




Cite this: *Org. Biomol. Chem.*, 2024, **22**, 7989

Received 26th July 2024,
 Accepted 27th August 2024

DOI: 10.1039/d4ob01233j

rs.c.li/obc

Unlocking nature's antioxidants: a novel method for synthesising plasmalogens†

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

Plasmalogens are glycerophospholipids distinguished by their *O*-(*Z*)-vinyl ether at the *sn*-1 position. These lipids are implicated in several disease states requiring analytical, diagnostic and therapeutic interventions, which demand synthetic availability for a variety of structural types. By deploying the new *O*-protecting group 1,4-dimethoxynaphthyl-2-methyl ('DIMON') and a new stereospecific method for accessing *Z*-vinyl ethers, a reproducible, versatile synthetic route to plasmalogens [plasmenyl phosphocholines] has been developed. A key intermediate is (*S,Z*)-1-((1,4-dimethoxynaphthalen-2-yl)methoxy)-3-(hexadec-1-en-1-yloxy)propan-2-ol, which in principle, permits plasmalogen synthesis 'à la carte' at scale. The methodology compares favourably with all previous synthetic routes by virtue of the very high configurational (>99% *Z*) and optical purity (>99% ee), including the ability to incorporate polyunsaturated fatty acyl chains (e.g. all *Z* docosahexaenoic acid) reliably at the *sn*-2 position.

Introduction

Cells are protected by a phospholipid membrane without which there would be no life on Earth as presently known. As well as providing a portal for the ingress and export of molecules and ions, there are membrane components that protect the cell against assault by reactive species. One such component is a family of 'ether lipids' called plasmalogens (Fig. 1), which are glycerophospholipids containing an alkenyl ether group at the *sn*-1 position, an unsaturated acyl moiety at *sn*-2 and usually either an ethanolamine or choline head group linked to a phosphate entity at *sn*-3.^{1–4}

Plasmalogens have been known for 100 years,⁵ with the structure elucidation⁶ of these relatively unstable molecules requiring decades of research after several missteps. The crucial *Z*-configured vinyl ether, a functionality quite rare in natural products,⁷ was established by infrared spectroscopy^{8,9} and NMR for the related 'neutral plasmalogens'.¹⁰ The biosynthesis of plasmalogens differs in aerobes and anaerobes: in the former the vinyl ether is created by dehydrogenation of an alkyl ('plasmanyl') precursor, whereas in the latter a sequence of carbonyl reduction and water elimination occurs from an

acyl precursor.¹¹ The unique vinyl ether entity of plasmalogens acts sacrificially to trap reactive oxygen species (ROS).^{12–15}

Paradoxically, although human life depends on dioxygen, this molecule can translate into ROS, which are highly damaging to DNA and proteins,¹⁶ seeding diseases and limiting human lifespan. Cancers are primarily spawned by DNA damage¹⁷ whilst protein oxidation may kindle Alzheimer's disease (AD) and other dementias.^{18,19} As the vinyl ether of plasmalogens provides an exquisite trap for ROS^{12,13} (Scheme 1), individuals with a deficiency of cellular plasmalogens may be especially vulnerable to diseases associated with oxidative damage to biomolecules. The complete range of plasmalogen activities is still subject to intensive research, which has accelerated in the last decade because of their connection to AD, certain cancers and rare hereditary diseases.^{2–4,20}

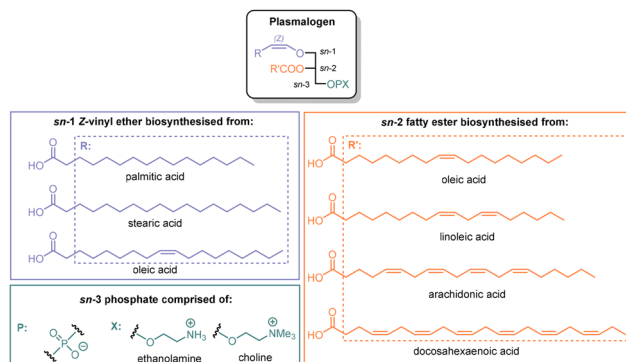


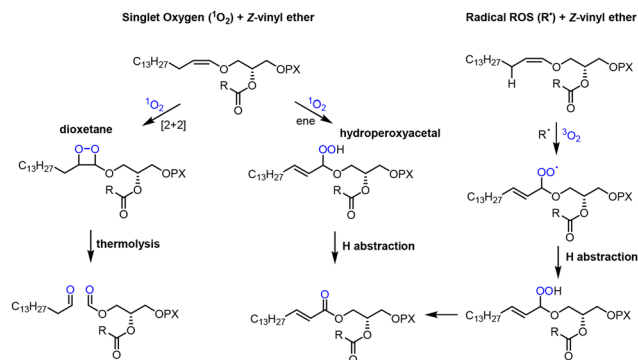
Fig. 1 General plasmalogen structure and their constituents.

^aSchool of Natural and Environmental Science – Chemistry, Newcastle University, Bedson Building, Newcastle University, Newcastle upon Tyne, NE1 7RU, UK. E-mail: bernard.golding@ncl.ac.uk

^bBiBerChem 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/d4ob01233j>





Scheme 1 Reactions of plasmalogen Z-vinyl ether with singlet oxygen (1O_2) and radical ROS (R^\bullet); R = oleoyl chain, P = phosphate, X = choline.

