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New methodology for the synthesis of tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one derivatives, synthons of natural products with biological interest

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Haloketones
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[3+2]-Cycloaddition
[4+3]-Cycloaddition

ABSTRACT

A new methodology is presented to synthesize in a regio and stereoselective manner tetrahydrofuro[3,2-b]furan-2(3*H*)-one, structural subunit present in a wide variety of natural products present in plant, fungi, algae, insects, and other living organisms. This secondary metabolites have important biological properties and have shown to be very active in different therapeutic areas. This method consists in the reaction of highly substituted 2-oxyallyl cations, generated in situ from the corresponding dihaloketone, and 2-functionalized furans (in our case 2-NHBoc-furan). It is a one-pot reaction that affords the desired furofuranones with high regio- and stereoselectivity. The new synthetic method is simple, straightforward and versatile, because a wide variety of furofuranones, and with wide molecular diversity, may be prepared by adequately designing the substituents of starting materials. The resulting furofuranones may be potentially derivatized to generate chemical libraries of high molecular diversity, which are very useful when developing structure–activity relationship studies.

1. Introduction

The tetrahydrofuro[3,2-b]furan-2(3*H*)-one structural subunit is present in natural products from many different living organisms: superior plants, fungi, algae, sponges, insects, etc. Some of these compounds like goniofufurone and analogs are active as cytotoxic agents against lymphocytic leukaemia and human lung carcinoma (Fig. 1).[1]

Secondary metabolites from Caribbean sponges like plakortones A-F constitute a new class of activators of cardiac SR-Ca^{2+}-pumping ATPase, and are relevant to correction of cardiac relaxation irregularities. Other plakortones exhibit in vitro cytotoxic activity on a murine fibrosarcoma cell line, so that overall, the plakortones represent a new family of natural products of substantial pharmacological interest.[2] On the other hand, the nortriterpenoids rubriflordilactones from *Schisandra rubriflora* (Fig. 1) are a class of structurally and biologically attractive compounds due to their promising *anti*-HIV activity.[3]

In addition, their attractive architectures represent a formidable synthetic challenge. Furthermore diachasmimorpholides secreted by abdominal glands of braconid wasps, *Diachasmimorpha longicaudata* and *Diachasmimorpha tryoni* are important fragrant volatile biological control agents acting as semiochemicals with great ecological interest.[4] It is also worth noting the interest of furofuranones derived from *D*-aldoses, as analogs of goniofufurone, with interesting cytotoxic activity.[5]

The structural subunit *cis*-2,6-dioxabicyclo[3.3.0]octane or perhydrofuro[3,2-*b*]furan is even more widely present in Nature than its furofuranone analog. Thus, natural products like mycotoxin erythroskyrine[6] from (*Penicillium islandicum*), Laurenenines A and B from algae (*Laurentia nipponica*)[7] are good examples. On the other hand, synthetic products like isosorbide (starting material for synthesis of biobased polymers and also for pharmaceutical applications),[8] isosorbide dinitrate (vasodilator of use in cardiac therapy[9] for angina pectoris, congestive heart failure, esophageal spasms and also to treat glaucoma[10]) or even 3-(trialkylammonium)-isosorbide derived salts (used as catalysts in asymmetric synthesis)[11]

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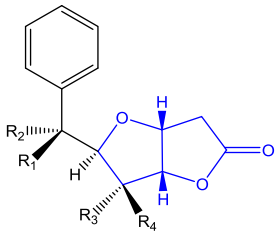
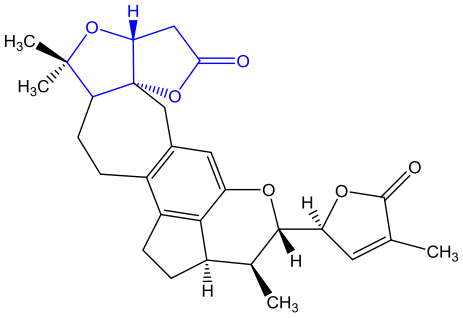
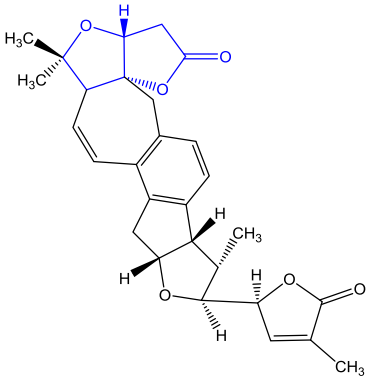


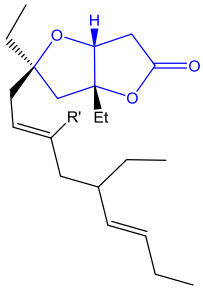
Goniofufurone:
R_1 = H, R_2 = OH, R_3 = H, R_4 = OH
7-*epi*-Goniofufurone:
R_1 = OH, R_2 = H, R_3 = H, R_4 = OH
(*Goniothalamus giganteus*)
Annonaceae



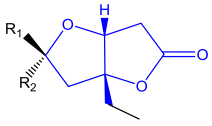
Rubriflordilactone A
(*Schisandra rubriflora*)
Schisandraceae



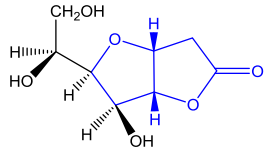
Rubriflordilactone B



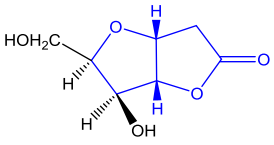
Plakortone A R' = Et
Plakortone B R' = Me
Plakortis halichondrioides and *Plakortis simplex*
(Caribbean sponges)



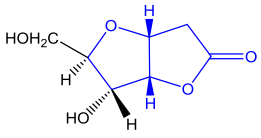
Diachasmimorpholides
R_1 = *n*-C_4H_9, R_2 = H
R_1 = *n*-C_6H_{13}, R_2 = H
R_1 = H, R_2 = *n*-C_4H_9
R_1 = H, R_2 = *n*-C_6H_{13}
Diachasmimorpha longicaudata and *Diachasmimorpha tryoni*
(Hymenoptera Braconidae, wasp parasitoid)



***cis-D*-Glucofurofuranone**



***cis-D*-Xylofurofuranone**



***cis-D*-Ribofurofuranone**

Fig. 1. Examples of natural products, having the substructure tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one, with interesting biological activities.

are also good examples of the versatility of this structural difuran framework.

For the aforementioned important properties, tetrahydrofuro [3,2-*b*]furan-2(3*H*)-ones have been a synthetic target since long time ago and several methodologies have been developed for this purpose.[1,12–16]

Based in our previous experience in the reactivity of oxyallyl cations, [4+3]-cycloaddition reactions and related methodologies,[17] we present here a new synthetic method, which is simple, straightforward and versatile, because a wide variety of furofuranones, and with wide molecular diversity, may be prepared by adequately designing the substituents of starting materials. This method consists in the reaction of highly substituted 2-oxyallyl cations, generated in situ from the corresponding dihaloketone **II**, and 2-functionalized furans **I** (in our case 2-NHBoc-furan) (Fig. 2) to afford alkylidene-furofuranones **III**, which can be transformed into a wide variety of derivatives (i.e., **IV, V** or **VI**) by straightforward reactions. The key reaction leading to **III** is a [3+2] cycloaddition that takes place by a one-pot process and with high regio- and stereoselectivity.