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아실 시아노포스포레인과 아민 유도체로 부터 γ-아미노부틸산에서 유도된 포스포리파제 A_2 저해제의 효과적인 합성

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An Efficient Synthesis of γ-Aminobutyric Acid-Derived Phospholipase A_2 Inhibitors from Acyl Cyanophosphoranes and Amine Derivatives

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요 약. 일련의 유효한 γ-아미노부틸산에서 유도된 인간 시토솔릭 포스포리파제 A_2 저해제를 아실 시아노포스포레인과 아민 유도체로 부터 수렴적으로 합성하였다. 저해제 내의 친전자적인 단편인 알파-케토 아미드 작용기는 불안정한 α,β-디케토 니트릴과 γ-아미노-부틸산 삼차-부틸에스테르 유도체와의 직접 융합반응에 의하여 -78 °C에서 양호한 수율로 합성하였다.

주제어: 리파제 저해, 포스포리파제 A_2 저해제, α-케토 아미드, 아실 시아노포스포레인

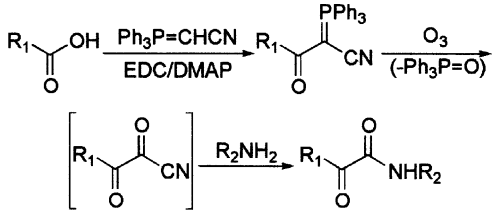
ABSTRACT. A series of γ-aminobutyric acid-derived, potent human cytosolic phospholipase A_2 inhibitors have been prepared from acyl cyanophosphoranes and amine derivatives in a convergent manner. The α-keto amide functionalities in the inhibitors have been introduced as electrophilic fragments via direct coupling reactions between the labile α,β-diketo nitriles and γ-aminobutyric acid *t*-butyl ester derivatives at -78 °C in moderate to good yields.

Keywords: Lipase Inhibition, Phospholipase A_2 Inhibitor, α-Keto Amide, Acyl Cyanophosphorane

INTRODUCTION

There has been a considerable research interest in phospholipase A_2 (PLA_2) inhibitors over the years since these compounds are known to have anti-inflammatory properties,[1] and therefore are considered to play key roles in controlling inflammatory diseases.[2] Several types of inhibitors *e.g.*, arachidonyl trifluoromethyl ketone,[3a] methyl arachidonyl fluorophosphonate,[3b] fatty acid tricarbonyls,[3c] amides of amino acids with long-chain amines,[2b] pyrrolidine-based inhibitors,[3d,e] and very recently lipophilic 2-oxoamide butyric acids[3f] have been reported. Among the electron-deficient carbonyl residues incorporated in the inhibitors, α-keto amide unit is of special interest since it is the most frequently encountered electrophilic ketone pharmacophore found in many potent inhibitors of proteolytic enzymes such as proteases, lipases and serine esterases.[4] A number of synthetic routes to a-keto amide unit including oxidation of α-hydroxy amide have been reported in the literature.[5] however, these approaches may have some limitations such as lengthy procedures, harsh reaction conditions, or limited scope.

Wasserman et. al. recently reported an elegant synthetic approach to this unit utilizing cyanophosphorane chemistry under mild conditions in a convergent manner (Eq. 1).[6]



This approach has been well exemplified in the syntheses of various biologically important natural products.[7] The same approach has been successfully applied to the synthesis of tricarbonyl unit.[8]

Very recently we have reported a convergent synthesis of 2-oxo amide triacylglycerol analogs of human gastric lipase inhibitors based on acyl cyanophosphorane chemistry.[9] As our continuing effort in this chemistry, we herein wish to report a successful synthesis of lipophilic 2-oxoamide g-aminobutyric acids, recently reported human cytosolic phospholipase A_2 inhibitors and a new analog, in a convergent manner.

EXPERIMENTAL SECTION

All reactions were carried out in oven-dried glassware under an argon atmosphere. THF was purified by distillation from Na/benzophenone, and CH_2Cl_2 was dried over CaH_2. Melting points were determined on an Electrothermal melting-point apparatus and were uncorrected. Optical rotations were measured on Jasco P-1020 Auto Polarimeter. FT IR spectra were obtained on a Jasco FT-IR/410 using KBr or as $CHCl_3$ solution. ^1H (400 MHz), ^{13}C NMR (100 MHz) and ^{19}F NMR (376 MHz) spectra were recorded on Jeol JNM-EX400 FT NMR spectrometer using $CDCl_3$ as solvent, and chemical shifts (δ) are given in ppm downfield with respect to the solvent or tetramethylsilane as an internal standard (for ^1H and ^{13}C NMR) or $CFCl_3$ as an external standard (for ^{19}F NMR). Mass spectra were measured with a VG Autospec Ultima instrument in EI (70 eV) mode. Flash column chromatography was carried out on silica gel (Merck, 230-400 mesh) and solvents were reported as V/V ratio mixtures. (Cyanomethylene)-triphenylphosphorane was synthesized from (cyanomethylene)tri-phenylphosphonium chloride according to the known procedure.[7a] IBX (*o*-Iodoxybenzoic acid) was prepared from 2-iodobenzoic acid following the literature procedure.[10] (Cyanomethylene)triphenylphosphonium chloride and *N*-Cbz-*L*-norleucine were purchased from Lancaster Synth. Inc.. EDCI, DMAP, NMM, HOBT, TFA (trifluoroacetic acid) and DME (1,2-dimethoxyethane) were purchased from Aldrich Chem. Co., and used without further purification. Other commercial reagents were purchased from commercial sources and used as received unless otherwise stated.

(Triphenylphosphoranylidene)pentadecanoylacetonitrile (2a). This ylide was prepared from pentadecanoic acid and (cyanomethylene)triphenylphosphorane (1.10 equiv) using EDCI (1.10 equiv)/DMAP (0.10 equiv) in 88% yield according to the literature procedure.[9] R_f – 0.32 (hexane/EtOAc, 2/1); mp 123.0-124.0 °C; IR (KBr) 3066, 2949, 2922, 2173, 1581 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J*–6.8 Hz, CH_3-), 1.25 (m, 22H, $CH_3(CH_2)_{11}$-), 1.66 (m, 2H, -CH_2CH_2C(=O)-), 2.68 (t, 2H, *J*=7.3 Hz, -CH_2C(=O)-), 7.45-7.73 (m, 15H, *aromatic*); ^{13}C NMR ($CDCl_3$) δ 14.13, 22.69, 25.62, 29.36, 29.44, 29.53, 29.62, 29.67, 29.71, 31.93, 39.66 (d, *J* = 6.7 Hz), 48.34 (d, *J*= 126.4 Hz), 122.85 (d, *J*=16.6 Hz), 123.48 (d, *J*=93.2 Hz), 129.08 (d, *J*=12.5 Hz), 133.00 (d, *J*–2.5 Hz), 133.58 (d, *J*–9.9 Hz), 197.68 (d, *J*–3.3 Hz).