Plasmalogens can be isolated from natural sources (e.g. scallops or chicken^{21,22}) but the extracts are mixtures, which are not ideal for investigating molecular mechanisms of action. In particular, plasmalogens with a polyunsaturated acyl (PUFA) moiety at the *sn*-2 position of the glycerol core (e.g. arachidonoyl) are of greatest interest because of their concentration in brain and heart tissues,^{4,23,24} and the possibility that the polyene component acts synergistically with the vinyl ether to trap ROS.¹³ To determine whether plasmalogens with polyunsaturated acyl groups are the most important defensive molecules, efficient scalable syntheses are required for all types of plasmalogen to enable their antioxidant characteristics and other properties to be compared. Further, ‘plasmalogen replacement therapy’^{4,25–27} seeks to remedy deficiency by supplementation and requires a dependable supply of individual plasmalogens with optimal properties. In this paper we describe a reliable synthesis of choline plasmalogens containing 4 and 6 Z double bonds in the PUFA component.

Biomimetic syntheses of plasmalogens are beyond the reach of current synthetic methodology. Nevertheless, ‘standard’ chemical synthesis of polyunsaturated plasmalogens is a challenging obstacle course, requiring judicious ordering of steps and the unavoidable use of protecting groups (PGs). Among the potential pitfalls are acyl migration from *sn*-2 to *sn*-1/*sn*-3²⁸ in any glycerol-derived intermediate with a free primary hydroxyl group, which also applies to the structurally related plasmanyl ether lipids,²⁹ and a myriad of unwanted reactions with the vinyl ether including isomerisation, oxidation, reduction, hydrolysis and cyclisation, the latter with a free hydroxyl group giving a cyclic acetal.³⁰ These processes may be acid- and/or base-catalysed, or for isomerisation, induced by a thiyl radical generated from a thiol by irradiation with ultraviolet light.³¹ Above all, an effective Z-vinyl ether synthesis is essential to access plasmalogens, but the stage of generation of this group needs careful consideration of its compatibility with subsequent steps.

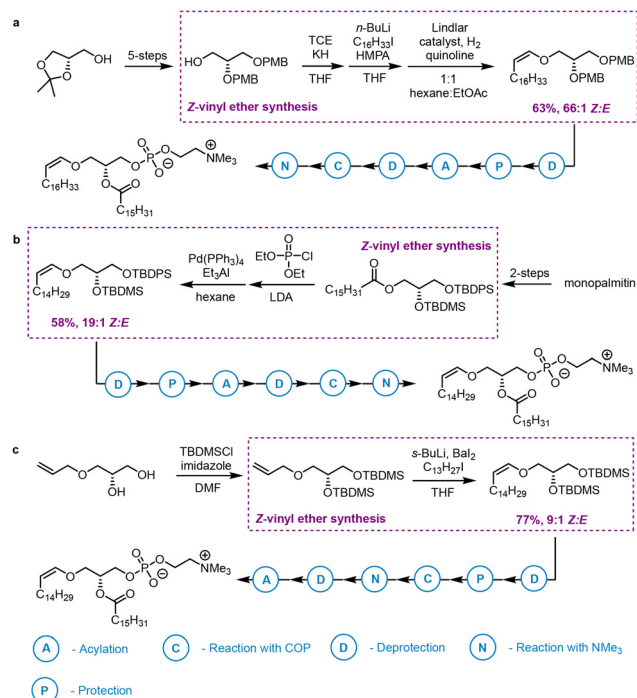
Following many heroic attempts to access plasmalogens,³² the first successful stereoselective synthesis gave one choline plasmalogen in relatively low yield.³³ The Z-vinyl ether was installed by reduction of a vinyl phosphonate (58% yield, 19 : 1

Z:E). Several other strategies towards plasmalogen Z-vinyl ethers have been published (Scheme 2), including Lindlar-catalysed alkynyl-ether reduction (63% yield, 66 : 1 Z:E),³⁴ reductive cleavage under Barbier conditions (47% yield, 49 : 1 Z:E),³⁵ and alkylation of lithioalkoxy allyl intermediates (77% yield, 9 : 1 Z:E).^{36,37} The latter method for installing the vinyl ether chain was also described in a patent,³⁸ which claimed the synthesis of a phosphoethanolamine plasmalogen containing a docosahexaenoyl group at C-2 of glycerol, although no supporting spectroscopic data was provided. Despite these achievements, at the outset of our research there was no published methodology affording a fully characterised polyunsaturated plasmalogen in high yield and with perfect stereocontrol at the Z-vinyl ether.

