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RESEARCH ARTICLE

SYNTHESIS AND PRELIMINARY DETERMINATION OF ANTIBACTERIAL ACTIVITY OF SOME 1,3-ENYNES

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ABSTRACT

The synthesis of five 1,3-enynes was performed and its activity against Gram-positive and Gram-negative bacteria was determined.

Key Words: *1,3-enynes, 1,3-dilithiopropyne, Antibacterial activity.*

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INTRODUCTION

The 1,3-enyne chemical framework has been found in a wide variety of natural products, many of which have shown important biologically activity. Some examples of these compounds are the (-)-callipeltosides A, B, 1, and C, (Figure 1) which were first isolated in 1996, from the New Caledonian lithistida sponge *Callipelta sp*. (Zampella, 1996). They are active against human bronchopulmonary non-small cell lung carcinoma (NSCLC-N6 and P388 cell lines) (Zampella, 1997 and Frost, 2015). Structurally related is the phorbaside A, 2, highly cytotoxic compound isolated from the Western Australian marine sponge *Phorbas sp*. (MacMillan, 2008 and Skepper, 2007). Neocarzinostatin, 3, isolated in 1965 from a culture of *Streptomyces carzinostaticus* (Ishida, 1965 and Edo, 1985), was the first enediyne antitumor antibiotic; and its capacity to cleave DNA in cells is the responsible for its antitumor activity (Beerman, 1974 and Maeda, 2001). Other examples of natural products containing the 1, 3-enyne, are the potent antitumors dynemicin A, 4, (Konishi, 1990), isolated from the bacteria *Micromonospora chersina* (Konishi, 1989); and calichemicin γ 1, 5 (Lee *et al*., 1987 and Lee *et al*., 1981), isolated from *Micromonospora echinospora*, which has been used against non-solid tumors of acute myeloid leukemia. From the skin of poison frogs from the family Dendrobatide (*Dendrobates histrionicus*), the histrionicotoxin gephyrotoxin, 6, has been isolated (Daly, 1997). Interestingly, the antimitotic (-)-tricholomenyn A, 7, was isolated from the fruiting bodies of the mushroom *Tricholoma acerbum* (Garlaschelli et al., 1995). The structurally similar (-)-harveynone, 8, was isolated from *Curvularia harveyi*, and it was found to possess antitumor activity (Miller and Johnson, 1997). An example of a synthetic 1,3-enyne, having biological properties is Terbinafine, 9, discovered in 1984, (Petranyi et al., 1984), and commercially available under the brand name of Lamisil. It was the first pharmaceutical agent to contain a (*E*)-1,3-enyne in its structure (Stütz, 1987). It has been used for the treatment of skin and toenail infections caused by dermatophytes such as *Trichophyton rubrum* and *Trichophyton mentagrophytes* (Jain and Sehgal, 2000). 1,3-Enynes are also very useful units for the construction of more complex molecules in organic synthesis. Several methods for the synthesis of 1,3-enynes have been developed (Negishi, 2003 and Trost and Masters, 2016), and among these the classical method, widely used, is the palladium-catalyzed Sonogashira cross-coupling reaction of terminal acetylenes with vinyl halides (Sonogashira, 1975). We would like to report herein the synthesis of five 1,3-enynes and the determination of its antimicrobial activity against some Gram (+) and Gram (-) bacteria.

RESULTS AND DISCUSSION

Synthesis: We recently reported (Umaña and Cabezas, 2017) that reaction of 2,3-dichloropropene, 10, with magnesium generated allene gas, 11, and when this was bubbled over an ethereal solution of *n*-butyllithium, at -78° C, the operational equivalent of dianion 1,3-dilithiopropyne, 12, was formed. When we reacted this dianion, 12, with benzophenone, 13, addition to the carbonyl group was achieved to obtain the corresponding alkoxy-acetylide intermediate, 14. We developed a procedure (Cabezas and 2018) to perform

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palladium cross-coupling reactions between this intermediate, 14, with substituted-aromatic iodides to obtain the

