ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2023, 59, 13333

Received 31st August 2023,
Accepted 16th October 2023

DOI: 10.1039/d3cc04292h

rsc.li/chemcomm

1,4-Dimethoxynaphthalene-2-methyl ('DIMON'), an oxidatively labile protecting group for synthesis of polyunsaturated lipids†

Jay Tromans,[a] Bian Zhang[b] and Bernard T. Golding *[a]

A new benzyl-type protecting group (1,4-dimethoxynaphthalene-2-methyl, 'DIMON') for hydroxyl functions can be selectively removed under oxidative conditions without damaging polyunsaturated fatty acyl groups. Its application is shown by the first synthesis of an ether (plasmanyl) phospholipid containing the docosa-(4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-hexaenoyl group.

Among the components of the human lipidome are alkylglycerophospholipids, which contain an alkyl group at the *sn*-1 position and an acyl group at the *sn*-2 position (so-called ether or plasmanyl phospholipids) in contrast to the familiar diacylglycerols and their corresponding phospholipids (Fig. 1).[1,2] Much interest is centred on those molecules where the fatty acyl moiety is derived from the polyunsaturated arachidonic acid (20 : 4) or docosahexaenoic acid (22 : 6).[3] We now report the first scalable synthesis of this type of ether phospholipid, thus making these molecules readily available for biological studies and potential medical applications.

A common impediment to the use of benzyl-type protecting groups in organic synthesis, notably for glycerolipids, is that their removal under oxidative, reductive or acidic conditions is incompatible with polyunsaturated fatty acyl groups. For example, although 4-methoxybenzyl (PMB) can be used for protection and deprotection in the presence of an oleoyl group, this group could not be removed oxidatively or by any other means in the presence of acyl groups containing two or more double bonds (*e.g.* linoleoyl).[4] Difficulty with oxidatively cleaving PMB in the presence of 1,3- and 1,4-dienes is a widely reported problem.[5–8] 3,4-Dimethoxybenzyl (DMB)[9] can be removed oxidatively more readily than PMB, but was also unsatisfactory for molecules with diene moieties.[10]

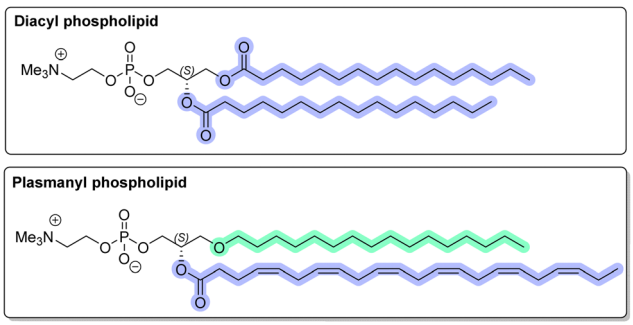


Fig. 1 Examples of diacyl and plasmanyl phospholipids.

We have found a novel benzyl-type protecting group (1,4-dimethoxynaphthalene-2-methyl, 'DIMON'), (Fig. 2) that can be removed under oxidative conditions without damaging polyunsaturated acyl groups. This group was selected after consideration of synthetic accessibility and, above all, redox potentials ($E_{1/2}$, V in MeCN solvent) for methoxy-substituted aromatic systems (for a review see ref. 11): methoxybenzene (1.76),[12] 1,2,-dimethoxybenzene (1.45),[12] 1,4-dimethoxybenzene, (1.34),[12] 1,4-dimethoxynaphthalene (1.10),[13] *cf.* benzene (2.08),[14] naphthalene (1.34).[14] These data were expected to mirror the ease of removal of the corresponding benzyl-type group with a reagent [*e.g.* 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)] operating *via* an electron transfer mechanism and therefore DIMON should be more easily removed than PMB or DMB.

The application of DIMON is illustrated by the synthesis of a variety of protected alcohols, phenols, amines and amides, and

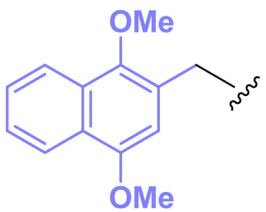


Fig. 2 Structure of novel benzyl-type protecting group DIMON.