Results and discussion

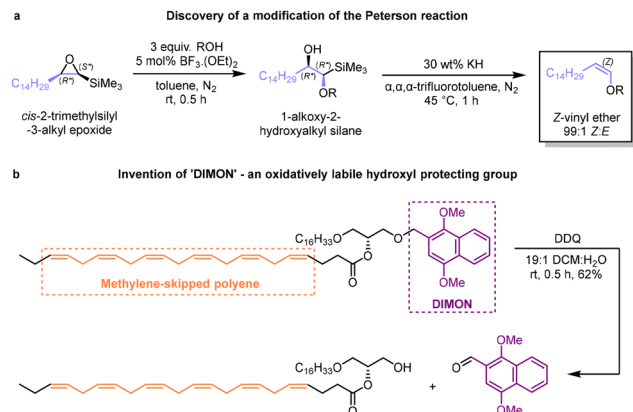
Synthesis of plasmalogens

We recently reported a modification of the Peterson olefination that afforded Z-vinyl ethers in high yield and with exceptional stereocontrol (99% Z).³⁹ The reaction of a *cis*-2-trimethylsilyl-3-alkyl epoxide with an excess of an alcohol under boron trifluoride catalysis gave a 1-alkoxy-2-hydroxylalkylsilane in up to 97% yield. Treatment of the silane with potassium hydride in α,α,α -trifluorotoluene (TFT), triggered a *syn*-elimination producing Z-vinyl ethers with 99 : 1 Z:E selectivity and up to 96% yield (Scheme 3a).



Scheme 2 Published strategies for the synthesis of plasmalogen-type Z-vinyl ethers: (a) vinyl phosphonate reduction;³³ (b) partial hydrogenation of an alkynyl ether;³⁴ (c) alkylation of a lithioalkoxy allyl intermediate.³⁶





Scheme 3 (a) Synthesis of plasmalogen-type *Z*-vinyl ethers via a modified Peterson reaction;³⁹ (b) selective oxidation of DIMON in the presence of a methylene-skipped polyene.⁴⁰

To functionalise glycerol selectively, PGs are required to distinguish the three hydroxyl groups. As silyl ethers require an acidic or basic source of fluoride for their cleavage, such conditions can catalyse acyl migration.²⁸ Electron-rich benzyl ethers may be suitable as this PG class can be cleaved under neutral conditions. However, Bittman *et al.*³⁴ showed that 4-methoxybenzyl (PMB) was not oxidatively cleavable using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or ceric(IV) ammonium nitrate (CAN) in the presence of a *Z*-vinyl ether. Instead, Birch reduction was used to remove the PMB group but partially isomerised the vinyl ether. Benzyl ethers are not oxidatively cleavable in the presence of 1,3- or 1,4-dienes,⁴⁰ which excludes polyunsaturated plasmalogens. Therefore, prior to our research, *no known*⁴¹ hydroxyl PG was compatible with both *Z*-vinyl ethers and PUFA acyl groups, thus restricting plasmalogen accessibility.

We recently reported⁴⁰ a novel benzyl-type protecting group, 1,4-dimethoxynaphthalene-2-methyl ('DIMON', Scheme 3b), that was oxidatively cleavable in the presence of a methylene-skipped polyene (*e.g.* 1*Z*,4*Z*,7*Z*,10*Z*-tetraene). We have found that DIMON can also be oxidatively removed without perturbing a *Z*-vinyl ether and is therefore compatible with all plasmalogen functionalities.

With the invention of DIMON⁴⁰ and the adaptation of the Peterson reaction for synthesising *Z* vinyl ethers³⁹ we were ready to synthesise natural plasmalogens 1–3 (Fig. 2), for which a retrosynthetic analysis guided our approach (Scheme 4). The plan required that the phosphate group is

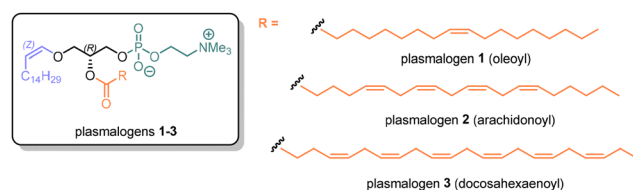
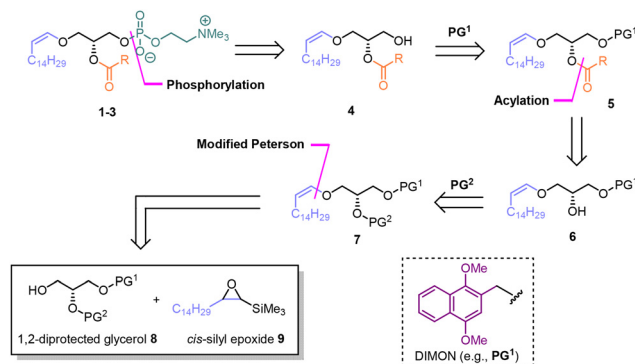


Fig. 2 Structure of plasmalogens 1–3.

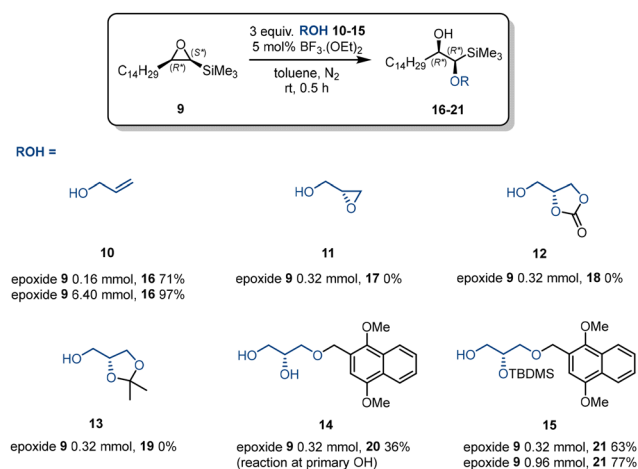


Scheme 4 Retrosynthetic analysis for plasmalogens.

introduced last, *via* alcohol 4, to avoid adverse solubility and chromatographic issues posed by this charged entity. Hence, the precursor of 4 is 5, protected at the *sn*-3 hydroxyl, preceded by alcohol 6, which is acylated. Compound 6 is derived by selective deprotection of 7, which bears the vinyl ether arising from combining 1,2-diprotected glycerol 8 with silyl epoxide 9. DIMON was one of the protecting groups (PG¹), whilst the other must be removed under conditions that enable the survival of DIMON and the vinyl ether. DIMON must be the only protecting group after the fatty acyl chain is installed.