(Triphenylphosphoranylidene)undecanoylacetonitrile (2b). Compound **2b** was prepared from undecanoic acid according to the same procedures described for **2a** in 85% yield. A white solid; R_f – 0.47 (Hexane/EtOAc, 3/2); mp 126.0-127.0 °C; IR (KBr) 3072, 3026, 2924, 2172, 1583 cm^{-1}; ^1H NMR ($CDCl_3$) d 0.88 (t, 3H, *J*=6.8 Hz, CH_3-), 1.26 (m, 14H, $CH_3(CH_2)_7$-), 1.66 (m, 2H, -CH_2CH_2C(=O)-), 2.68 (t, 2H, *J*=7.6 Hz, -CH_2C(=O)-), 7.42-7.70 (m, 15H, *aromatic*); ^{13}C NMR ($CDCl_3$) d 14.13, 22.69, 25.62, 29.35, 29.44, 29.51, 29.61, 31.92, 39.66 (d, *J* –6.7 Hz), 48.34 (d, *J*–125.6 Hz), 122.85 (d, *J*–17.4

Hz), 123.48 (d, *J*=93.2 Hz), 129.08 (d, *J*=13.3 Hz), 133.00 (d, *J*=2.5 Hz), 133.58 (d, *J*=9.9 Hz), 197.68 (d, *J*=3.3 Hz); MS (EI) m/z 183, 252, 262, 301, 318, 328, 343, 469; HRMS calcd for $C_{31}H_{36}NOP$ 469.2535, found 469.2551.

***t*-Butyl *N*-(benzyloxycarbonyl)-γ-aminobutyrate (5).** A stirred solution of *N*-(benzyloxycarbonyl)-γ-aminobutyric acid **4**[11] (834 mg, 3.52 mmol) in THF (10 mL) was treated successively with Et_3N (491 mL, 1.0 equiv) and 2,4,6-trichlorobenzoyl chloride (550 mL, 1.0 equiv), and the resulting mixture was stirred for 40 min at rt under Ar. The reaction mixture was filtered, and the filter-cake was washed with dry THF (10 mL). The solvent was evaporated under Ar to afford the mixed anhydride as a white gummy residue, which was dissolved again in dry benzene (10 mL). To this solution was transferred a solution of *t*-BuOH (673 μL, 2.0 equiv) and DMAP (860 mg, 2.0 equiv) in dry benzene (5 mL) *via* cannula, and the resulting mixture was stirred for 1.5 h at rt under Ar. The reaction mixture was diluted with Et_2O (30 mL), washed successively with 0.1 N HCl, H_2O, and saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide an oily residue. Flash column chromatography of the residue on SiO_2 using (Hexane/EtOAc, 3/1) gave pure compound **5**[11] (675 mg, 65%) as a colorless oil. R_f=0.43 (Hexane/EtOAc, 2/1); IR ($CHCl_3$) 3452, 3019, 2981, 1720, 1517 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H, -C(CH_3)$_3$), 1.79 (m, 2H, -$CH_2CH_2CH_2$-), 2.27 (t, 2H, *J*=7.3 Hz, -CH_2CO_2-), 3.23 (q, 2H, *J*=6.5 Hz, -NHCH_2-), 4.93 (br s, 1H, -N*H*-), 5.09 (s, 2H, PhCH_2-), 7.35 (m, 5H, *aromatic*); ^{13}C NMR ($CDCl_3$) δ 25.19, 28.07, 32.80, 40.51, 66.63, 80.53, 128.09, 128.35, 128.51, 136.57, 156.41, 172.61; MS (EI) m/z 57 , 91, 107, 108, 237, 293; HRMS calcd for $C_{16}H_{23}NO_4$ 293.1627, found 293.1611.

***t*-Butyl g-aminobutyrate (3a).** A stirred suspension of compound **5** (337 mg, 1.15 mmol) and 10% Pd/C (65 mg, ca. 20%) in EtOH (10 mL) was hydrogenated using H_2 balloon (1 atm) for 1.5 h at rt. The mixture was filtered over Celite, and the filter-cake was washed with EtOH, then Et_2O. The solvent was carefully evaporated under reduced pressure while maintaining the bath temperature below 20 °C to afford pure amine **3a**[11,12] (173 mg, 95%) as a colorless oil. IR ($CHCl_3$) 3446, 2980, 1719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H, -C(CH_3)$_3$), 1.74 (m, 2H, -$CH_2CH_2CH_2$-), 1.85 (br s, 2H, NH_2-), 2.27 (t, 2H, *J*=7.3 Hz, -CH_2CO_2-), 2.74 (br s, 2H, NH_2CH_2-); ^{13}C NMR ($CDCl_3$) δ 28.02, 28.79, 32.92, 41.35, 80.16, 172.84; MS (EI) m/z 55, 57, 71, 84, 86, 91, 102, 159; HRMS calcd for $C_8H_{17}NO_2$ 159.1259, found 159.1258.

(2*S*)-2-[(Benzyloxycarbonyl)amino]pentan-1-ol (7). To a stirred, precooled (-15 °C) solution of *N*-Cbz-*L*-norleucine (408 mg, 1.54 mmol) in DME (10 mL) was added *N*-methylmorpholine (190 mL, 1.0 equiv), followed by *i*-butyl chloroformate (226 mL, 1.0 equiv) and the resulting mixture was stirred for 1 min under Ar. The white solid of *N*-methylmorpholine·HCl formed immediately. The reaction mixture was filtered, and the filter-cake was washed with DME (10 mL). The combined filtrate was cooled again in an ice bath, then treated successively with $NaBH_4$ (98.1 mg, 1.5 equiv) in H_2O (2 mL) then H_2O (30 mL) immediately. The reaction mixture was stirred for additional 5 min at 0 °C, quenched with 0.1N HCl (15 mL), and extracted with EtOAc (15 mL × 3). The combined organic layers were washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by flash column chromatography on SiO_2 (Hexane/EtOAc, 3/2) gave 277 mg (72%) of **7** as a white solid. R_f= 0.53 (Hexane/EtOAc, 1/1); mp 91.0-92.0 °C; $[\alpha]_D^{23}$ -22.0° (c 0.78, CH_2Cl_2); IR (KBr) 3319, 3065, 2952, 2858, 1687, 1542 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (br s, 3H, -CH_3), 1.23-1.48 (m, 5H, -CHC*H*H- overlapped with -(CH_2)$_2$$CH_3$), 1.52 (m, 1H, -CHCH*H*-), 2.44 (br s, 1H, -O*H*), 3.55 (br s, 1H, -NHC*H*-), 3.68 (d, 2H, *J*=8.4 Hz, -CH_2OH), 4.92 (d, 1H, *J*=6.4 Hz, -N*H*-), 5.10 (s, 2H, PhCH_2O-), 7.35 (m, 5H, *aromatic*); ^{13}C NMR ($CDCl_3$) δ 13.96, 22.56, 28.13, 31.13, 53.31, 65.62, 66.87, 128.12, 128.18, 128.55, 136.40, 156.86; MS (EI) m/z 91, 176, 220, 251; HRMS calcd for $C_{13}H_{21}NO_3$ 251.1521, found 251.1521.

