH_2Cl_2, 3/1); ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H, *J* = 6.6 Hz, C*H*$_3$-), 1.26 (bs, 14H, CH_3CH_2 (C*H*$_2$)$_7$-), 1.58-1.63 (m, 2H, CH_3CH_2-), 3.39 (d, 4H, *J* = 5.4 Hz, 2 × -C*H*$_2$N$_3$), 3.55-3.59 (m, 3H, -C*H*$_2$O-, -OC*H*-); ^{13}C-NMR ($CDCl_3$) δ 14.09, 22.66, 25.92, 29.28, 29.39, 29.53, 29.91, 31.87, 51.65, 70.77, 77.85; IR (CH_2Cl_2) 2925, 2877, 1461, 1284, 1113 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{24}N_2O$ (M-2N$_2$) 226.2045, found 226.2050.

1,3-Diamino-2-decyloxypropane (3): A suspension Pd-C (10%) (146.0 mg, 20%) and **8** (730.0 mg, 2.59 mmol) in ethanol (15 mL) was hydrogenated under atmospheric pressure of hydrogen at room temperature for *ca*. 6 h. The catalyst was filtered and washed well with MeOH (15 mL). Removal of the solvent *in vacuo* gave diamine **3** (578.5 mg, 97%) as a white viscous semisolid. ^{1}H-NMR (CD_3OD) δ 0.89 (t, 3H, *J* = 6.9 Hz, C*H*$_3$-), 1.29 (bs, 14H, $CH_3CH_2(CH_2)_7$-), 1.56-1.61 (m, 2H, CH_3CH_2-), 2.69 (dd, 2H, J_1 = 13.3 Hz, J_2 = 6.1 Hz, -C*H*$_2$NH$_2$), 2.75 (dd, 2H, J_1 = 13.3 Hz, J_2 = 4.9 Hz, -C*H*$_2$NH$_2$), 3.29 (m, 1H, -OC*H*-), 3.53 (t, 2H, *J* = 6.6 Hz, -C*H*$_2$O-); ^{13}C-NMR (CD_3OD) δ 14.49, 23.73, 27.33, 30.46, 30.63, 30.71, 30.76, 31.24, 33.06, 43.30, 70.90, 82.16; IR (CH_2Cl_2) 3336, 2924, 2854, 1628, 1494, 1344 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{30}N_2O$ 230.2358, found 230.2363.

***N*-[2-Decyloxy-3-[(2-oxohexadecanoyl)amino]propyl]-2-oxohexadecanamide (1a)**. A solution of ylide **2a** (245.6 mg, 2.20 equiv) in 25 mL of dry CH_2Cl_2 containing a small amount of activated molecular sieve (4-Å, *ca*. 100 mg) was treated with O_3 for 20 min at -78 °C and the resulting deep gray mixture was purged with Ar for 15 min at -78 °C. To this pale yellow solution was transferred a solution of diamine **3** (49.0 mg, 0.213 mmol) in mixed organic solvent (rt, 15 mL, DMSO/CH_2Cl_2, 1/2) via cannula, and the resulting mixture was stirred for 1 h in an ice bath under Ar. After removal of molecular sieve by filtration, the organic solution was washed with saturated brine (30 mL) and the aqueous layer was extracted further with CH_2Cl_2 (10 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. Flash column chromatography of the residue on SiO_2 using (Hexane/EtOAc, 5/1) provided **1a** (79.4 mg, 51%) as a white solid: R_f = 0.38 (Hexane/EtOAc, 3/1); mp 75.0-76.0 °C (lit.[3e] 61.0-63.0 °C); ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 9H, *J* = 6.6 Hz, 3 × C*H*$_3$-), 1.25 (bs, 58H, 29 × -C*H*$_2$-), 1.54-1.64 (m, 6H, 3 × CH_3CH_2-), 2.91 (t, 4H, *J* = 7.3 Hz, 2 × -C(=O)C*H*$_2$-), 3.27-3.34 (m, 2H, -C*H*$_2$NH-), 3.43-3.54 (m, 5H, -OC*H*-, -C*H*$_2$NH-, -C*H*$_2$O-), 7.40 (m, 2H, 2 × -N*H*-); ^{13}C-NMR ($CDCl_3$) δ 14.10, 22.67, 23.15, 26.06, 29.06, 29.34, 29.42, 29.43, 29.56, 29.59, 29.63, 29.66, 29.67, 29.87, 31.89, 31.90, 36.80, 39.64, 70.17, 75.74, 160.67, 198.73; IR

(KBr) 3335, 2922, 2852, 1714, 1667, 1542, 1648, 1135 cm^{-1}.