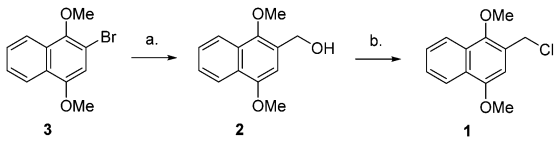
[a] *School of Natural & Environmental Sciences – Chemistry, Bedson Building, Newcastle University, Newcastle upon Tyne, NE1 7RU, UK. E-mail: bernard.golding@ncl.ac.uk*
[b] *BiBerChem Research Ltd, The Biosphere, Draymans Way, Newcastle Helix, Newcastle upon Tyne, NE4 5BX, UK*

† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d3cc04292h

1-alkyl-2-acyl glycerols, where the acyl groups are derived from polyunsaturated fatty acids including (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-docosa-4,7,10,13,16,19-hexaenoic acid (DHA). It is critically important that the latter acyl moiety survives removal of DIMON without double bond perturbation or acyl migration.

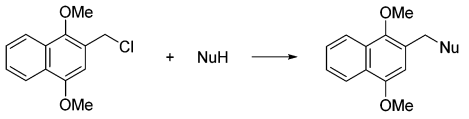
DIMON protection of heteroatoms requires 2-(chloromethyl)-1,4-dimethoxynaphthalene (**1**, DIMONCl), which has been prepared either by chloromethylation of 1,4-dimethoxynaphthalene[15,16] or by treatment of (1,4-dimethoxynaphthalen-2-yl)methanol (**2**) with thionyl chloride[17] or methanesulfonyl chloride[18] Compound **2** is available either by reduction of methyl 1,4-dimethoxy-2-naphthoate[18] or from 2-bromo-1,4-dimethoxynaphthalene *via* the corresponding Grignard reagent, which was reacted with dimethylformamide followed by reduction with sodium borohydride.[19] We have prepared compound **2** from commercially available 2-bromo-1,4-dimethoxynaphthalene **3**[20] by lithiation followed by treatment with formaldehyde (Scheme 1). DIMONCl **1** was obtained in quantitative yield simply from reaction of **2** in a two-phase system of diethyl ether and 12 M hydrochloric acid. Separation of the organic phase, drying and evaporation gave **2** as an air-stable, crystalline solid.

DIMON protection of alcohols and amides (for selected examples see Table 1) was efficiently achieved under standard conditions *via* the corresponding alkoxide/amide anion, which was alkylated using DIMONCl in the presence of catalytic tetrabutylammonium bromide in THF at room temperature or at reflux for the steroidal substrates. With glycidol **4e** (entry 5, oxiran-2-ylmethanol), a key intermediate for phospholipid synthesis, DMF solvent was preferred to THF.



Scheme 1 Synthesis of 2-(chloromethyl)-1,4-dimethoxynapthalene (DIMONCl **1**): (a) (i) *n*-BuLi, −78 °C, 2 h (ii) paraformaldehyde, 2 h, rt, Et_2O, Ar, 62%; (b) conc. HCl, Et_2O, rt, 1 h, 100%.

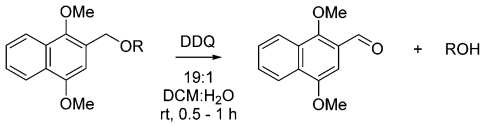
Table 1 DIMON installation onto *O*- and *N*-nucleophiles



Entry	NuH	Product	Yield (%)	Method
1	Eicosanol **4a**	**5a**	93	A
2	Octan-1-ol **4b**	**5b**	75	A
3	Oct-2-en-1-ol **4c**	**5c**	79	A
4	Propargyl alcohol **4d**	**5d**	82	A
5	Glycidol **4e**	**5e**	85	A[a]
6	4-Methoxybenzyl alcohol **4f**	**5f**	93	A
7	Cholesterol **4g**	**5g**	91	A[b]
8	Ergosterol **4h**	**5h**	89	A[a]
9	L-Menthol **4i**	**5i**	71	A
10	4-Chlorophenol **4j**	**5j**	91	B
11	Thymol **4k**	**5k**	80	B
12	Naphth-1-ol **4l**	**5l**	89	B
13	Morpholine **4m**	**5m**	68	C
14	*N*-Methylbenzamide **4n**	**5n**	86	A