(2*S*)-2-[(Benzyloxycarbonyl)amino]pentanal (8). IBX (393 mg, 1.5 equiv) was added to a solution of amino alcohol **7** (235 mg, 0.935 mmol) in dry DMSO

(5 mL) and the resulting mixture was stirred for 5h at rt under Ar. The solution was diluted with H_2O (20 mL), filtered over Celite, and extracted with Et_2O (15 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. Filtration of the crude product through short column (SiO_2, Hexane/EtOAc, 3/1) provided aldehyde **8** (182 mg, 78%) as a colorless oil, which was pure enough for the next reaction. This almost pure aldehyde **8** was subjected immediately to the next reaction without further purification. R_f = 0.38 (Hexane/EtOAc, 2/1); $[\alpha]^{23}_{D}$+26.6° (c 0.80, CH_2Cl_2); IR ($CHCl_3$) 3435, 2960, 2863, 1717, 1508 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, *J*=6.1 Hz, -C*H*$_3$), 1.33 (m, 4H, -(C*H*$_2$)$_2$CH$_3$), 1.89 (m, 1H, -CHCH*H*-), 2.17 (m, 1H, -CHCH*H*-), 4.31 (dd, 1H, J_1=13.0 Hz, J_2= 7.0 Hz, -NHC*H*-), 5.12 (s, 2H, PhC*H*$_2$O-), 5.38 (d, 1H, *J*=6.0 Hz, -N*H*-), 7.36 (m, 5H, *aromatic*), 9.58 (s, 1H, -C*H*(=O)); ^{13}C NMR ($CDCl_3$) δ 13.81, 22.47, 27.13, 28.88, 60.24, 67.11, 128.14, 128.27, 128.58, 136.17, 156.10, 199.39; MS (EI) m/z 91, 92, 176, 220, 249; HRMS calcd for $C_{14}H_{19}NO_3$ 249.1365, found 249.1351.

***t*-Butyl (*E*, 4*S*)-4-[(benzyloxycarbonyl)amino]oct-2-enoate (9).** A solution of amino aldehyde **8** (169 mg, 0.679 mmol) and (*t*-butoxycarbonylmethylene)triphenyl-phosphorane (282 mg, 1.10 equiv) in dry THF (10 mL) was heated at reflux for 1.5 h under Ar. After evaporation of the solvent in vacuo, the oily residue was purified by flash column chromatography on SiO_2 (Hexane/Et_2O, 2/1) to afford **9** (171 mg, 73%) as a colorless oil. R_f = 0.32 (Hexane/Et_2O, 2/1); $[\alpha]^{23}_{D}$-10.8° (c 1.08, CH_2Cl_2); IR ($CHCl_3$) 3439, 3019, 2980, 2934, 2862, 1712, 1508 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (br s, 3H, -(CH$_2$)$_3$C*H*$_3$), 1.20-1.75 (m, 15H, -(C*H*$_2$)$_3$CH$_3$ overlapped with -C(C*H*$_3$)$_3$), 4.33 (m, 1H, -NHC*H*-), 4.76 (d, 1H, *J*=8.3 Hz, -N*H*-), 5.11 (dd, 2H, J_1=18.0 Hz, J_2=12.0 Hz, PhC*H*$_2$O-), 5.84 (d, 1H, *J*=15.5 Hz, -CH=C*H*CO$_2$-), 6.73 (dd, 1H, J_1=15.5 Hz, J_2=5.6 Hz -C*H*=CHCO$_2$-), 7.35 (m, 5H, *aromatic*); ^{13}C NMR ($CDCl_3$) δ 13.88, 22.38, 27.72, 28.11, 34.38, 51.95, 66.94, 80.57, 122.66, 128.16, 128.20, 128.56, 136.32, 146.74, 155.68, 165.61; MS (EI) m/z 91, 156, 190, 200, 234, 290, 291, 347; HRMS calcd for $C_{20}H_{29}NO_4$ 347.2097, found 347.2066.

***t*-Butyl (4*S*)-4-aminooctanoate (3b).** Compound **3b** was prepared from **9** according to the same procedures described for **3a**[12] in 100% yield. A colorless oil; $[\alpha]^{23}_{D}$-2.8° (c 0.85, CH_2Cl_2); IR ($CHCl_3$) 2964, 1719 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, *J*=6.3 Hz, -C*H*$_3$), 1.15-1.62 (m, 16H, -CHCH*H*- overlapped with -C*H*$_3$CH$_2$CO$_2$-, -(C*H*$_2$)$_2$CH$_3$, -C(C*H*$_3$)$_3$), 1.74 (br s, 3H, -CHCH*H*- overlapped with -N*H*$_2$), 2.29 (m, 2H, -C*H*$_2$CO$_2$H), 2.71 (br s, 1H, -NH$_2$C*H*-); ^{13}C NMR ($CDCl_3$) δ 13.96, 22.66, 27.99, 28.17, 32.29, 32.86, 37.52, 50.63, 80.02, 173.10; MS (EI) m/z 55, 57, 71, 84, 86, 91, 102, 215; HRMS calcd for $C_{12}H_{25}NO_2$ 215.1885, found 215.1880.

***S*-MTPA amide (10a).** To an ice-cooled solution of amine **3b** (15.0 mg, 0.0698 mmol) and HOBT (11.3 mg, 1.20 equiv) in CH_2Cl_2 (5 mL) was added *S*-(-)-MTPA (19.6 mg, 1.20 equiv), followed by EDCI (16.1 mg, 1.20 equiv), and the resulting mixture was stirred for 1 h at 0 °C then overnight at rt under Ar. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with H_2O and saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product was done by preparative-TLC (SiO_2, Hexane/Et_2O, 3/1). R_f = 0.41 (Hexane/EtOAc, 5/1); ^{1}H NMR ($CDCl_3$) δ 0.84 (t, 3H, *J*=6.8 Hz, -C*H*$_3$), 1.16-1.74 (m, 16H, -CHCH*H*(CH$_2$)$_2$- overlapped with -C*H*$_2$CH$_2$CO$_2$-, -(C*H*$_2$)$_2$CH$_3$, -C(C*H*$_3$)$_3$), 1.87 (m, 1H, -CHCH*H*(CH$_2$)$_2$-), 2.29 (m, 2H, -C*H*$_2$CO$_2$-), 3.41 (s, 3H, -OC*H*$_3$), 3.96 (m, 1H, -NHC*H*-), 6.64 (d, 1H, *J*=9.3 Hz, -N*H*-), 7.40 (br t, 3H, *J*=3.2 Hz, Ar-*H*^{m,p}), 7.52 (d, 1H, *J*=3.9 Hz, Ar-*H*^{o}); ^{19}F NMR ($CDCl_3$) d 11.10 (s, -OC*F*$_3$)