A variety of protected glycerols or C₃ glycerol precursors have been used for the synthesis of glycerophospholipids.^{42–44} To apply our *Z*-vinyl ether synthesis required ring-opening of an intermediate *cis*-silyl epoxide, *e.g.* trimethyl(-3-tetradecyloxiran-2-yl)silane 9, by a suitable glycerol derivative or surrogate (Scheme 5). Six glycerol moieties were investigated: allyl alcohol 10, glycidol 11, 4-(hydroxymethyl)-1,3-dioxolan-2-one 12, solketal 13, mono-protected glycerol 14, and di-protected glycerol 15.

Allyl alcohol 11 requires an asymmetric epoxidation to introduce a second oxygen into the molecule followed by



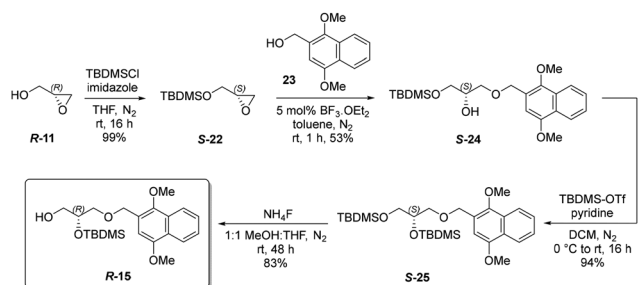
Scheme 5 Results of epoxide 9 ring-opening reactions with alcohols 10–15.



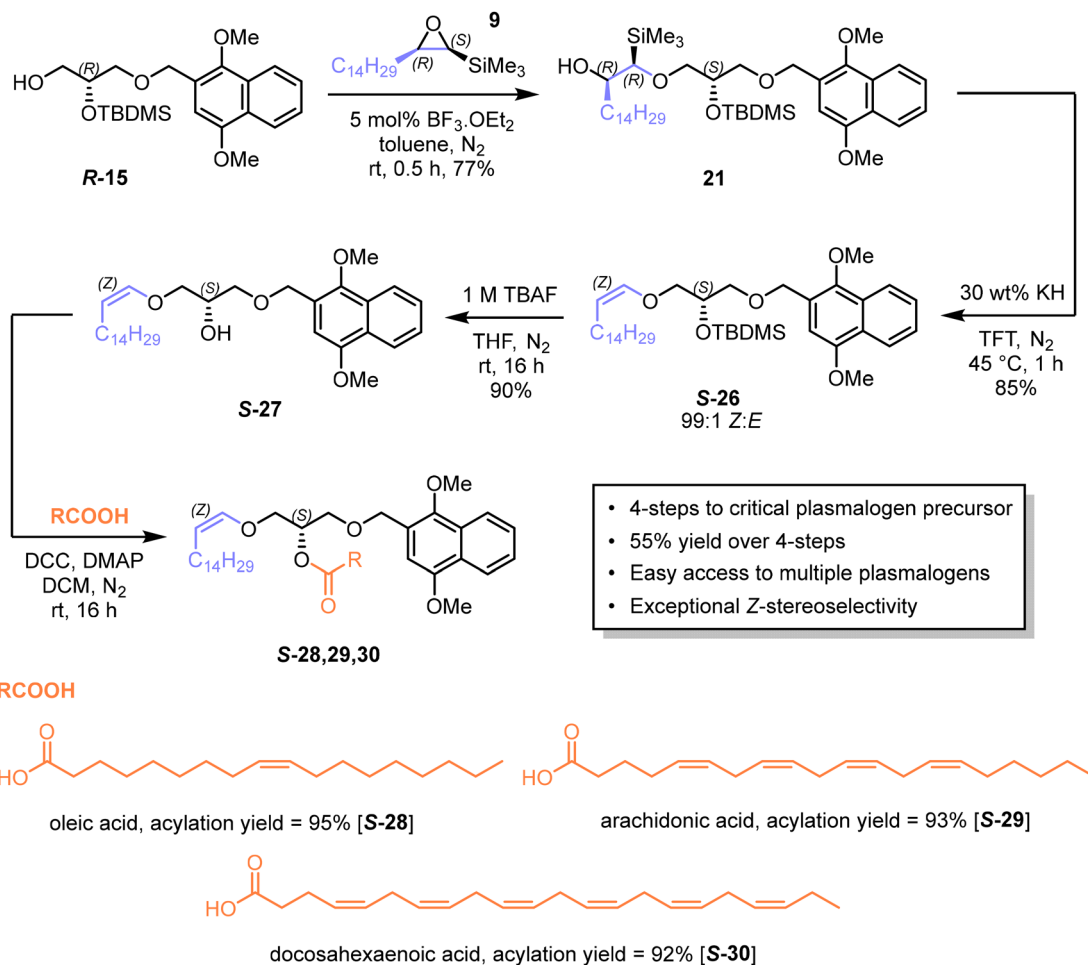
epoxide ring-opening to introduce a third. 4-(Hydroxymethyl)-1,3-dioxolan-2-one **12** is not commercially available as a single enantiomer corresponding to a natural plasmalogen. Single enantiomers of glycidol **11** and solketal **13** are commercially available, with compound **11** being the more attractive starting material, as **13** would require acid-catalysed hydrolysis of the ketal at a later stage. Reactions of alcohols **10–15** with epoxide **9** to form 1-alkoxy-2-hydroxyalkylsilanes **16–21** were attempted with boron trifluoride (BF_3), a commonly used catalysis for

