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Communication

SYNTHESIS OF ALKYLLYSOPHOSPHOLIPID ANALOGUES WITH READILY FUNCTIONALIZED 1-*O*-ALKYL SIDE CHAIN

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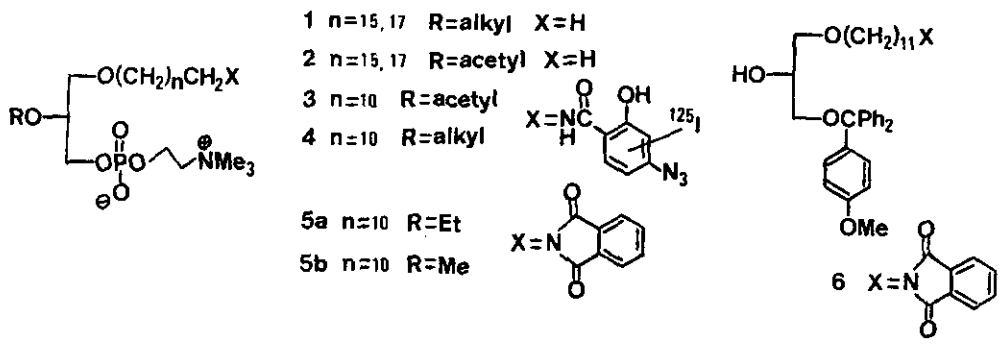
Synthesis of alkyllysophospholipid analogues **5a** *and* **5b** *are described. These lipids have imide functional group attached on the terminal of* 1-*O*-alkyl *side chain suitable for further manipulations. Our approach features the use of mesylate* **8** *in which the mesyl group serves both as protecting group and electrophile.*

Alkyllysophospholipids (ALPs) (1) are interesting compounds possessing useful biological activities.[1] However, the mechanism of their anticancer property is still argumentative.[2-6] There is the proposal that the lack of an *O*-alkyl cleavage enzyme in tumor cells led to the selective destruction of human leukemic cells by 1.[2,3] Others believe that different affinities to lysophosphocholine acyltransferases in sensitive cells were responsible.[6] In a project aimed at the identification of the receptor of platelet-activating factor (PAF) (2),[1,7,8] a photoaffinity labeled compound 3 was used.[9,10] We felt that similar compound such as 4 may also have the potential to serve as an useful tool in the study of the mechanistic aspect of ALP's functions. Herein we wish to report our synthesis of phospholipids 5 in which the imide moiety serves as a latent amino group ready for further functionalization.[10]

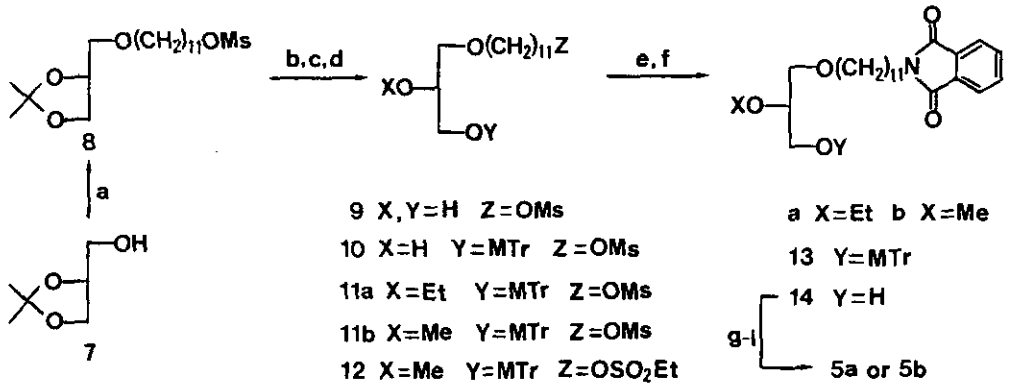
During the synthesis of lipid 3,[10] alcohol 6 was prepared. An apparent quick entry into 5 is via the alkylation of 6; however, we found that under basic condition (1 equiv. NaH, THF; 1 equiv. EtBr) the alkoxide attacked the imide preferentially. Related in our synthesis of 3,[9] mesylate 8 (scheme I) was prepared (91%) via alkylation of 7 with bromoundecyl mesylate. It is noteworthy that the mesyl group had survived without being attacked by the alkoxide. Stimulated by this result, we were successful in an approach which benefit from this finding.

As shown in scheme I, 8 was hydrolyzed to give diol 9 (84%). Selective protection of the primary alcohol with 4-methoxyphenyldiphenylmethyl group (MTr) gave 10 (94%) which was alkylated with excess ethyl bromide and sodium hydride to obtain **11a** (73%). Note that the mesyl group was left intact under both acidic and basic conditions. Coupling of **11a** with potassium phthalimide gave the imide **13a** (84%). However, methylation of 10 gave **11b** (72%) in addition to 18% of ethanesulfonate **12**.[11] This side product was presumably derived from deprotonation of the methanesulfonate moiety by excess sodium hydride, followed by methylation of the resulting carbanion. Since 12 can also react with potassium phthalimide, it was combined with **11b** and used in the next step to give **13b** (93%). Deprotection (**14a**, 84%; **14b**, 85%) followed by phosphocholine formation[12] gave **5a** (56%) and **5b** (50%)[13], respectively.