***R*-MTPA amide (10b).** Compound **10b** was prepared from **3b** and *R*-(+)-MTPA according to the same procedures described for **10a**. R_f = 0.41 (Hexane/EtOAc, 5/1); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, *J*=6.8 Hz, -C*H*$_3$), 1.15-1.74 (m, 16H, -CHCH*H*(CH$_2$)$_2$- overlapped with -C*H*$_2$CH$_2$CO$_2$-, -(C*H*$_2$)$_2$CH$_3$, -C(C*H*$_3$)$_3$), 1.86 (m, 1H, -CHCH*H*(CH$_2$)$_2$-), 2.16 (m, 2H, -C*H*$_2$CO$_2$-), 3.43 (s, 3H, -OC*H*$_3$), 3.96 (m, 1H, -NHC*H*-), 6.69 (d, 1H, *J*=9.3 Hz, -N*H*-), 7.40 (br t, 3H, *J*=3.4 Hz, Ar-*H*^{m,p}), 7.54 (br d, 2H, *J*=3.9 Hz, Ar-*H*^{o}); ^{19}F NMR ($CDCl_3$) δ 11.10 (s, -OC*F*$_3$)

***t*-Butyl 4-[(2-oxohexadecanoyl)amino]butanoate**

(11a). A precooled (-78 °C) solution of phosphorane ylide **2a** (228 mg, 1.3 equiv) in CH_2Cl_2 (25 mL) was bubbled with O_3 for 5 min, then purged with Ar for 5 min to afford a pale yellow solution. To this solution was transferred a precooled (-78 °C) solution of amine **3a** (53.2 mg, 0.335 mmol) in CH_2Cl_2 (5 mL) via cannula, and the resulting solution was stirred for 30 min at -78 °C, then allowed to warm to rt over 30 min under Ar. The solvent was evaporated under reduced pressure to afford a pale yellow solid, which was purified by flash column chromatography on SiO_2 using (Hexane/EtOAc/CH_2Cl_2, 16/2/1) to give the coupled product **11a** (77.0 mg, 56%) as an off-white solid. R_f = 0.53 (Hexane/Et_2O, 1/1); mp 59.0-60.5 °C; IR (KBr) 3348, 2981, 2956, 2920, 2850, 1728, 1660, 1523 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J*=6.8 Hz, -CH_3), 1.25 (br s, 22H, -$(CH_2)_{11}CH_3$), 1.45 (s, 9H, -C$(CH_3)_3$), 1.59 (m, 2H, -CH_2CH_2C(=O)-), 1.84 (m, 2H, -NHCH$_2CH_2CH_2$-), 2.28 (t, 2H, *J*=7.2 Hz, -CH_2CO_2-), 2.91 (t, 2H, *J*=7.4 Hz, -CH_2C(=O)-), 3.33 (q, 2H, *J*=6.7 Hz, -NHCH_2-), 7.12 (br s, 1H, -N*H*-); ^{13}C NMR ($CDCl_3$) δ 14.13, 22.70, 23.20, 24.49, 28.09, 29.08, 29.34, 29.37, 29.45, 29.60, 29.65, 29.68, 29.69, 31.93, 32.83, 36.75, 38.75, 80.73, 160.32, 172.28, 199.27; MS (EI) m/z 57, 86, 112, 130, 186, 225, 338, 411; HRMS caled for $C_{24}H_{45}NO_4$ 411.3349, found 411.3316.

4-[(2-Oxohexadecanoyl)amino]butanoic acid (1a). To a solution of **11a** (42.0 mg, 0.102 mmol) in CH_2Cl_2 (1.5 mL) was added TFA (1.5 mL) by syringe, and the resulting solution was stirred for 1.5 h at rt under Ar. The volatiles were evaporated in vacuo to provide a brown residue, which was flash column chromatographed on SiO_2 using (CH_2Cl_2/EtOAc/AcOH, 7/1/1%) as eluent. The fractions containing the desired product were combined, diluted with heptane, concentrated in vacuo while maintaining bath temperature below 20 °C, and dried under high vacuum to afford **1a**[3f] (35.8 mg, 99%) as an off-white solid; mp 99-100 °C; R_f = 0.53 (CH_2Cl_2/EtOAc/AcOH, 2/1/1%); IR (KBr) 3334, 2916, 2850, 1717, 1658, 1525 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J*=6.8 Hz, -CH_3), 1.25 (br s, 22H, -$(CH_2)_{11}CH_3$), 1.59 (m, 2H, -CH_2CH_2C(=O)-), 1.91 (m, 2H, -NHCH$_2CH_2$-), 2.43 (t, 2H, *J*=6.8 Hz, -CH_2CO_2H), 2.91 (t, 2H, *J*= 7.2 Hz, -CH_2C(=O)-), 3.38 (q, 2H, *J*=6.4 Hz, -NHCH_2-), 7.15 (br s, 1H, -N*H*-); ^{13}C NMR ($CDCl_3$) δ 14.13, 22.71, 23.20, 24.23, 28.08, 29.37, 29.46, 29.61, 29.67, 29.68, 29.70, 31.20, 31.94, 36.77, 38.59, 160.47, 178.06, 199.22; MS (EI) m/z 55, 57, 71, 85, 86, 112, 130, 225, 355; HRMS caled for $C_{20}H_{37}NO_4$ 355.2723, found 355.2725.

***t*-Butyl (4*S*)-4-[(2-oxododecanoyl)amino] octanoate (11b).** Compound **11b** was prepared from **2b** and **3b** according to the same procedures described for **11a** in 52% yield. A colorless oil; R_f = 0.38 (Hexane/Et_2O, 3/1); $[\alpha]^{26}_D$ -4.2° (c 1.05, CH_2Cl_2); IR ($CHCl_3$) 3391, 2929, 2857, 1719, 1684, 1521 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 6H, *J*=6.6 Hz, 2 x (-CH_3)), 1.20-1.75 (m, 32H, -CHC*H*CH- overlapped with -$CH_2CH_2CO_2$-, -$(CH_2)_2CH_3$, -C$(CH_3)_3$, -$(CH_2)_8CH_3$), 1.87 (m, 1H, -CHCH*H*-), 2.23 (m, 2H, -CH_2CO_2-), 2.91 (td, 2H, J_1=7.4 Hz, J_2=1.5 Hz, -CH_2C(=O)-), 3.86 (m, 1H, -NHC*H*-), 6.75 (d, 1H, *J*=9.2 Hz, -N*H*-); ^{13}C NMR ($CDCl_3$) δ 13.94, 14.12, 22.49, 22.69, 23.23, 27.96, 28.08, 29.09, 29.31, 29.35, 29.45, 29.56, 29.92, 31.90, 32.15, 34.82, 36.81, 49.37, 80.55, 159.96, 172.53, 199.53; MS (FI) m/z 57, 125, 142, 143, 168, 186, 338, 411; HRMS caled for $C_{24}H_{45}NO_4$ 411.3349, found 411.3357.

