Pergamon

Tetrahedron Letters, Vol. 37, No. 32, pp. 5705-5706, 1996
Copyright © 1996 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01218-X

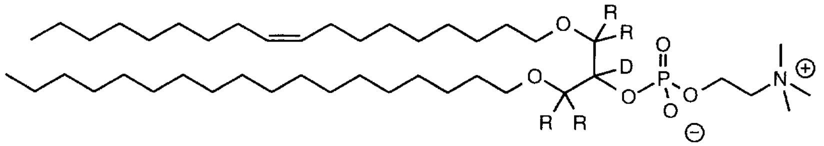
Synthesis of Glycerol Deuterated Ether Phospholipids

Simone Nuss[a], Pierre Oudet[b], Luc Lebeau[a]* and Charles Mioskowski[a]

[a]Université Louis Pasteur
Laboratoire de Synthèse Bioorganique associé au CNRS - Faculté de Pharmacie
74, route du Rhin - BP 24 - 67401 Illkirch - France
[b]Université Louis Pasteur
IGBMC - 1, rue Laurent Fries - Parc d'Innovation - 67404 Illkirch - France

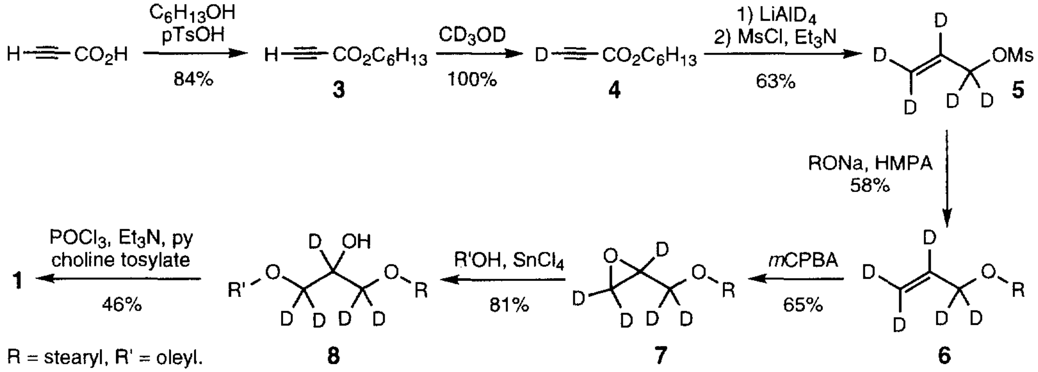
Abstract: 1,3-Dialkyl glycerophosphocholines deuterated on the glycerol moiety were synthesized starting either from propiolic acid to yield a pentadeuterated compound, or from epibromohydrin to give a monodeuterated substance. Copyright © 1996 Elsevier Science Ltd

Although a number of techniques have been used to study fluidity parameters at interfaces,[1] the measure of absolute fluidity inside a two-dimensional assembly still remains a challenge, and only results obtained using the same technique can be reliably compared. Among spectroscopic methods, ^{2}H-NMR has been widely used, either to study oriented lipid bilayers or lamellar phases.[2] For such purposes, different deuterated lipid probes have been prepared presenting various hydrogen/deuterium substitutions at the fatty chains or at the polar heads. Herein, we wish to describe the synthesis of two new glycerophospholipid probes **1** and **2**, differently deuterated at the glycerol moiety. These molecules were designed to perform fluidity measurements in synthetic 1,3-diether glycerolipid membranes that will be used in two-dimensional crystallization experiments of soluble proteins.



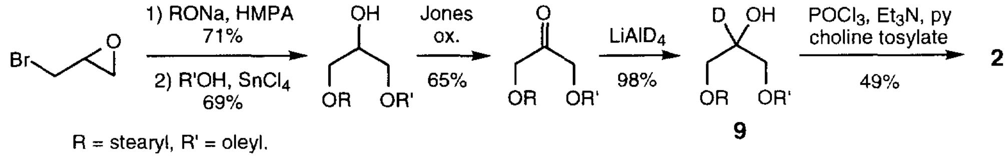
1 : R = D.
2 : R = H.