In conclusion, a seven step synthesis of **5a** and **5b** from isopropylidene glycerol (7) was accomplished in 21% and 25% overall yield, respectively. Although racemic 7 was used in current study, there is no doubt that homochiral 5 can be prepared if homochiral 7 is used. Furthermore, the chain length of the C-1 *O*-alkyl group can be varied. Since the amino group in 5 can be freed by treatment of the



Scheme I



(a) NaH (3 equiv), $Br(CH_2)_{11}OMs$ (1.5 equiv), DMSO, THF, 0°C, 2 h (b) TsOH (cat), MeOH, H_2O (c) 4-methoxyphenyldiphenylmethyl chloride (MTr-Cl), Et_3N, CH_2Cl_2 (d) EtBr (10 equiv), DMSO, NaH (3 equiv), RT, 2.5 h, or MeI (4 equiv), DMSO, NaH (3 equiv), RT, 20 min (e) potassium phthalimide, DMF, 80°C, 3 h (f) CH_3COOH/H_2O (4/1), RT, 4 h (g) $Cl_2PO_2CH_2CH_2Br$, $CHCl{=}CCl_2$, 0°C → RT (h) NaOAc, EDTA, H_2O, THF, RT, 3h (i) Me_3N (45%), 2-PrOH, CH_3CN, $CHCl_3$, 50°C, 10 h

imide with hydrazine,[10] our approach would allow an useful entry to the synthesis of an array of ALP analogues for biochemical studies.

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Key Word Index– alkyllysophospholipids, anticancer, PAF

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11. ^{1}H NMR spectrum ($CDCl_3$) of this compound is almost identical with that of **11b** except the presence of a *t* at δ 1.40, J = 7.5 Hz, and a *q* at δ 3.09, J=7.5 Hz, these signals are due to the ethyl group on sulfur. Anal. Calcd for $C_{37}H_{52}O_7S$: C, 69.34; H, 8.18. Found: C, 69.25; H, 8.22.
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13. **5a**: ^{1}H NMR (CD_3OD, 300 MHz) δ 1.16 (*t*, J = 7 Hz, 3H, CH_3 of ethyl), 1.20–1.40 (*m*, 14 H, methylene manifold), 1.52 (*quin*, collapsed when irradiated at 3.42, J = 6.5 Hz, 2H, C(16)H_2), 1.63 (*quin*, collapsed when irradiated at 3.63, J = 6.5 Hz, 2H, 2H, C(14)H_2), 3.20 (*s*, 9H, NCH_3), 3.40–3.60 (*m* overlapped with *t*, J = 6.5 Hz, at 3.42, 4H, C(5)H_2, C(3)H_2), 3.60–3.70 (*m* overlapped with *q*, J = 7 Hz, at 3.65, 7H, NCH_2 of choline, C(2)H-OCH_2-, C(15)H_2), 3.89 (two overlapped *td*, AB of ABMX, with ν_A at 3.86 and ν_B at 3.90, J_{AB} = J_{AM} = J_{BM} = 11 Hz, J_{AX} = J_{BX} = 5 Hz, when irradiated at 3.63 the signal collapsed into two overlapped *dd*, AB of ABX, 2H, C(1)H_2), 4.26 (br *s*, 2H, OCH_2 of choline), 7.73-7.83 (*m*, 4H, ArH); mass spectrum, *m/e* (rel. intensity) 586 (13), 585 (M^+, 46), 571 (6), 527 (32), 526 (84), 420 (35), 402 (19), 356 (8), 316 (13), 300 (76), 195 (37), 167 (16), 160 (62), 97 (28), 85 (30), 72 (100), 59 (70). **5b**: ^{1}H NMR (CD_3OD, 300 MHz) δ 1.20–1.40 (*m*, 14H, methylene manifold), 1.53 (*quin*, J = 6.5 Hz, 2H, C(6)H_2), 1.64 (*quin*, J = 6.5 Hz, 2H, C(14)H_2), 3.20 (*s*, 9H, NCH_3), 3.40–3.70 (*m* with *s* at 3.43, 12H, OCH_3, C(2)H, C(3)H_2, C(5)H_2, C(15)H_2, and NCH_2 of coline), 3.82–3.99 (two overlapped *td*, AB of ABMX with ν_A at 3.87 and ν_B at 3.93, J_{AB} = J_{AM} = J_{BM} = 18 Hz, J_{AX} = J_{BX} = 5.5 Hz, 2H, C(1)H_2), 7.70–7.85 (*m*, 4H, ArH); mass spectrum, *m/e* (rel. intensity) 572 (17), 571 (M^+, 66), 569 (7), 517 (20), 514 (72), 513 (31), 512 (100), 406 (14), 388 (16), 300 (80), 196 (19), 195 (12), 183 (16), 181 (23), 160 (39), 97 (14), 72 (57), 58 (37). These two compounds are highly hygroscopic and are very difficult to obtain correct microanalysis. All other new compounds described here all gave satisfactory IR, NMR, and microanalysis.