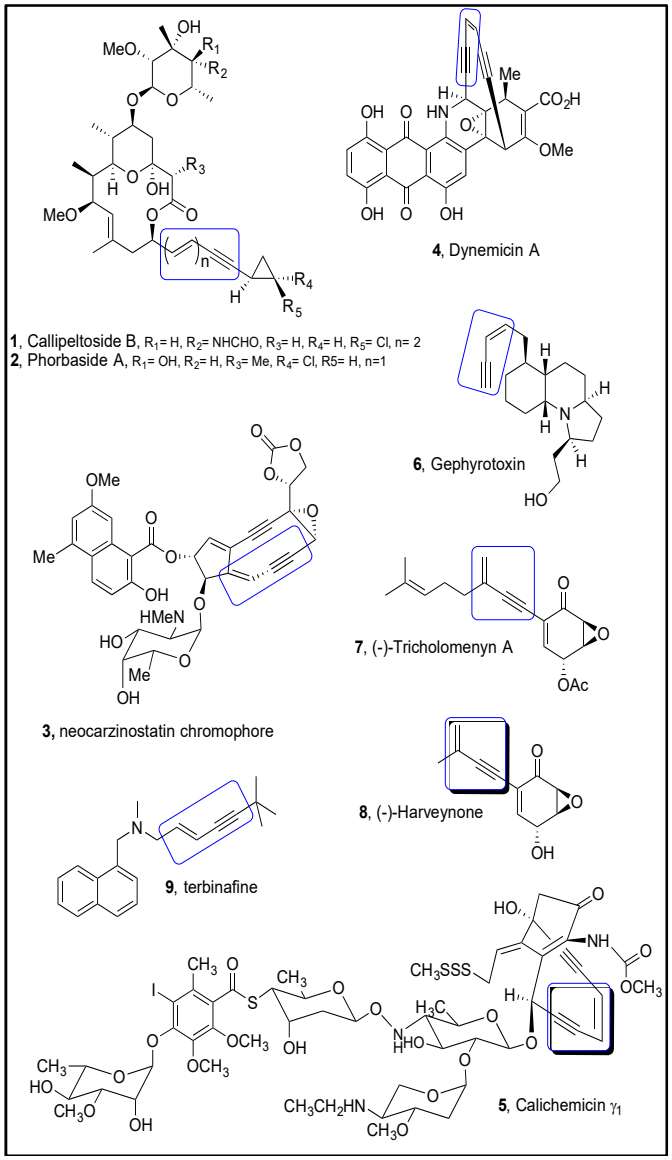
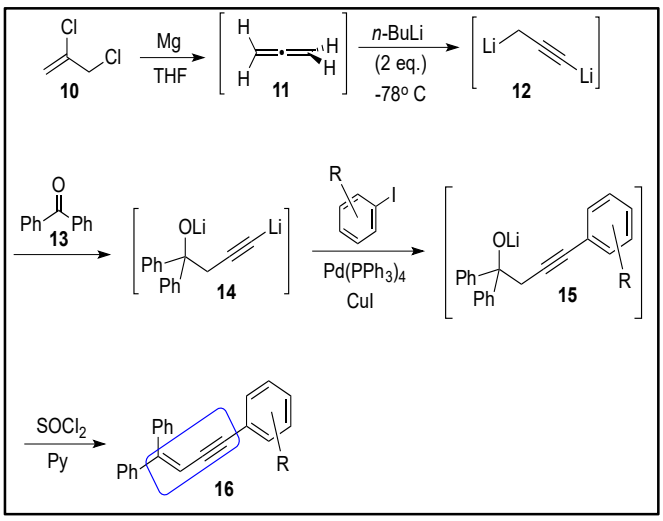
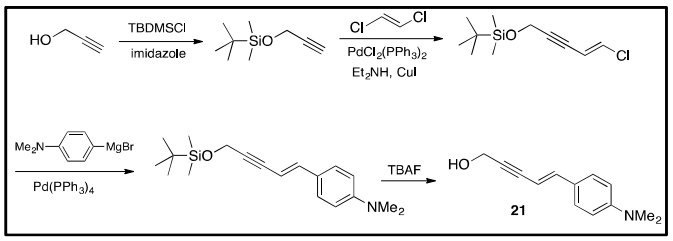


Figure 1. Examples of some biologically active compounds containing the 1,3-enyne unit



Scheme 1. Synthetic strategy used for the preparation of 1,1,4-triphenyl-1,3-enynes



Scheme 2. Synthetic preparation of compound 21

corresponding alkoxy intermediates 15, which upon treatment with thionyl chloride, in the presence of pyridine, generated the corresponding 1,1,4-triphenyl substituted 1,3-enynes, 16 (Scheme 1). We used this synthetic strategy (Scheme 1) to prepare 1,3-enynes 17, 18, 19 and 20 (Figure 2), in 71, 60, 68 and 43 % overall yield respectively (Cabezas, 2018). Additionally, the 1,3-enyne, 21, was synthesized, according to the chemical sequence described in Scheme 2, as previously reported (Cabezas, 2018).

Antibacterial activity: The antibacterial activity of these compounds (Figure 2), at a concentration of 50 µg/mL, was determined against Gram-positive and Gram-negative bacteria, as shown in Table 1.