(4*S*)-4-[(2-Oxododecanoyl)amino]octanoic acid (1b). Compound **1b** was prepared from **11b** according to the same procedures described for **1a** in 98% yield. An off-white solid; mp 57.0-59.0 °C (lit.[3f] mp 50-52 °C); R_f = 0.32 (CH_2Cl_2/EtOAc/AcOH, 7/1/1%); $[\alpha]^{23}_D$ -6.3° (c 0.74, $CHCl_3$) (lit.[3f] $[a]_D$ -1.8° (c 0.5, $CHCl_3$)); IR (KBr) 3312, 2953, 2850, 1733, 1717, 1698, 1661, 1541 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 6H, *J*=6.2 Hz, 2 x (-CH_3)), 1.20-1.62 (m, 22H, $CH_2CH_2CO_2H$ overlapped with -$(CH_2)_2CH_3$, -$(CH_2)_8CH_3$)), 1.74 (m, 1H, -CHC*H*H-), 1.95 (m, 1H, -CHCH*H*-), 2.37 (m, 2H, -CH_2CO_2H), 2.92 (td, 2H, J_1=7.4 Hz, J_2=1.3 Hz, -CH_2C(=O)-), 3.92 (m, 1H, -NHC*H*-), 6.82 (d, 1H, *J*=9.6 Hz, -N*H*-); ^{13}C NMR($CDCl_3$) δ 13.93, 14.12, 22.46, 22.69, 23.22, 27.98, 29.08, 29.32, 29.36, 29.46, 29.57, 29.97, 30.73, 31.90, 34.79, 36.85, 49.34, 160.19, 177.93, 199.46; MS (EI) m/z 55, 57, 71, 83, 97, 117, 125, 143, 168, 186, 355; HRMS caled for $C_{20}H_{37}NO_4$ 355.2723, found 355.2723.

***t*-Butyl (4*S*)-4-[(2-oxohexadecanoyl)amino]octanoate**

(11c). Compound **11c** was prepared from **2a** and **3b** according to the same procedures described for **11a** in 50% yield. An off-white solid; R_f = 0.41 (Hexane/Et_2O, 4/1); mp 45.0-45.5 °C; $[\alpha]^{26}_D$ -4.3° (c 0.65, CH_2Cl_2); IR (KBr) 3333, 2918, 2849, 1721, 1664, 1528 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 6H, *J*=6.6 Hz, 2 x (-CH_3)), 1.18-1.75 (m, 40H, -CHC*H*H- overlapped with -$CH_2CH_2CO_2H$, -$(CH_2)_2CH_3$, -$C(CH_3)_3$, -$(CH_2)_{12}CH_3$), 1.86 (m, 1H, -CHCH*H*-), 2.23 (m, 2H, -CH_2CO_2-), 2.91 (td, 2H, J_1=7.4 Hz, J_2=1.7 Hz, -CH_2C(=O)-), 3.86 (m, 1H, -NHC*H*-), 6.74 (d, 1H, *J*=9.2 Hz, -N*H*-); ^{13}C NMR ($CDCl_3$) δ 13.94, 14.13, 22.49, 22.70, 23.23, 27.95, 28.08, 29.09, 29.37, 29.46, 29.61, 29.66, 29.68, 29.69, 29.91, 31.93, 32.15, 34.81, 36.82, 49.37, 80.56, 159.96, 172.53, 199.53; MS (EI) m/z 57, 73, 91, 117, 147, 207, 221, 265, 281, 295, 355, 369, 429, 467; HRMS calcd for $C_{28}H_{53}NO_4$ 467.3975, found 467.3952.

(4*S*)-4-[(2-Oxohexadecanoyl)amino]octanoic acid (1c). Compound **1c** was prepared from **11c** according to the same procedures described for **1a** in 98% yield. An off-white solid; R_f = 0.40 (CH_2Cl_2/EtOAc/AcOH, 5/1/1%); mp 77.0-78.0 °C; $[\alpha]^{26}_D$ -5.8° (c 0.69, $CHCl_3$); IR (KBr) 3327, 2954, 2916, 2849, 1733, 1717, 1699, 1655, 1541 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 6H, *J*=6.4 Hz, 2 x (-CH_3)), 1.18-1.65 (m, 30H, -$CH_2CH_2CO_2H$ overlapped with -$(CH_2)_2CH_3$, -$(CH_2)_{12}CH_3$), 1.75 (m, 1H, -CHC*H*H-), 1.94 (m, 1H, -CHCH*H*-), 2.36 (m, 2H, -CH_2CO_2H), 2.92 (td, 2H, J_1=7.2 Hz, J_2=2.1 Hz -CH_2C(=O)-), 3.92 (m, 1H, -NHC*H*-), 6.83 (d, 1H, *J*=9.6 Hz, -N*H*-); ^{13}C NMR ($CDCl_3$) δ 13.93, 14.13, 22.46, 22.71, 23.22, 27.98, 29.09, 29.37, 29.47, 29.62, 29.67, 29.68, 29.70, 29.97, 30.72, 31.93, 34.79, 36.85, 49.34, 160.19, 177.93, 199.45; MS (EI) m/z 55, 57, 71, 83, 97, 125, 143, 168, 186, 225, 411; HRMS calcd for $C_{24}H_{45}NO_4$ 411.3349, found 411.3349.

RESULTS AND DISCUSSION

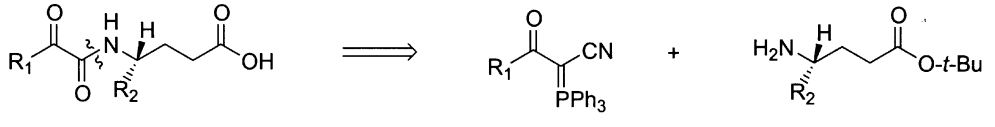
Two most active inhibitors **1a**/**b** among the several inhibitors tested in the recent study[3f] have been chosen as target molecules in our synthesis, and a simple retrosynthetic analysis of **1a**/**b** showed that they should be readily accessed from acyl cyanophosphoranes and the amine derivatives under mild conditions (*Scheme* 1).

The required acyl cyanophosphoranes **2a**/**b** were readily prepared in high yields from the commercially available carboxylic acids and cyanomethylenetriphenyl-phosphorane[13] according to the method described in the literature.[6]

To synthesize the appropriate amine derivatives for the key coupling reactions, *t*-butyl ester was adopted as an acid protecting group since it could be easily deblocked with TFA[14] under mild conditions in the final step (*Scheme* 2).