Method A: 1 equiv. NuH, 1.2 equiv. DIMONCl, 10 mol% TBAI, 1.2 equiv. NaH 60% dispersion in mineral oil, dry THF, N_2, rt, 16 h. [a] DMF used as solvent. [b] Reaction at reflux. B: 1 equiv. NuH, 1.2 equiv. DIMONCl, 1.1 equiv. Cs_2CO_3, dry MeCN, N_2, reflux, 16 h. C: 1 equiv. NuH, 1.2 equiv. DIMONCl, 1.2 equiv. NEt_3, dry THF, N_2, rt, 16 h.

Table 2 Oxidative cleavage of DIMON by DDQ

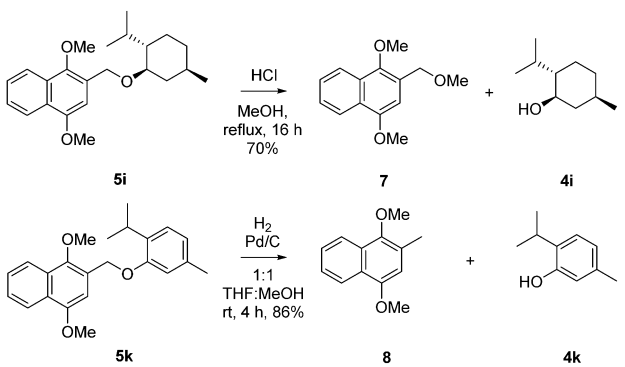


Entry	DIMON-OR	ROH	Yield (%)
1	**5a**	Eicosanol **4a**	91
2	**5c**	Oct-2-en-1-ol **4c**	85
3	**5d**	Propargyl alcohol **4d**	99
4	**5f**	Methoxybenzyl alcohol **4f**	86
5	**5h**	Ergosterol **4h**	80
6	**5j**	4-Chlorophenol **4j**	88

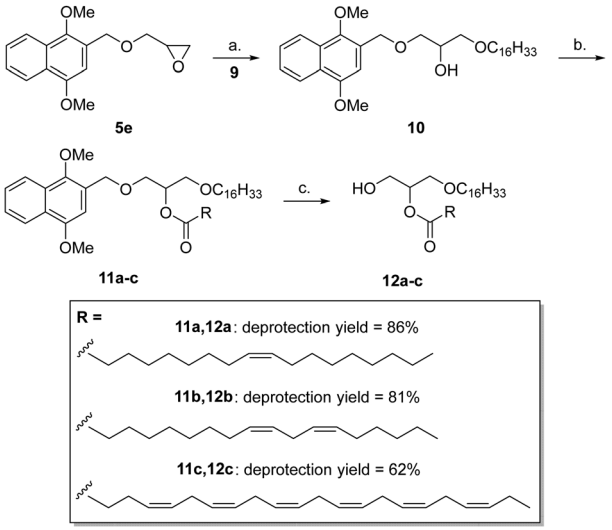
Method: 1 equiv. DIMON-Nu, 1.1 equiv. DDQ, 19 : 1 DCM : H_2O, rt, 0.5–1 h.

Phenols were reacted with DIMONCl using Cs_2CO_3 as base, whilst triethylamine sufficed for amines. DIMON was efficiently removed from protected alcohols and phenols within one hour at 20 °C by exposure to 2,3-dichloro-4,5-dicyanobenzoquinone (DDQ) in wet DCM (Table 2). After deprotection, the protecting moiety was easily separated chromatographically as 1,4-dimethoxy-2-naphthaldehyde **6** and could be recycled, whilst any residual DDQ was reduced by aqueous ascorbic acid to 2,3-dichloro-5,6-dicyano-1,4-quinol, which was extracted into an aqueous phase. Importantly, the DIMON ether was selectively oxidised over the PMB ether (Table 2, entry 4) in a 9 : 1 ratio by ^{1}H NMR analysis. This agreed with the redox potentials of DIMON and PMB, and showed that DIMON can be orthogonally removed in the presence of PMB.

