Pergamon

Tetrahedron Letters 42 (2001) 1875–1877

TETRAHEDRON LETTERS

Synthesis of an amphiphilic aldehyde using as a key step the condensation of a lipophilic glyoxylic acid amide derivative with tris(hydroxymethyl)aminomethane

Dominique Bonnet, Pascal Joly, Hélène Gras-Masse and Oleg Melnyk*

UMR 8525, CNRS, Institut Pasteur de Lille, Université de Lille 2, Institut de Biologie de Lille, 1 rue du Pr Calmette, 59021 Lille Cedex, France

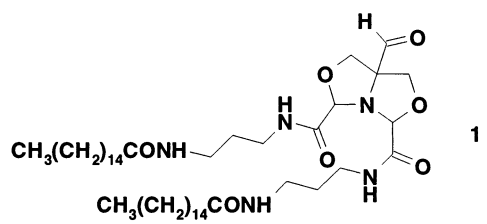
Received 5 January 2001; accepted 6 January 2001

Abstract—Spontaneous condensation of a glyoxylic acid amide derivative incorporating a palmitoyl group with tris(hydroxymethyl)aminomethane followed by Dess–Martin oxidation led to an heterocyclic amphiphilic aldehyde, which was successfully engaged in hydrazone formation in partial aqueous media. © 2001 Published by Elsevier Science Ltd.

The modification of the surface properties of a phospholipid bilayer, such as the introduction of adhesion motifs,[1] or of receptor ligands,[2] can be accomplished by insertion of a peptide or oligosaccharide into the membrane. Most of the time, these biomolecules are highly hydrophilic so that their stable anchoring into phospholipid bilayers requires their derivatization by a lipidic foot composed of at least two alkyl chains.[3] However, the modification of peptides or oligosaccharides by hydrophobic moieties is often a challenging task due to the generally low solubility of the conjugates. To circumvent these difficulties, convergent strategies have been developed where the purified biomolecule is chemoselectively ligated to a functionalized lipidic anchor already inserted in the membrane.[4]

In the search of novel lipophilic aldehydes for the membrane immobilization of unprotected peptides through hydrazone ligation, we have developed a rapid and low cost access to amphiphilic aldehyde **1** (Fig. 1). Compound **1**, composed of an aldehyde group and two palmitic acid-derived arms assembled on a 1-aza-3,7-dioxabicyclo(3.3.0)octane core, was synthesized in four steps starting from D,L-tartaric acid (Schemes 1 and 2). D,L-Tartaric acid was esterified in ethanol in the presence of Amberlyst resin. Diester **2** was then treated with an excess of 1,3-diaminopropane to give diamine **3** in 81% yield. Diamine **2** was solubilized in water and the pH was adjusted to 3.25 with solid citric acid before the periodic oxidation. Compound **4** was not isolated due to its high solubility in water. Thus, the pH of the reaction mixture was adjusted to 8.5 with tris(hydroxymethyl)aminomethane (THAM) followed by the addition of palmitic acid succinimidyl ester and *t*-BuOH to allow the solubilization of the fatty-acid derivative. This procedure led to the isolation of alcohol **5** as the major product (52% starting from diamine **3**, one diastereoisomer[5]), together with 13% of the α-oxo-aldehyde **6**.[6] Compound **5** could be hydrolyzed back to α-oxo-aldehyde **6** in the presence of trifluoroacetic acid (Scheme 1).

The ease of formation of 1-aza-3,7-dioxabicyclo-(3.3.0)octane derivative **5** in an aqueous medium is unexpected on the basis of the few papers describing the synthesis of this heterocycle.[7] For example, Pierce and co-workers synthesized 1-aza-2,8-dialkyl-5-hydroxymethyl-3,7-dioxabicyclo(3.3.0)octanes by reaction of aliphatic or aromatic aldehydes with THAM in refluxing benzene using a water separator. Analogously, Broadbent et al. isolated 2,6-dioxa-10-azatricyclo-(5.2.1.0)decanes by reaction of 2-amino-1,3-propane-