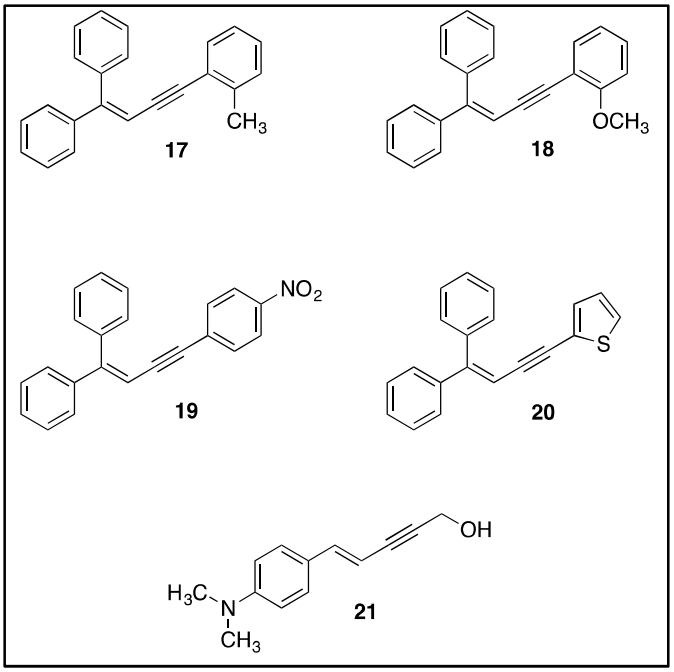


Figure 2. 1,3-Enynes synthesized to test antimicrobial activity

Table 1. Comparison of Antibacterial Activity of 1,3-Enynes 17-21, Against Gram-Positive and Gram-Negative Bacteria Compound (50 µg/mL)

Microorganism	17	18	19	20	21
Staphylococcus Aureus (G+)	-	-	-	+	-
Pseudomonas sp (G-)	-	+	+	+	-
Escherichia coli (G-)	-	+	+	+	-
Salmonella sp (G-)	-	-	+	+	+

(-) growth, (+) inhibition

These results show that, compound 17, which has no polar substituents (i.e. electro-withdrawing or electro-donating groups) does not inhibit any of the strains tested. Remarkably, the presence of a methoxy group in 18, in comparison with a methyl group in 17, in this common carbon-skeleton, is enough to inhibit the growth of both *Pseudomonas* and *E. coli*.

The presence of a highly electro-withdrawing group, such as a nitro group, in the *para* position of the phenyl ring, at the position 4 of the 1,3-enyne, 19, enhances the activity of this 1,3-enyne against the bacteria tested. Particularly important is the presence of a thiophene group in enyne 20. In this case inhibition of all strains tested was observed. In recent years the increase in antimicrobial resistance has become a public health problem. The World Health Organization (WHO) has emphasized in the need for the development of new antibacterial compounds (Kaplan, 2004). The chemical compound 20, showed preliminary promising results and further studies have to be done to determine its activity against some other strains and the values of the minimal inhibitory concentration (MIC). Also it is important to perform other chemical changes in its structure in order to establish a structure-activity correlation. Compound 21, did not show good inhibition of the strains tested.

Conclusions

In this study five synthetic enynes were tested against Gram-positive and Gram-negative bacteria. In the type of compounds chosen for this study, possessing a common framework (17-20) the presence of polar groups is necessary to observe some growth inhibition in the strains tested. A very interesting effect was observed with the presence of a thiophene group in enyne 20. In this case a strong inhibition was observed in both, Gram-positive and Gram-negative bacteria.

Experimental Section

Synthesis. General Information: All glassware and syringes were dried in an oven overnight at 140º C and flushed with nitrogen immediately prior to use. Transfers of reagents were performed with syringes equipped with stainless-steel needles. All reactions were carried out under a positive pressure of nitrogen. Nitrogen was passed through a Drierite gas-drying unit. Diethyl ether and tetrahydrofuran were refluxed and freshly distilled from sodium and potassium/ benzophenone ketyl respectively, under nitrogen atmosphere. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a 400 MHz Bruker spectrometer. High resolution mass were measured on a Waters Synapt HMDS G1, Q-TOF. Infrared spectra were recorded on a Perkin Elmer FT-IR Spectrum 1000. 1,3-Enynes 17-20 were synthesized according to the procedure of Cabezas *et al.* (Cabezas, 2018). Enyne 21, was synthesized according to Cabezas *et al*. (Cabezas, 2018).

Bactereological tests: For the diffusion methods, the solvent used was dimethylsulfoxide (DMSO)

Test bacteria: Antibacterial activity was assessed against *Pseudomonas sp*(ATCC 27853)*, Salmonella sp*(ATCC 14028), *Staphylococcus aureus* (ATCC 25923) and *Escherichia coli* (ATCC 25922).

Suspension preparation: Each microorganism was inoculated into trypticase soy broth (TSB) + yeast (Oxoid®) and cultured at 37°C until the desired concentration was reached. The suspension of bacteria to be cultured was equivalent to 0,5 McFarland standard, (1,5 x10^{8} CFU/ml).

Agar diffusion method: All tests were performed by duplicate. The microorganism to be tested was uniformly spreaded with sterile cotton swab over blood agar plates. All agar plates were prepared using 20 ml of agar and allowed to solidify uniformly. 7 mm diameter holes were cut in the agar gel, 20 mm apart from each one. 100 µL of inoculum suspension was swabbed uniformly in the corresponding agar plates. These were incubated at 35^{o} C for 24 h.

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Conflicts of interest: The authors declare that there is no conflict of interest.

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