***N*-[2-Decyloxy-3-[(2-oxoundecanoyl)amino]propyl]-2-oxoundecanamide (1b)**: Compound **1b** was obtained following the same procedure as described for **1a** from **2b** and **3** in 53% yield: White solid; R_f = 0.35 (Hexane/EtOAc, 3/1); mp 68.0-69.0 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 9H, *J* = 6.8 Hz, 3 × C*H*$_3$-), 1.26 (bs, 38H, 19 × -C*H*$_2$-), 1.60 (m, 6H, 3 × CH$_3$C*H*$_2$-), 2.91 (t, 4H, *J* = 7.4 Hz, 2 × -C(=O)C*H*$_2$-), 3.29-3.32 (m, 2H, -C*H*$_2$NH-), 3.43-3.53 (m, 5H, -OC*H*-, -C*H*$_2$NH-, -C*H*$_2$O-); ^{13}C-NMR ($CDCl_3$) δ 14.08, 22.64, 22.67, 23.14, 26.05, 29.04, 29.23, 29.32, 29.38, 29.41, 29.55, 29.87, 31.84, 31.88, 36.79, 39.63, 70.17, 75.74, 160.66, 198.72; IR (KBr) 3342, 2922, 2854, 1722, 1667, 1530, 1132 cm^{-1}; HRMS (EI) calcd for $C_{35}H_{66}N_2O_5$ 594.4972, found 594.4970.

***N*-[2-Decyloxy-3-[(2-oxophenylacetoyl)amino]propyl]-2-oxophenylacetamide (1c)**: Compound **1c** was obtained following the same procedure as described for **1a** from **2c** and **3** in 47% yield: Colorless semisolid; R_f = 0.49 (Hexane/EtOAc, 2/1); ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 9H, *J* = 6.6 Hz, 3 × C*H*$_3$-), 1.26 (bs, 14H, 7 × -C*H*$_2$-), 1.58-1.60 (m, 2H, CH$_3$C*H*$_2$-), 3.43-3.46 (m, 2H, -C*H*$_2$NH-), 3.58-3.68 (m, 5H, -OC*H*-, -C*H*$_2$NH-, -C*H*$_2$O-), 7.49 (t, 4H, *J* = 7.8 Hz, *aromatic*-H), 7.58 (m, 2H, 2 × -N*H*-), 7.63 (t, 2H, *J* = 7.6 Hz, *aromatic*-H), 8.33 (d, 4H, *J* = 6.8 Hz, *aromatic*-H); ^{13}C-NMR ($CDCl_3$) δ 14.09, 22.65, 26.07, 29.28, 29.42, 29.54, 29.92, ν 31.85, 39.70, 70.24, 75.82, 128.48, 131.14, 133.19, 134.41, 162.38, 187.30; IR (KBr) 3339, 2927, 2855, 1667, 1523, 1220, 679 cm^{-1}; HRMS (EI) calcd for $C_{29}H_{38}N_2O_5$ 494.2780, found 494.2781.

Conclusion

We have shown that acyl cyanophosphorane methodology is an efficient tool for the synthesis of bis-2-oxo amide triacylglycerol analogues in a convergent way. The reaction conditions were mild and the yields were moderate to excellent. The methodology developed in this study should be valuable in the synthesis of other types of bis-2-oxo amide triacylglycerol analogues in a concise manner.

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15. Since diamine **3** was nearly insoluble in organic solvents such as CH_2Cl_2, THF and CH_3CN, polar solvent system (DMSO/CH_2Cl_2, rt) was utilized.
16. One minor by-product separated is thought to be a cyclized compound. The characterization is underway, and will be reported in due course.