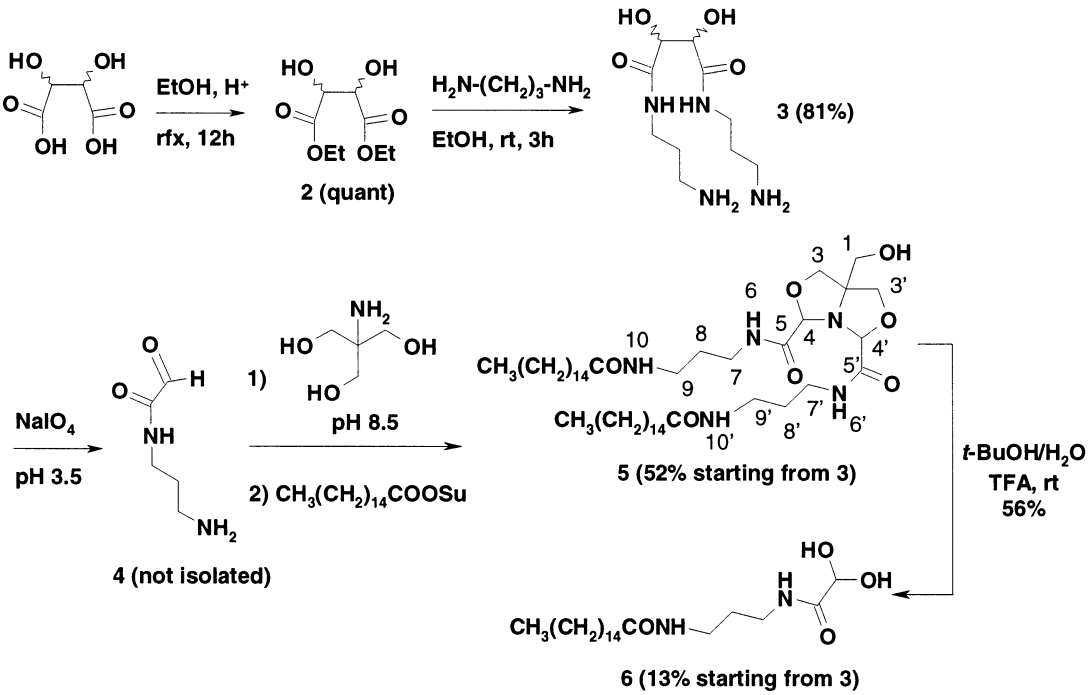


1

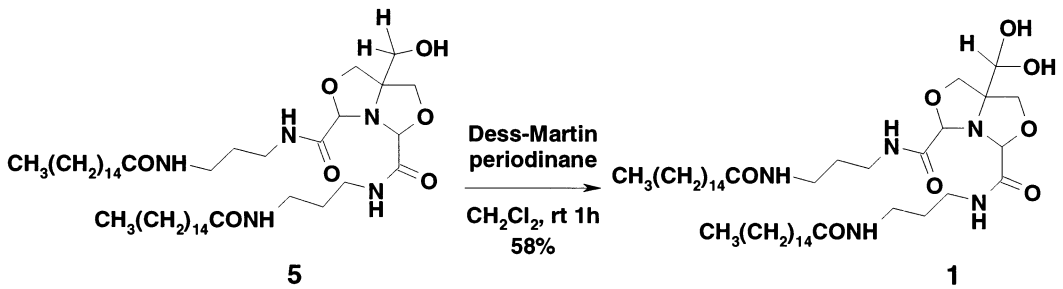
Figure 1. Amphiphilic aldehyde **1**.

* Corresponding author. Tel.: 33 (0)3320871215; fax: 33 (0)-320871233; e-mail: oleg.melnyk@pasteur-lille.fr

0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(01)00032-6



Scheme 1.



Scheme 2.

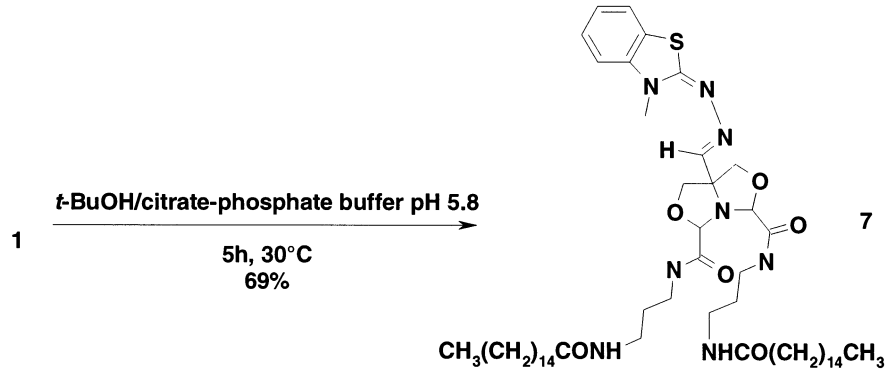
diols with 2,5-hexanediones. To our knowledge, glyoxylic amide derivatives were never studied in this context. Spontaneous formation of the 1-aza-3,7-dioxabicyclo(3.3.0)octane heterocycle may result from both the use of a large excess of THAM and the high reactivity of α-oxo-aldehydes, which are essentially in the hydrated form in aqueous media.[8]

With compound **5** in hand, we turned our attention to the last step of the synthesis, i.e. the oxidation of the primary hydroxyl group (Scheme 2). This conversion was cleanly effected using the Dess–Martin periodinane reagent, which was selected for its mildness, to take into account the sensitivity of **5** to acid catalyzed hydrolysis.[9] Dess–Martin periodinane was freshly prepared using the modification of Frigerio et al.[10] Using ^{1}H NMR, compound **1** was found to be essentially in the hydrated form (92%).

The reactivity of the aldehyde moiety of compound **1** was examined using 3-methyl-2-benzothiazolinone hydrazone (MBTH), which is known to react efficiently with aldehydes (Scheme 3).[11] Aldehyde **1** was found to be readily soluble in partial aqueous media. Reaction with MBTH at pH 5.8 led to hydrazone **7** in 69% yield following purification, thus showing that the aldehyde moiety of **1** is accessible to hydrophilic reagents and not masked by aggregation. Further studies devoted to the reactivity of heterocycle **1** in liposome formulations are under way.

