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Synthesis of phospholipids via “Click-Chemistry”

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Abstract

This work aims the synthesis of edelfosine analogues to resensitize tumor cells to the apoptotic process.

Key-words:

Edelfosine, cancer, click chemistry

Introduction

Cancer is the second leading cause of death by disease in the world. It is a very heterogeneous pathology and the exact mechanism of the disease is unclear. However, it is now known that its etiology and progression are related to the loss of the apoptotic machinery in the neoplastic cells, resulting in increased proliferation and survival of the tumor cells.[1]

The alkyl phospholipid edelfosine (1-*O*-octadecyl-2-*O*-methyl-sn-glycero-3-phosphocholine) is able to resensitize tumor cells to the apoptosis "in vitro", without affecting non-neoplastic cells. This could reflect clinically in the absence of the side effects that are frequently observed in the classical chemotherapy (*e.g.* bone narrow, alopecia and nausea). However, clinical trials showed that the high cytotoxicity of edelfosine observed "in vitro" was not maintained "in vivo",[2] which prompted us for the design of new synthetic analogues.

Results and discussion

These results refer to the first and second steps of the proposed synthesis (Figure 1.) The first step, which consisted of protecting the primary hydroxyl of glycerol with a trityl group, rendered an average yield of 42%. The first attempts on the tritylation yielded around 13% of the first synthetic intermediate while the latter optimized reactions yielded around of 54%.

The second step emerged as a challenging Williamson Synthesis due to the characteristics of the reactants. Simultaneous microwave and ultrasound irradiation (abbreviated SMUI) has been described as a promising strategy to assist Williamson Synthesis due to its more efficient heating and mixing effects.[3] However, in the absence of required apparatus for SMUI, several different approaches to the second step of this work have been tried.

The following strategies did not rendered acceptable yields of the desired product: overnight reflux under magnetically stirring; ultrasound at RT, ultrasound and intermittent heating (warm bath); ultrasound and intermittent microwave heating; and finally microwave heating varying time (10s to 30s) and potency (90w to 360w). The faced challenges varied from choosing the proper organic solvent to promote a uniform heating in the microwave, to the cleavage of the trityl group at the high temperatures achieved with microwave irradiation.

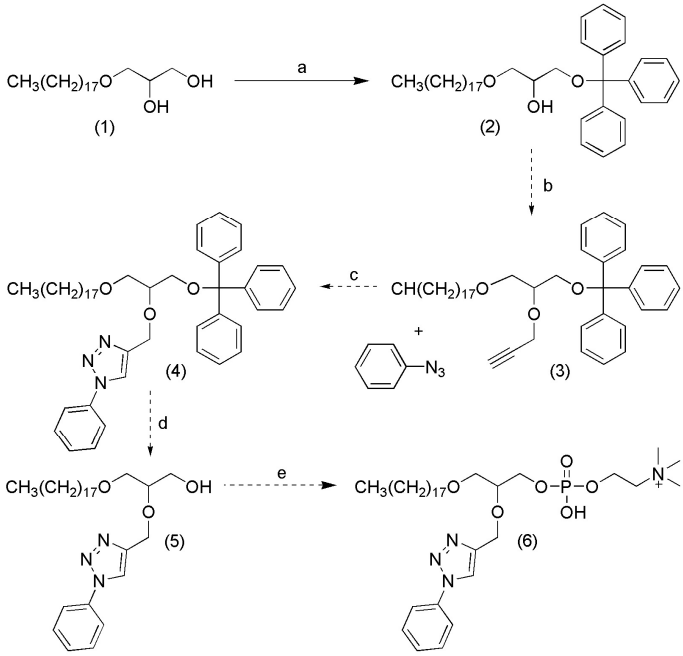

Figure 1. *Reagents and conditions: (a) Trityl chloride, THF/Acetonitrile, 66°C, 24h, 42%; (b) Propargyl bromide, tetrabutylammonium bromide, Ethyl ether/NaOHaq 50%, rt, 24h; (c) t-BuOH/water, sodium ascorbate, CuSO4, MW, 18W, 70°C, 15 min.; (d) Acetic Acid, reflux, 5h, 80%; (e) POCl3, triethylamine, THF, 0°C, 2h, then choline chloride, triethylamine, CHCl3, rt, 24h.*

Conclusions

Protecting the primary hydroxyl group has been achieved with fairly good yields, however the second step proved to be quite challenging. Current studies focus on determining if the formation of the alcoxide was hindering the reaction or if it was produced but did not react with the haloalkane.

Acknowledgments

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