reactions of epoxides with nucleophiles. Glycidol **11**, 4-(hydroxymethyl)-1,3-dioxolan-2-one **12**, and solketal **13** all failed to afford the desired product. Mono-protected glycerol **14** afforded the desired product in 36% yield, whilst 1,2-diprotected glycerol **15** gave product in 63% (0.32 mmol scale) or 77% yield (0.96 mmol scale). Allyl alcohol **11** gave a near quantitative conversion of epoxide to 1-alkoxy-2-hydroxyalkylsilane (6.40 mmol scale). All the reactions described exhibited, as required, very high regioselectivity for attack at the silyl-substituted centre in line with previous observations with amines.⁴⁵

Despite the efficiency of the ring-opening with allyl alcohol, further elaboration required enantioselective epoxidation of intermediate **16**. Many excellent methods have been described for such epoxidations [e.g. ref. 46], and now for terminal alkenes high enantioselectivity can be achieved with synthetically accessible catalysts [see e.g. ref. 47]. However, although we explored this possibility it led to incompatibility of functional groups when attempting to generate the *Z* vinyl ether. We therefore chose to proceed with the *R*-enantiomer (**R-15**) of the DIMON-protected glycerol derivative **15**, which was obtained from the readily available precursor (*R*)-glycidol **R-11** in 4 steps with 41% overall yield (Scheme 6).



Scheme 6 Synthesis of (*R*)-2-((*tert*-butyldimethylsilyloxy)-3-((1,4-dimethoxynaphthalen-2-yl)methoxy)propan-1-ol **R-15**.



Scheme 7 Synthesis of plasmalogen precursors **S-28,29,30**.

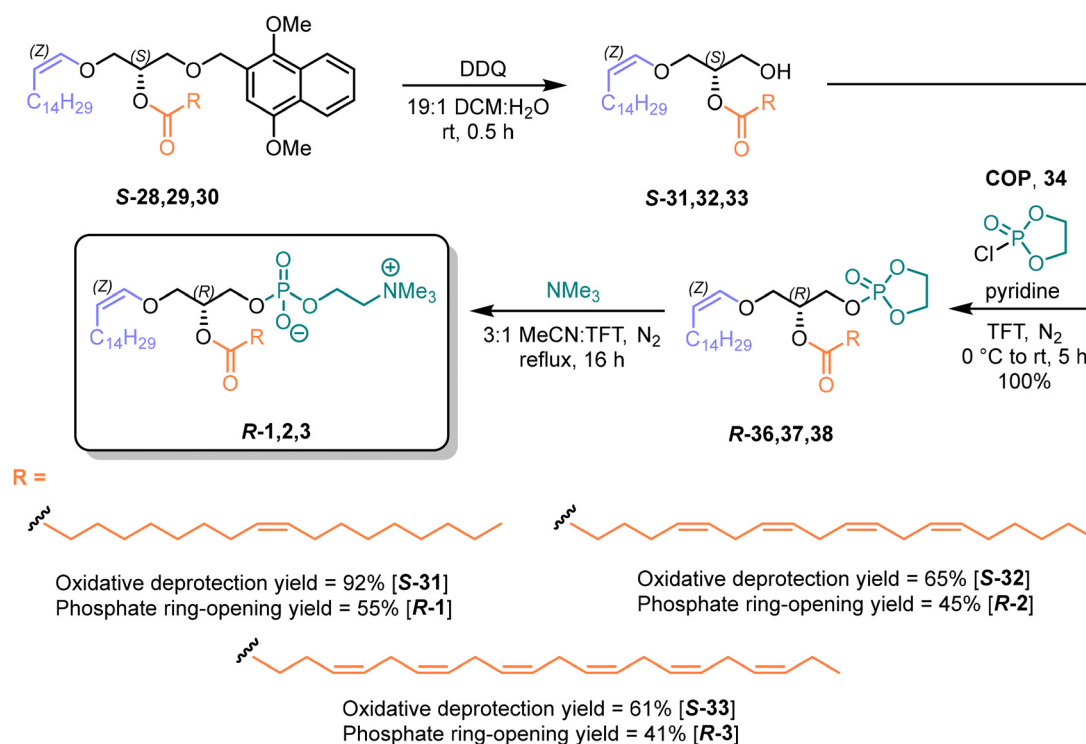


Thus, (*R*)-glycidol **R-11** was silylated with *tert*-butyldimethylsilyl chloride (TBDMSCl) to afford protected glycidol **S-22**⁴⁸ in quantitative yield. This compound was subjected to acid-catalysed epoxide ring-opening with DIMON alcohol **23** to give the 1,3-diprotected glycerol **S-24** in 53% yield. The 1,2-di-protected glycerol isomer was obtained in 17% yield, but readily separated chromatographically. Regioisomer **S-24** was silylated with TBDMSCl to give tri-protected glycerol **S-25** in 94% yield.