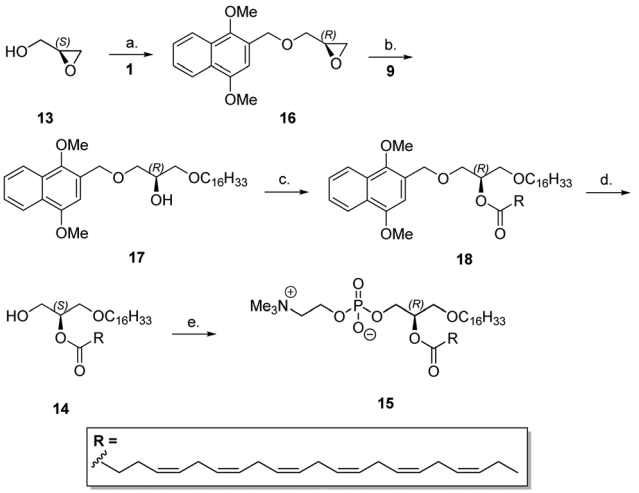
DIMON could also be removed under acidic catalysis (TFA in DCM or HCl in MeOH) or by catalytic hydrogenation (Pd/H_2) with substrates derived from alcohols lacking a non-aromatic C=C bond (see Scheme 2 and ESI†).



Scheme 2 Acidic and reductive cleavage of DIMON from DIMON-menthol to give menthol and DIMON-thymol to afford thymol, respectively.



Scheme 3 Oxidative cleavage of DIMON in the presence of unsaturated and polyunsaturated functionality. (a) 1 equiv. (*rac.*)-DIMON-glycidol **5e**, 3 equiv. hexadecanol **9**, 5 mol% $BF_3{\cdot}OEt_2$, dry toluene, N_2, rt, 16 h, 75%; (b) 1 equiv. alcohol **10**, 1.2 equiv. fatty acid ((i) oleic acid, (ii) linoleic acid, (iii) docosahexaenoic acid), 1.5 equiv. DCC, 0.5 equiv. DMAP, dry DCM, rt, 24 h, (i) 93%, (ii) 79%, (iii) 98%; (c) 1 equiv. DIMON-alcohol **11a-c**, 1 equiv. DDQ, 19 : 1, rt, 0.5 h, (i) 86%, (ii) 81%, (iii) 62%.



Scheme 4 Synthesis of plasmanyl phospholipid **15** *via* DIMON-protected *S*-glycidol **16** (a) 1.2 equiv. DIMONCl **1**, 1.2 equiv. NaH 60% dispersion in mineral oil, 10 mol% TBAI, dry DMF, N_2, rt, 16 h, 77%; (b) 3 equiv. hexadecanol **9**, 5 mol% $BF_3{\cdot}OEt_2$, dry toluene, N_2, rt, 16 h, 75%; (c) 1.2 equiv. docosahexaenoic acid, 1.5 equiv. DCC, 0.5 equiv. DMAP, dry DCM, rt, 24 h, 98%; (d) 1 equiv. DDQ, 19 : 1, rt, 0.5 h, 61%; (e) (i) 1.5 equiv. COP, 3 equiv. pyridine, dry TFT, N_2, rt, 1 h, 100%; (ii) 2 M NMe_3 in MeCN, dry TFT, reflux, 16 h, 35%.

To define conditions suitable for the synthesis of alkyl phospholipids, DIMON-protected *rac*.-glycidol **5e** was reacted with a 3-fold excess of hexadecan-1-ol **9** in the presence of either catalytic ytterbium triflate or boron trifluoride, the latter giving a better yield of compound **10** (Scheme 3). Acylation of **10** was performed with three representative fatty acids giving the corresponding esters **11a-c:** from oleic acid (18 : 1) in 93% yield, from linoleic acid (18 : 2) in 79% and docosahexaenoic acid (22 : 6) in 91% yield.

All three esters were smoothly deprotected by DDQ giving the corresponding primary alcohols **12a-c** in 86% (oleyl), 81% (linoleyl) and 62% yield (docosahexaenoyl) with no evidence of double bond perturbation or acyl migration.