Therefore, several *t*-butyl ester protecting methods *e.g.*, *t*-BuOH/(EDCI, DMAP),[15a] *t*-BuOH/(CDI, DBU)[15b] and *t*-BuOH/(2,4,6-trichlorobenzoyl chloride, DMAP)[15c] were attempted for *N*-Cbz g-aminobutyric acid **4**, and *t*-BuOH/(2,4,6-trichlorobenzoyl chloride, DMAP) gave the best result. This *N*-Cbz g-aminobutyric acid *t*-butyl ester **5** was then catalytically hydrogenated with Pd-C (10%)/H_2 (1 atm)[16] to provide g-aminobutyric acid *t*-butyl ester **3a** in excellent yield.

The synthesis of another amine derivative **3b** began with the commercially available *N*-Cbz-*L*-norleucine **6**, which was treated with *i*-butyl chloroformate/$NaBH_4$[17] to afford amino alcohol **7** in 72% yield. In order to oxidize amino alcohol **7** to amino

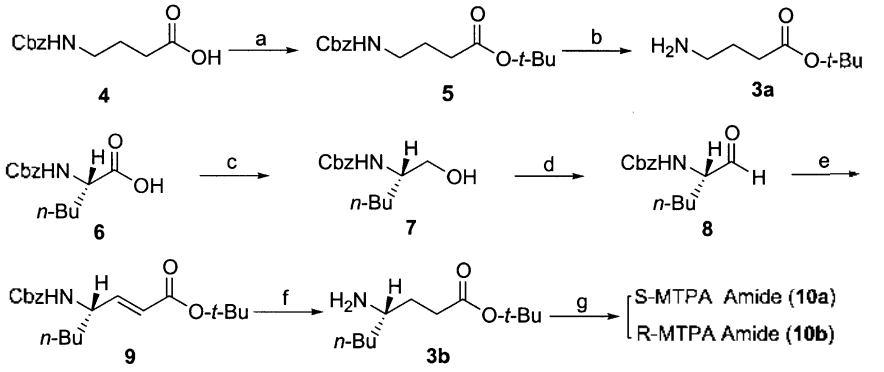


1a (R_1= -$(CH_2)_{13}CH_3$, R_2= -H)
1b (R_1= -$(CH_2)_9CH_3$, R_2= -*n*-Bu)
1c (R_1= -$(CH_2)_{13}CH_3$, R_2= -*n*-Bu)

2a (R_1= -$(CH_2)_{13}CH_3$)
2b (R_1= -$(CH_2)_9CH_3$)

3a (R_2= -H)
3b (R_2= -*n*-Bu)

Scheme 1. Retrosynthetic analysis of γ-aminobutyric acid-based phospholipase A_2 inhibitors **1a**, **b**, **c**.

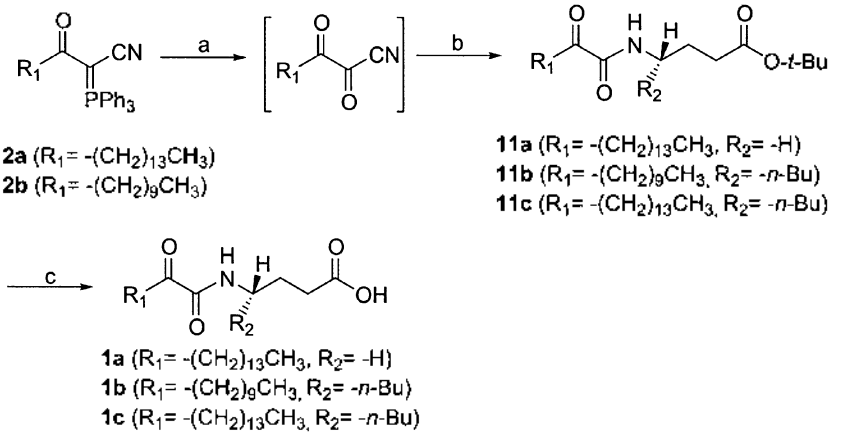


Reagents and conditions: (a) 2,4,6-Trichlorobenzoyl chloride, Et_3N, THF, then *t*-BuOH, DMAP, C_6H_6 (65%) (b) Pd-C (10%), H_2 (1atm), EtOH, 1.5 h (95%) (c) NMM, *i*-BuO_2CCl, THF, then $NaBH_4$, MeOH (72%) (d) IBX, DMSO, 5h (78%) (e) $Ph_3P{=}CHCO_2C(Me)_3$, THF, reflux, 1.5h (73%) (f) Pd-C (10%), H_2 (1atm), EtOH, 1.5h (100%) (g) **3b**, HOBT, S-(-)/R-(+)-MTPA, EDCI, CH_2Cl_2, 0 °C, 1h, then warmed to rt, overnight

Scheme 2. Synthesis of γ-aminobutyric acid *t*-butyl ester derivatives **3a**, **b**.

aldehyde **8**, several oxidizing reagents such as Swern oxidation,[18a] TCT/(DMSO, Et_3N),[18b] and IBX (2-iodoxybenzoic acid)[18c] were attempted. Among these, IBX was determined to be the best in terms of operational simplicity and overall yield (78%). This amino aldehyde **8** are known to be generally unstable and easily racemized, so it was subjected immediately under the Wittig reaction conditions with (*t*-butoxycarbonylmethylene)tri-phenylphosphorane to give **9** as a colorless oil in 73% yield. Catalytic hydrogenation of the double bond and simultaneous unmasking of *N*-Cbz group were accomplished by the use of Pd-C (10%)/H_2 (1 atm) to provide the required amine derivative **3b** as a colorless oil. At this stage, we have checked possible racemization that could have occurred during the last three steps: amine **3b** was reacted with *S*-(-)-MTPA, and *R*-(+)-MTPA in the presence of EDCI/HOBT,[19] and NMR (^{19}F & ^1H) spectra of each crude and purified MTPA amide were carefully compared. Unfortunately, CF_3-peaks of both MTPA amides (**10a/b**) appeared at the exactly same position (11.10 ppm) as a sharp singlet in ^{19}F NMR. However, several proton peaks corresponding to N*H*- (d), CH_3O- (s), CH_3- (t) and especially -CH_2COO- (m) of purified *S*-MTPA amide (**10a**) were well resolved from those of diastereomeric *R*-MTPA amide (**10b**) by 0.046 ppm (18.4 Hz), 0.018 ppm (7.2 Hz), 0.051 ppm (20.4 Hz) and 0.13 ppm (52.0 Hz), respectively. The ^1H NMR spectra of crude *S*-MTPA and *R*-MTPA amide did not have any corresponding diastereomeric amide proton peaks at all, which demonstrated that no racemization took place during last three steps and optical integrity at the chiral center was retained.