Finally, the primary silyl group was selectively cleaved by ammonium fluoride to afford 1,2-di-protected glycerol **R-15** in 83% yield (see ESI for full characterisation of this intermediate†). The epoxide ring-opening was also performed in dichloromethane or with ytterbium triflate as catalyst but did not improve on BF₃ in toluene. The optical purity and configuration of **R-15** was confirmed by high-performance liquid chiral chromatography analysis (>99% ee, see ESI†). The diastereomeric mixture denoted as compound **21** was subjected to Peterson elimination with potassium hydride in TFT (Scheme 7), which consumed all diastereoisomers and afforded the *Z*-vinyl ether **S-26** in 85% yield and with a *Z*:*E* isomeric ratio determined by ¹H NMR (see ESI†) to be 99:1. This compound is a convenient, storable intermediate for synthesising a variety of plasmalogens. Compound **S-26** was desilylated with tetrabutylammonium fluoride (TBAF) to give intermediate **S-27**, which was acylated with three fatty acids to afford the corresponding esters in high yields: 95% (**S-28**), 93% (**S-29**) and 92% (**S-30**) (see ESI for representative NMR spectra, which showed that the ratio of *Z*:*E* isomers remained at 99:1†).

With the *sn*-1 and *sn*-2 functionalities installed, it remained to attach a phosphocholine headgroup at the *sn*-3 position. To install this group, the DIMON was cleaved oxidatively with DDQ (Scheme 8). This was a critical step as success depended on whether the selection of DIMON based on consideration of oxidation potentials⁴⁰ was valid. Gratifyingly, all three reactions proceeded well to afford the desired primary alcohols in 92% (oleoyl, **S-31**), 65% (arachidonoyl, **S-32**), and 61% (docosahexaenoyl, **S-33**) yield. That the vinyl ether was undisturbed and the acyl group had not migrated, were confirmed by ¹H NMR (see ESI†). As there was no evidence of a new aldehyde proton, the *Z*-vinyl ether had not been affected. For compound **S-33** the hydroxyl proton was assigned to the triplet at 1.78 ppm (1 H, *J* = 6.2 Hz), which was coupled to the doublet of doublets at 3.75 ppm (2 H, *J* = 6.1, 4.7 Hz) assigned to the neighbouring methylene protons. Therefore, the compound contained a primary alcohol and no acyl migration had occurred. Further, the resonance at 5.04 ppm for the CH at the chiral centre was consistent with a CH group bearing an OCOR moiety. The very specific, near neutral conditions for DIMON removal are therefore perfectly compatible with the susceptible functionalities in plasmalogens and related glycerophospholipids.

The final challenge was to install the phosphate head group for which several methods were explored including the use of phosphorus oxychloride⁴⁹ and tris(2,2,2-trifluoroethyl)phosphate.⁵⁰ In each case sequential substitutions were attempted (with *e.g.* *tert*-butyl (2-hydroxyethyl)carbamate, di-protected glycerol) but did not proceed satisfactorily beyond monosubstitu-



Scheme 8 Synthesis of plasmalogens **R-1,2,3**.



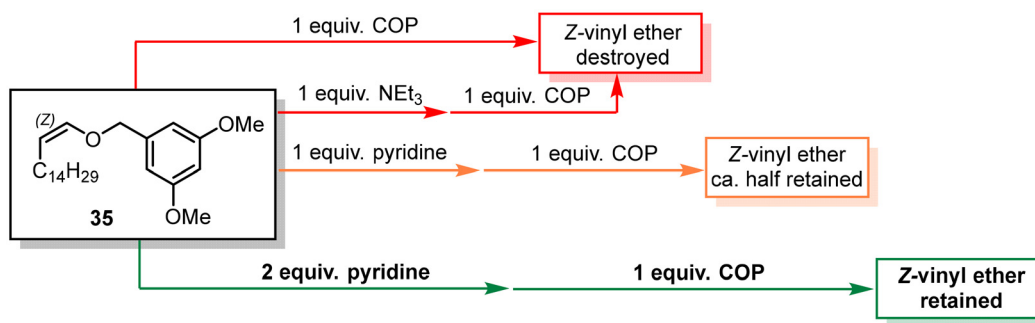


Fig. 3 Vinyl ether stability to COP, triethylamine, and pyridine.

tion (see ESI†). We therefore employed the well-established reagent 2-chloro-1,3,2-dioxaphospholane 2-oxide **34** (COP⁵¹). The compatibility of this reagent with a model compound (**35**) containing a Z vinyl ether was explored (Fig. 3), showing that COP could only be used in the presence of an excess of pyridine provided this base was added first.