To illustrate the application of DIMON in total synthesis of polyunsaturated phospholipids, we repeated the synthetic route shown in Scheme 3 starting from (*S*)-glycidol **13**, giving intermediate **14** in 35% overall yield (*cf.* Scheme 4). Compound **14** was converted into the naturally occurring plasmanyl phospholipid **15** using a known phosphorylation method, reaction with 2-chloro-1,3,2-dioxophospholane 2-oxide (COP) then trimethylamine, to afford a choline derivative.[21] This is the first reported synthesis of such an ether phospholipid. The corresponding oleoyl derivative was made from **12a** in a similar manner (data not shown).

Although this paper describes a specific application of DIMON, we believe that this new protecting group will find application in the synthesis of a wide range of natural products.

We thank the European Research and Development Fund (ERDF) and BiBerChem Research (Newcastle upon Tyne, UK) for financial support (to JT), the NMSF at Swansea University for HRMS and Masuma Begum for technical support.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 H. Goldfine, *Prog. Lipid Res.*, 2010, **49**, 493.
2 N. Jiménez-Rojo and H. Riezman, *FEBS Lett.*, 2019, **593**, 2378.
3 See the collection of reviews and papers in *Frontiers in Cell Developmental and Biology*, *e.g.* J. Koch, K. Watschinger, E. R. Werner and M. A. Keller, *Front. Cell Dev. Biol.*, 2022, **10**, 864716.
4 A. B. Maude, PhD thesis, Newcastle University, 1992.
5 T. Onoda, R. Shirai and S. Iwasaki, *Tetrahedron Lett.*, 1997, **38**, 1443.
6 M. Hutchings, D. Moffat and N. S. Simpkins, *Synlett*, 2001, 661.
7 R. A. Pilli, I. R. Correa Jr., A. O. Maldaner and G. B. Rosso, *Pure Appl. Chem.*, 2005, **77**, 1153.
8 A. Furstner, L. C. Bouchez, J. Funel, V. Liepins, F. Poree, R. Gilmour, F. Beaufils, D. Laurich and M. Tamiya, *Angew. Chem., Int. Ed.*, 2007, **46**, 9265.
9 K. Horita, T. Yoshioka, T. Tanaka, Y. Oikawa and A. Yonemitsu, *Tetrahedron*, 1986, **42**, 3021.
10 K. A. Scheidt, T. D. Bannister, A. Tasaka, M. D. Wendt, B. M. Savall, G. J. Fegley and W. R. Roush, *J. Am. Chem. Soc.*, 2002, **124**, 6981.
11 N. L. Weinberg and H. R. Weinberg, *Chem. Rev.*, 1968, **68**, 449.
12 A. Zweig, W. G. Hodgson and W. H. Jura, *J. Am. Chem. Soc.*, 1964, **86**, 4124.
13 A. Zweig, A. H. Maurer and B. G. Roberts, *J. Org. Chem.*, 1967, **32**, 1322.
14 J. W. Loveland and G. R. Dimeler, *Anal. Chem.*, 1961, **33**, 1196.
15 B. R. Baker and G. H. Carlson, *J. Am. Chem. Soc.*, 1942, **64**, 2657.
16 G. A. Kraus and M. D. Hagen, *J. Org. Chem.*, 1983, **48**, 3265.
17 X. Ning, H. Qi, R. Li, Y. Li, Y. Jin, M. A. McNutt, J. Liu and Y. Yin, *Eur. J. Med. Chem.*, 2017, **138**, 343.
18 E. Vieira, A. Binggeli, V. Breu, D. Bur, W. Fischli, R. Gueller, G. Hirth, H.-P. Maerki, M. Mueller, C. Oefner, M. Scalone, H. Stadler, M. Wilhelm and W. Wostl, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1397.
19 U. Ackermann, D. Sigmund, S. D. Yeoh, A. Rigopoulos, G. O'Keefe, G. Cartwright, J. White, A. M. Scott and H. J. Tochon-Danguy, *J. Labelled Compd. Radiopharm.*, 2011, **54**, 788.
20 J.-Y. Jeong, J. Sperry, J. A. Taylor and M. A. Brimble, *Eur. J. Med. Chem.*, 2014, **87**, 220.
21 J. M. Zeidler, W. Zimmermann and H. J. Roth, *Chem. Phys. Lipids*, 1990, **55**, 155.