With both requisite starting materials **2**,**3** in hand we carried out the key coupling reaction according to the reported procedures (*Scheme* 3):[9] A precooled (-78 °C) solution of **2a** (1.3 equiv) in CH_2Cl_2 was treated first with O_3, then purged with dry Ar to afford a pale yellow solution which was reacted with amine derivative **3a** under the mild reaction condition. TLC-analysis of the crude product clearly showed that one major compound considered to be the desired product formed together with several byproducts. Purification of the crude product by flash column chromatography (SiO_2) afforded pure coupled product **11a** in 56% yield. Attempts to increase the yield by using more amount of ylide **2a** or extending O_3-bubbling time/Ar-purging time turned out to be fruitless at all. The structure of the coupled product **11a** was easily confirmed mainly by NMR: in ^1H NMR, the amide proton (1H) appeared at 7.11 ppm as a broad singlet, and the methlene



2a (R_1= -$(CH_2)_{13}CH_3$)
2b (R_1= -$(CH_2)_9CH_3$)

11a (R_1= -$(CH_2)_{13}CH_3$, R_2= -H)
11b (R_1= -$(CH_2)_9CH_3$, R_2= -*n*-Bu)
11c (R_1= -$(CH_2)_{13}CH_3$, R_2= -*n*-Bu)

1a (R_1= -$(CH_2)_{13}CH_3$, R_2= -H)
1b (R_1= -$(CH_2)_9CH_3$, R_2= -*n*-Bu)
1c (R_1= -$(CH_2)_{13}CH_3$, R_2= -*n*-Bu)

Reagents and conditions: (a) O_3-bubbling, CH_2Cl_2, -78 °C, 5min, then Ar-purging, -78 °C, 5min (b) **3a/b**, CH_2Cl_2, -78 °C, 30 min, then warmed to rt, 30 min (50-56%) (c) TFA/CH_2Cl_2 (1/1), rt, 1.5h (98-99%)

Scheme 3. Synthesis of γ-aminobutyric acid-based phospholipase A_2 inhibitors **1a**, **b**, **c**.

protons (2H) adjacent to dicarbonyl unit appeared at 2.90 ppm as a triplet, and *t*-butyl protons (9H) appeared at 1.45 ppm as a sharp singlet, *etc.*; in ^{13}C NMR, three carbonyl carbons due to a-carbonyl carbon, amide carbon, and *t*-butyl ester carbon appeared at 199.27, 160.32, and 172.28 ppm, respectively. IR and LR/HR mass also strongly supported the proposed structure of **11a**.

The next step for the final product **1a** seemed to be straightforward. Deblocking of *t*-butyl ester group of **11a** with TFA was smoothly progressed under mild conditions (rt, 1.5h), and after purification by flash column chromatography on SiO_2 (CH_2Cl_2/EtOAc/AcOH, 7/1/1%) the first target molecule **1a** was obtained as a white solid in almost quantitative yield. All spectral data including ^1H and ^{13}C NMR unequivocally confirmed the proposed structure of pure acid **1a**.

Having established the optimum reaction condition for coupling/deprotection of *t*-butyl ester group, we then attempted to synthesize the second target molecule **1b** by following the similar reaction protocol as for **1a**. Thus, treatment of **2b** with O_3/Ar to provide the diketo nitrile intermediate as a pale yellow solution, which was then reacted with amine **3b** to afford the coupled product **11b** as a colorless oil in 52% yield after flash column chromatography. ^1H and ^{13}C NMR were very informative for the proposed structure of **11b**: in ^1H NMR, the amide proton peak (1H) appeared at 6.75 ppm as a broad doublet, and the chiral proton peak (1H) appeared at 3.86 ppm as a multiplet, and the two methyl proton peaks (6H) appeared at 0.88 ppm as a triplet, *etc.*; in ^{13}C NMR, three carbonyl carbon peaks corresponding to a-carbonyl carbon, amide carbon, and *t*-butyl ester carbon appeared at 199.53, 159.96, and 172.53 ppm, respectively, together with exactly 19 carbon peaks as expected. Having the coupled product **11b** in hand, we then carried out the deprotection reaction of **11b** with TFA, and the crude product was purified by flash column chromatography on SiO_2 to provide pure acid **1b** in 98% yield as an off-white solid. All spectral data of **1b** including ^1H and ^{13}C NMR were matched well with those of the literature.[3f] Quite surprisingly, however, mp (57.0-59.0 °C) and especially $[\alpha]^{24}_D$(-6.3°, c 0.74, $CHCl_3$) of our product **1b** were considerably higher than reported values (mp 50.0-52.0 °C; $[\alpha]_D$(-1.8°, c 0.5, $CHCl_3$)), which implied that our product was much purer chemically and optically than the same compound reported in the literature. We are not sure of the plausible reasons for these big differences espe-

cially in $[\alpha]_D$ value at this point, however, possible racemization during the peptide coupling step using EDCI/HOBT might be the source of the problem.[20] Anyway, our synthetic approach turned out to be a racemization-free methodology for the synthesis of this kind of compounds.[b]

Some of the reported phospholipase A_2 inhibitors were incorporating a longer aliphatic side chain than dodecanoic acid,[20,3c] therefore it seemed worthwhile to attach a longer aliphatic side chain to the amine derivative **3b**, and also in order to prove the generality of our approach for the synthesis of this kind of molecules, we next tried phosphorane ylide **2a** for the coupling reaction with amine derivative **3b**. By following the similar procedures as for **11a/b**, the new coupled product **11c** was obtained in 50% yield. This coupled product **11c** was then deprotected with TFA as above to give a new, potentially active γ-aminobutyric acid-based phospholipase A_2 inhibitor **1c** in 98% yield.

CONCLUSION

We have shown that acyl cyanophosphoranes are efficient starting materials for the convergent synthesis of γ-aminobutyric acid-based, potent human cytosolic phospholipase A_2 inhibitors. The conditions of the key coupling reaction between the diketo nitrile intermediates and the amine derivatives are mild, and the yields are moderate to good. The synthetic approach developed in this study should be applicable to the synthesis of a diverse group of γ-aminobutyric acid-based, potent human cytosolic phospholipase A_2 inhibitor analogs simply by varying acyl cyanophosphoranes for a specific amine derivative or vice versa in a concise way. Furthermore the most active inhibitor **1b** prepared by our synthetic route has higher mp and $[\alpha]_D$ value than the same compound reported in the literature, which demonstrates that acyl cyanophosphorane approach is a racemization-free methodology.