Applying this methodology to **S-31** afforded cyclic phosphate **R-36** quantitatively, which on reaction with an excess of trimethylamine afforded plasmalogen **R-1** in 55% yield, with no evidence of vinyl ether hydrolysis according to ¹H NMR. The plasmalogen was characterised by ¹H, ³¹P, ¹H-¹H COSY, ¹H-¹³C HMBC and ¹H-¹³C HSQC NMR, as well as LCMS and HRMS (ESI†).

Plasmalogen precursors **S-32** and **S-33** were reacted with COP and pyridine affording intermediates **R-37** and **R-38**, respectively, in quantitative yield. The proton-decoupled ³¹P NMR analysis showed both products had a single, singlet peak at 17.5 ppm, which agreed with the observed resonance for compound **R-36**. The ¹H NMR spectra exhibited the phosphate ethylene peak at 4.41 ppm (multiplet, 4 H) and showed no evidence of vinyl ether hydrolysis. The intermediates were subjected to the NMe₃ ring-opening reaction, which afforded plasmalogens **R-2** and **R-3** in 45% and 41% yield, respectively.

To the best of our knowledge, this is the first time that plasmalogens **R-1**, **R-2** or **R-3** have been synthesised *and fully characterised* with respect to both the integrity of the vinyl ether configuration and enantiomeric purity. The overall yields were 28% (oleoyl **R-1**), 16% (arachidonoyl **R-2**), and 14% (docosahexaenoyl **R-3**) over 7 steps from compound **R-15**. While the two-step phosphorylation reaction was lower yielding than desired, it was the best method found for installing the phosphocholine functionality.

Conclusions

We have shown that the combination of the novel O-protecting group DIMON and a modified Peterson reaction provides a new general synthetic route to plasmalogens, illustrated by the synthesis of three such molecules differing with respect to the *sn-2* acyl group. Previous studies have only reported plasmalogens containing either a saturated (e.g. palmitoyl) or mono-

unsaturated (oleoyl) acyl moiety or have lacked full characterisation of the polyunsaturated molecules described. The present studies provide a new adaptable method for the synthesis of the most important natural plasmalogens, *i.e.* those containing polyunsaturated acyl groups. This should assist the development of novel diagnostic, prognostic, and therapeutic tools for diseases implicating plasmalogens, including AD.

Author contributions

Jay Tromans: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - original draft, Writing - review & editing. Bian Zhang: Funding acquisition, Project administration, Supervision, Writing - review & editing. Bernard T. Golding: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing - original draft, Writing - review & editing.

Data availability

All data reported in this paper is available on request from the corresponding author.

Conflicts of interest

There are no conflicts to declare.

References

- 1 E. L. Gottfried and M. M. Rapport, *J. Biol. Chem.*, 1962, **237**, 329[first in a series of papers].
- 2 M. Vítova, A. Palyzov and T. Rezanka, *Prog. Lipid Res.*, 2021, **83**, 101111.
- 3 F. Dorninger, J. Berger and M. Honsho, *Front. Cell Dev. Biol.*, 2023, **11**, 1137868: introducing a series of papers in an e-book collection.
- 4 F. Dorninger, E. R. Werner, J. Berger and K. Watschinger, *Front. Cell Dev. Biol.*, 2022, **10**, 946393.