The pentadeuterated lipid **1** was prepared according to scheme 1. Propiolic acid was esterified and replacement of the alkynyl proton with deuterium in propiolate ester **3** was effected by handling the compound in a deuterated protic solvent such as CD_3OD. The ester was half deuterated over 24 hours. Solvent was removed and the operation was repeated three times to accomplish total deuterium exchange. Propiolate ester **4** was then reduced into deuterated allylic alcohol which was directly converted into the corresponding methanesulfonyl ester **5** without intermediate purification. Nucleophilic displacement of the leaving group with sodium stearate, epoxidation and opening of the resulting compound **7** with oleyl alcohol in the presence of a catalytic amount of $SnCl_4$ afford diglyceride analog **8**. This compound was converted into the corresponding phosphocholine in a "one pot" procedure using phosphorus oxychloride and choline tosylate in a triethylamine-pyridine mixture.[3] The modest yield obtained in that last step of the synthesis is essentially due to real difficulties to achieve purification of the compound to homogeneity.



Scheme 1

The monodeuterated probe **2** was more readily obtained starting from epibromohydrin to prepare monodeuterated precursor **9** that was transformed into compound **2** following the same procedure as for **8** (Scheme 2).[4]



Scheme 2

In conclusion, we describe here two new deuterated phospholipids **1** and **2** which are presently used as probes to investigate the fluidity of synthetic lipids in two-dimensional associations by the solid phase ^{2}H-NMR technique.

Acknowledgment: This work was supported in part by a grant from Institut Scientifique Roussel.

References

1 For a review, see for example : Ulman, A. *An Introduction to Ultrathin Organic Films, From Langmuir-Blodgett to Self-Assembly*; Academic Press Inc.: San Diego, **1991**; pp. 1-83.

2 (a) Krajewski-Bertrand, M.A.; Nakatani, Y.; Ourisson, G.; Dufourc, E.J.; Milon, A. *J. Chim. Phys.* **1992**, *89*, 237-242. (b) Davis, J.H. *Biochim. Biophys. Acta* **1983**, *737*, 117-171. (c) Seelig, A.; Seelig, J. *Biochemistry* **1974**, *13*, 4839-4845. (d) Schuler, I.; Milon, A.; Nakatani, Y.; Ourisson, G.; Albrecht, A.-M.; Benveniste, P.; Hartmann, M.-A. *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 6926-6930. (e) Krajewski-Bertrand, M.-A.; Milon, A.; Nakatani, Y.; Ourisson, G. *Biochim. Biophys. Acta* **1992**, *1105*, 213-220. (f) Auger, M.; Smith, I.C.P.; Jarrell, H.C. *Biophys. J.* **1991**, *59*, 31-38. (g) Auger, M.; Jarrell, H.C. *Chem. Phys. Lett.* **1990**, *165*, 162-167. (h) Auger, M.; Carrier, D.; Smith, I.C.P.; Jarrell, H.C. *J. Am. Chem. Soc.* **1990**, *112*, 1373-1381. (i) Smith, I.C.P.; Jarrell, H.C. *Pure and Appl. Chem.* **1991**, *63*, 529-534. (j) Roux, M.; Bloom, M. *Biochemistry* **1990**, *29*, 7077-7089.

3 Compound 1: ^{1}H-NMR ($CDCl_3/CD_3OD$ 1:1, 200 MHz): d 5.31 (m, 2 H); 4.26 (m, 2 H); 3.55 (m, 2 H); 3.43 (t, J = 6.4 Hz, 4 H); 3.17 (s, 9 H); 1.96 (m, 4 H); 1.50 (m, 4 H); 1.23 (m, 52 H); 0.84 (t, J = 6.3 Hz, 6 H). HRMS: *m/z* for $C_{41}H_{76}D_5O_6P$ [MH^+-NMe_3], calc.: 705.6069; found: 705.6064.

4 Compound 2: ^{1}H-NMR ($CDCl_3/CD_3OD$ 1:1, 200 MHz): d 5.31 (m, 2 H); 4.26 (m, 2 H); 3.58 (m, 4 H); 3.53-3.41 (m, 6 H); 3.19 (s, 9 H); 1.96 (m, 4 H); 1.53 (m, 4 H); 1.23 (m, 52 H); 0.86 (t, J = 6.3 Hz, 6 H). HRMS: *m/z* for $C_{41}H_{80}DO_6P$ [MH^+-NMe_3], calc.: 701.5822; found: 701.5830.

(*Received in France* 30 *May* 1996; *accepted* 20 *June* 1996)