REFERENCES

1. (a) Cirino, G. *Biochem. Pharmacol.* **1998**, *55*, 105. (b) Balsinde, J.; Dennis, E. A. *J. Biol. Chem.* **1996**, *271*, 6758.
2. (a) Ackerman, E. J.; Conde-Frieboes, K.; Dennis, E. A. *J. Biol. Chem.* **1995**, *270*, 445. (b) Kokotos, G.; Constantinou-kokotu, V.; Noula, C.; Nicolaou, A.; Gibbons, W. A. *Int. J. Peptide Protein Res.* **1996**, *48*, 160.
3. (a) Street, I. P.; Lin, H.-K.; Laliberte, F.; Ghomashchi, F.; Wang, Z.; Perrier, H.; Tremblay, N. M.; Huang, Z.; Weech, P. K.; Gelb, M. H. *Biochemistry* **1993**, *32*, 5935. (b) Ghomashchi, F.; Loo, R.; Balsinde, J.; Bartoli, F.; Apitz-Castro, R.; Clark, J. D.; Dennis, E. A.; Gelb, M. H. *Biochim. Biophys. Acta* **1999**, *1420*, 45. (c) Conde-Frieboes, K.; Reynolds, L. J.; Lio, Y.-C.; Hale, M. R.; Wasserman, H. H.; Dennis, E. A. *J. Am. Chem. Soc.* **1996**, *118*, 5519. (d) Seno, K.; Okuno, T.; Nishi, K.; Murakami, Y.; Watanabe, F.; Matsuura, T.; Wada, M.; Fujii, Y.; Yamada, M.; Ogawa, T.; Okada, T.; Hashizume, H.; Kii, M.; Hara, S.-I.; Hagishita, S.; Nakamoto, S.; Yamada, K.; Chikazawa, Y.; Ueno, M.; Teshirogi, I.; Ono, T.; Ohtani, M. *J. Med. Chem.* **2000**, *43*, 1041. (e) Ghomashchi, F.; Stewart, A.; Hefner, Y.; Ramanadham, S.; Turk, J.; Leslie, C. C.; Gelb, M. H. *Biochim. Biophys. Acta* **2001**, *1513*, 160. (f) Kokotos, G.; Kotsovolou, S.; Six, D. A.; Constantinou-Kokotou, V.; Beltzner, C. C.; Dennis, E. A. *J. Med. Chem.* **2002**, *45*, 2891.
4. (a) Hagihara, M.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6570. (b) Fusetani, N.; Sugarawa, T.; Matsunaga, S.; Hirota, H. *J. Am. Chem. Soc.* **1991**, *113*, 7811. (c) Kobayashi, J.; Itagaki, F.; Shigemori, H.; Ishibashi, M.; Takahashi, K.; Ogura, M.; Nagasawa, S.; Nakamura, T.; Hirota, H.; Ohta, T.; Nozoe, S. *J. Am. Chem. Soc.* **1991**, *113*, 7812. (d) Aoyagi, T.; Nagai, M.; Ogawa, K.; Kojima, F.; Okada, M.; Ikeda, T.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1991**, *44*, 949. (e) Toda, S.; Kotake, C.; Tsuno, T.; Narita, Y.; Yamasaki, T.; Konishi, M. *J. Antibiot.* **1992**, *45*, 1580.
5. (a) Ocain, T. D.; Rich, D. H. *J. Med. Chem.* **1992**, *35*, 451. (b) Wipf, P.; Kim, H. *J. Org. Chem.* **1993**, *58*, 5592. (c) Harbeson, S. L.; Abelleira, S. M.; Akiyama, A.; Barrett, R.; Carroll, R. M.; Straub, J. A.; Tkacz, J. N.; Wu, C.; Musso, G. F. *J. Med. Chem.* **1994**, *37*, 2918. (d) Li, Z.; Ortega-Vilain A.-C.; Patil, G. S.; Chu, D.-L.; Foreman, J. E.; Eveleth, D. D.; Powers, *J. Med. Chem.* **1996**, *39*, 4089. (e) Kobayashi, T.; Tanaka, M. *J. Organometal. Chem.* **1982**, *233*, C64. (f) Khim, S.-K.; Nuss, J. M. *Tetrahedron. Lett.* **1999**, *49*, 1827. (g) Ozawa, F.; Yamamoto, A. *Chem. Lett.* **1982**, 865. (h) Yang, Z.; Zhang, Z.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *Org. Lett.* **2002**, 1103. (i) Sibi, M. P.; Marvin, M.; Sharma, R. *J. Org. Chem.* **1995**, *60*, 5016.
6. Wasserman, H. H.; Ho, W.-B. *J. Org. Chem.* **1994**, *59*, 4364.

7. (a) Wasserman, H. H.; Petersen, A. K. *Tetrahedron. Lett.* **1997**, *38*, 953. (b) Wasserman, H. H.; Petersen, A. K. *J. Org. Chem.* **1997**, *62*, 8972. (c) Wasserman, H. H.; Xia, M.; Petersen, A. K.; Jorgensen, M. R.; Curtis, E. A. *Tetrahedron. Lett.* **1999**, *40*, 6163. (d) Wasserman, H. H.; Wang, J. *J. Org. Chem.* **1998**, *63*, 5581.
8. Wasserman, H. H.; Lee, K.; Xia, M. *Tetrahedron. Lett.* **2000**, *41*, 2511.
9. Lee, K. *Bull. Kor. Chem. Soc.* **2002**, *23*, 351.
10. Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.
11. Fosker, A. P.; Law, H. D. *J. Chem. Soc.* **1965**, 7305.
12. Amine derivatives **3a**/**b** (especially **3a**) were highly volatile under high vacuum. Therefore, these compounds were dried only by rotary evaporator while maintaining bath temperature below 20 °C to give the pure products as colorless oils, which were determined to be pure enough for the next reaction (by NMR, IR, and Mass spectroscopy).
13. Schiemenz, G. P.; Engelhard, H. *Chem. Ber.* **1961**, *94*, 578.
14. Bryan, D. B.; Hall, R. F.; Holden, K. G.; Huffman, W. F.; Gleason, J. G. *J. Am. Chem. Soc.* **1977**, *99*, 2353.
15. (a) Dhaon, M.; Olsen, R. K.; Ramasamy, K. *J. Org. Chem.* **1982**, *47*, 1962. (b) Ohta, S.; Shimabayashi, A.; Aono, M.; Okamoto, M. *Synthesis* **1982**, 833. (c) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
16. Greene, T. W.; Wuts, P. G. In *Protective Groups in Organic Synthesis, 2nd Ed.*; John Wiley & Sons, Inc.; New York, 1991; pp 335-338.
17. Rodriguez, M.; Llinares, M.; Doulut, S.; Heitz, A.; Martinez, J. *Tetrahedron. Lett.* **1991**, *32*, 923.
18. (a) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. (b) Luca, L. D.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2001**, *66*, 7907. (c) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272.
19. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
20. (a) Sieber, P.; Kamber, A.; Hartmann, A.; Joehl, A.; Riniker, B.; Rittel, W. *Helv. Chim. Acta.* **1977**, *60*, 27. (b) Windridge, G. C.; Jorgensen, E. C. *J. Chem. Soc., Chem. Commun.* **1988**, 419.