- 5 R. Feulgen and K. Voit, *Pfluegers Arch. Gesamte Physiol.*, 1924, **206**, 389.
- 6 J. Koch, K. Watschinger, E. R. Werner and M. A. Keller, *Front. Cell Dev. Biol.*, 2022, **10**, 864716.
- 7 T. B. Poulsen, *Acc. Chem. Res.*, 2021, **54**, 1830.
- 8 W. T. Norton, E. L. Gottfried and M. M. Rapport, *J. Lipid Res.*, 1962, **3**, 456.
- 9 H. R. Warren and W. E. M. Lands, *J. Am. Chem. Soc.*, 1963, **85**, 60.
- 10 H. H. O. Schmid, W. J. Baumann and K. Mangold, *J. Am. Chem. Soc.*, 1967, **89**, 4797.
- 11 H. Goldfine, *Prog. Lipid Res.*, 2010, **49**, 493.
- 12 O. Skaff, D. I. Pattison and M. J. Davies, *Biochemistry*, 2008, **47**, 8237.
- 13 R. C. Murphy, *Chem. Res. Toxicol.*, 2001, **14**, 463.
- 14 A. M. Luoma, F. Kuo, O. Cakici, M. N. Crowther, A. R. Denninger, R. L. Avila, P. Brites and D. A. Kirschner, *Free Radicals Biol. Med.*, 2015, **84**, 296.
- 15 N. Jimenez-Rojo and H. Riezman, *FEBS Lett.*, 2019, **593**, 2378.
- 16 H. B. Gray and J. R. Winkler, *Acc. Chem. Res.*, 2018, **51**, 1850.
- 17 S. P. Jackson and J. Bartek, *Nature*, 2009, **461**(7267), 1071.
- 18 W. R. Markesbery and M. A. Lovell, *Arch. Neurol.*, 2007, **64**, 954.
- 19 D. A. Butterfield, *Antioxidants*, 2023, **12**, 462.
- 20 S. Paula, G. I. Lancaster and P. J. Meikle, *Prog. Lipid Res.*, 2019, **74**, 186.
- 21 M. S. Hossain, S. Mawatari and T. Fujino, *Front. Cell Dev. Biol.*, 2022, **10**, 828282.
- 22 M. Fujino, J. Fukuda, H. Isogai, T. Ogaki, S. Mawatari, A. Takaki, C. Wakana and T. Fujino, *Front. Cell Dev. Biol.*, 2022, **10**, 894734.
- 23 N. E. Braverman and A. B. Moser, *Biochim. Biophys. Acta*, 2012, **1822**, 1442.
- 24 R. V. Panganamala, L. A. Horrocks, J. C. Geer and D. G. Cornwell, *Chem. Phys. Lipids*, 1971, **6**, 97.
- 25 T. Fujino, T. Yamada, T. Asada, Y. Tsuboi, C. Wakana, S. Mawatari and S. Kono, *EBioMedicine*, 2017, **17**, 199.
- 26 Y. Zhou, N. Yu, J. Zhao, Z. Xie, Z. Yang and B. Tian, *Front. Cell Dev. Biol.*, 2020, **8**, 765.
- 27 D. B. Goodenowe, J. Haroon, M. A. Kling, M. Zielinski, K. Mahdavi, B. Habelhah and L. Shtilkind, *Front. Cell Dev. Biol.*, 2022, **10**, 864842.
- 28 J. A. Laszlo, D. L. Compton and K. E. Vermillion, *J. Am. Oil Chem. Soc.*, 2008, **85**, 307.
- 29 M. A. G. B. Gomes, A. Bauduin, C. Le Roux, R. Fouinneteau, W. Berthe, M. Berchel, H. Couthon and P.-A. Jaffrès, *Beilstein J. Org. Chem.*, 2023, **19**, 1299.
- 30 W. J. Baumann, T. H. Madson and B. J. Weseman, *J. Lipid Res.*, 1972, **13**, 640.
- 31 C. Ferreri, A. Ferocino, G. Batani, C. Chatgililoglu, V. Randi, M. V. Riontino, F. Vetica and A. Sansone, *Biomolecules*, 2023, **13**, 730.
- 32 A. J. Slotboom, G. H. De Haas and L. L. M. Van Deenen, *Chem. Phys. Lipids*, 1967, **1**, 192.
- 33 (a) Y. Rui and D. H. Thompson, *J. Org. Chem.*, 1994, **59**, 5758; (b) Y. Rui and D. H. Thompson, *Chem. – Eur. J.*, 1996, **2**, 1505.
- 34 D. Qin, H. S. Byun and R. Bittman, *J. Am. Chem. Soc.*, 1999, **121**, 662.
- 35 J. Shin, O. Gerasimov and D. H. Thompson, *J. Org. Chem.*, 2002, **67**, 6503.
- 36 (a) J. Shin and D. H. Thompson, *J. Org. Chem.*, 2003, **68**, 6760; (b) J. V. Bossche, J. Shin and D. H. Thompson, *J. Org. Chem.*, 2007, **72**, 5005.
- 37 S. Maeda, T. Mohri, T. Inoue, Y. Asano, Y. Otoki, M. Enomoto, K. Nakagawa, S. Kuwahara and Y. Ogura, *Biosci. Biotechnol. Biochem.*, 2021, **85**, 1383.
- 38 M. A. Khan, P. L. Wood and D. Goodenowe, *US Patent*, 2015, 9,169,280 B2.
- 39 J. Tromans, B. Zhang and B. T. Golding, *Chem. – Eur. J.*, 2023, e202302708.
- 40 J. Tromans, B. Zhang and B. T. Golding, *Chem. Commun.*, 2023, **59**, 13333.
- 41 *Greene's Protective Groups in Organic Synthesis*, ed. P. G. M. Wuts, John Wiley & Sons, Inc., New Jersey, 5th edn, 2014.
- 42 F. Paltauf and A. Hermetter, *Prog. Lipid Res.*, 1994, **33**, 239.
- 43 S. D. Stamatov and J. Stawinski, *Org. Biomol. Chem.*, 2010, **8**, 463.
- 44 Z. X. Guistra and K. L. Tan, *Chem. Commun.*, 2013, **49**, 4370.
- 45 P. F. Hudrlik, A. M. Hudrlik and A. K. Kulkarni, *Tetrahedron Lett.*, 1985, **26**, 139.
- 46 Q. He, M.-P. Pu, Z. Jiang, H. Wang, X. Feng and X. Liu, *J. Am. Chem. Soc.*, 2023, **145**, 15611–15618.
- 47 M. Lansing, H. Engler, T. M. Leuther, J.-M. Neudörfl and A. Berkessel, *ChemCatChem*, 2016, **8**, 3706.
- 48 C. P. Bold, C. Klaus, B. Pfeiffer, J. Schurmann, R. Lombardi, D. L. Agell, J. F. Diaz and K. H. Altmann, *Org. Lett.*, 2021, **23**, 2238.
- 49 H. Eibl, *Chem. Phys. Lipids*, 1980, **26**, 415.
- 50 K. Tsubaki, H. Shimooka, M. Kitamura and T. Okauchi, *Org. Lett.*, 2019, **21**, 9779.
- 51 N. S. Chandrakumar and J. Hajdu, *J. Org. Chem.*, 1983, **48**, 1197.