Acknowledgements

We thank Bernadette Coddeville and Guy Ricart for the ES-MS studies (Université des Sciences et Technologies de Lille), and Dr. Steve Brooks for proofreading the manuscript. We gratefully acknowledge financial support from the Institut Pasteur de Lille, Agence Nationale de Recherche sur le SIDA (ANRS) and Centre National de la Recherche Scientifique (CNRS). Dominique Bonnet holds a CNRS Région Nord-Pas-de-Calais fellowship.



Scheme 3.

References

1. Hojo, H.; Kojima, T.; Yamauchi, K.; Kinoshita, M. *Tetrahedron Lett*. **1996**, *37*, 7391–7394.
2. (a) Sugimoto, M.; Ohishi, K.; Fukasawa, M.; Shikata, K.; Kawai, H.; Itakura, H.; Hatanaka, M.; Sakakibara, R.; Ishiguro, M.; Nakata, M.; Mizuochi, T. *FEBS Lett*. **1995**, *363*, 53–56; (b) Fukasawa, M.; Shimizu, Y.; Shikata, K.; Nakata, M.; Sakakibara, R.; Yamamoto, N.; Hatanaka, M.; Mizuochi, T. *FEBS Lett*. **1998**, *441*, 353–356.
3. Epand, R. M. *Biopolymers* **1997**, *43*, 15–24.
4. (a) Boeckler, C.; Frisch, B.; Schuber, F. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2055–2058; (b) Martin, F. J.; Papahadjopoulos, D. *J. Biol. Chem*. **1982**, *257*, 286–288; (c) Kung, V. T.; Redeman, C. T. *Biochim. Biophys. Acta* **1986**, *862*, 435–439.
5. Compound **5**: ES-MS $[M+H]^+$ calcd 823.2, found 822.7. ^{1}H NMR (pyridine-d_5, 300 MHz): δ 9.07 and 8.89 (two t, 2×1H, $H_{6,6'}$; 6.1 Hz), 8.55 and 8.50 (two t, 2×1H, $H_{10,10'}$, 5.7 Hz), 6.80 (t, 1H, OH, 5.1 Hz), 5.50 (s, 1H, $H_{4'}$) correlated in the ROESY spectrum with the proton $H_{3'b}$, 5.40 (s, 1H, H_4) correlated in the ROESY spectrum with H_3 and H_1, 4.48 (d, 1H, $H_{3'a}$, 8.7 Hz), 4.08 (d, 1H, $H_{3'b}$, 8.7 Hz), 4.07 (s, 1H, H_3), 3.99 (s, 2H, H_1), 3.60 (m, 8H, $H_{7,7'}$ and $H_{9,9'}$), 2.40 (t, 2H, -C$\underline{H}_2$CO-, 7.2 Hz), 2.37 (t, 2H, -C$\underline{H}_2$CO-, 7.2 Hz), 1.83 (m, 8H, -C$\underline{H}_2$CH$_2$CO- and $H_{8,8'}$), 1.25 (m, 48H, $CH_3(C\underline{H}_2)_{12}$-), 0.86 (t, 6H, C$\underline{H}_3$-). ^{13}C NMR (pyridine-d_5, 75 MHz): δ 175.2, 171.4, 94.7, 93.7, 76.2, 75.5, 74.0, 65.2, 38.0, 37.5, 31.1, 27.5, 24.2, 15.6.
6. Compound **6** was recently described as a useful lipophilic vector for the synthesis lipopeptides using hydrazone ligation. See: Bonnet, D.; Bourel, L.; Gras-Masse, H.; Melnyk, O. *Tetrahedron Lett*. **2000**, *41*, 10003–10007.
7. (a) Pierce, J. S.; Lunsford, C. D.; Raiford, R. W.; Rush, J. L.; Riley, D. W. *J. Am. Chem. Soc*. **1951**, *73*, 2595–2596; (b) Pierce, J. S.; Lunsford, C. D. *J. Am. Chem. Soc*. **1951**, *73*, 2596–2598; (c) Broadbent, H. S.; Burnham, W. S.; Sheeley, R. M.; Olsen, R. K. *J. Heterocyclic Chem*. **1976**, *13*, 337–348; (d) Zaitsev, V. P.; Purygin, P. P.; Sharipova, S. K. H. *Khim. Geterotsikl. Soedin*. **1990**, *10*, 1394–1395; (e) Okawara, T.; Ehara, S.; Hakui, N.; Furukawa, M. *Chem. Express* **1992**, *8*, 621–6244.
8. Cooper, A. J. L.; Redfield, A. G. *J. Biol. Chem*. **1975**, *250*, 527–532.
9. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155–4156; (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277–7287.
10. Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem*. **1999**, *64*, 4537–4538.
11. See for example: Mikolajczyk, S. D.; Meyer, D. L.; Starling, J. J.; Law, K. L.; Rose, K.; Dufour, B.; Offord, R. E. *Bioconjugate Chem*. **1994**, *5*, 636–646.